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Nanomedicines in B Cell-Targeting Therapies

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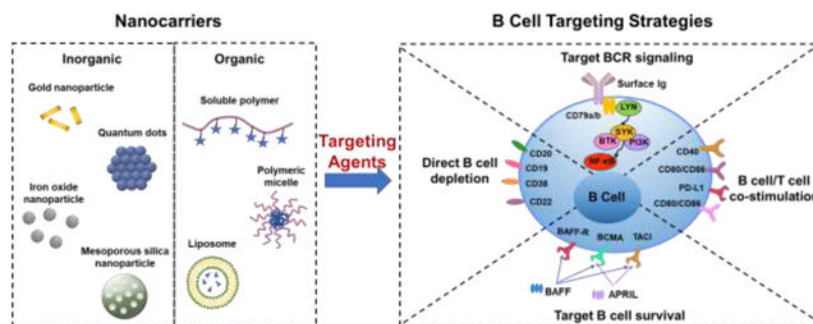
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Abstract

B cells play multiple roles in immune responses related to autoimmune diseases as well as different types of cancers. As such, strategies focused on B cell targeting attracted wide interest and developed intensively. There are several common mechanisms various B cell targeting therapies have relied on, including direct B cell depletion, modulation of B cell antigen receptor (BCR) signaling, targeting B cell survival factors, targeting the B cell and T cell costimulation, and immune checkpoint blockade. Nanocarriers, used as drug delivery vehicles, possess numerous advantages to low molecular weight drugs, reducing drug toxicity, enhancing blood circulation time, as well as augmenting targeting efficacy and improving therapeutic effect. Herein, we review the commonly used targets involved in B cell targeting approaches and the utilization of various nanocarriers as B cell-targeted delivery vehicles.

Graphical Abstract



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Competing Interest

J.K. and J.Y. are co-inventors of US Patent 9,289,510 a patent application related to combination chemo- and immunotherapy. The University of Utah licensed both to TheraTarget, Inc. J.K. is Chief Scientific Advisor and J.Y. Scientific Advisor for Bastion Biologics. Otherwise, the authors declare no competing financial interests.

Keywords

Nanomedicines; B cell targeting; Autoimmunity; Immunotherapy

1. INTRODUCTION

Nanocarrier-based drug delivery, a promising area in medicine development, is effective in diagnosis and treatment of disease. The physicochemical properties of nanocarriers such as size, charge, biocompatibility and absence of toxicity make them superior carriers for drug delivery. Manipulating the size of nanocarriers enables control of the intravascular half-life [1, 2]. Simultaneously, capture of nanocarriers by the mononuclear phagocyte system (MPS) can be minimized by adjusting their size, chemical composition and/or surface characteristics.

Nanocarriers can be broadly divided into two categories: inorganic nanocarriers and organic nanocarriers. The inorganic nanocarriers generally consist of an inorganic core such as gold [3], quantum dots [4], iron oxide [5] or silica nanoparticles [6] and a shell (usually synthetic polymers) to provide a linker for biomolecule conjugation or prevent core damage due to unwanted physicochemical interactions within the biological microenvironment. The organic nanocarriers include water soluble polymers [7–9], polymeric micelles [10, 11], liposomes [12], vesicular carriers [13–16], etc. Both inorganic and organic nanocarriers can be used as diagnostics and delivery vehicles by conjugation or entrapment with therapeutic agents such as peptides, proteins, siRNA, and drugs [17–21]. The large surface-to-volume ratio of nanocarriers enables them to possess a high-loading capacity to deliver therapeutic or imaging agent. Surface modification of nanocarriers with amphiphilic polymers such as polyethylene glycol (PEG) could reduce the uptake by the MPS, liver, and spleen [22, 23]. The utilization of nanocarriers elongates drug circulation time, minimizes toxicity, protects active drug against degradation and attains controlled drug release. The biophysical and biocompatible properties of tunable nanocarriers could be easily adjusted, which makes them versatile in application in biomedical use [24].

Passive targeting of nanomedicines in tumor tissue takes advantages of the enhanced permeation and retention (EPR) effect due to blood vessel leakage and inefficiency of lymphatic drainage in tumor tissues [25–28]. Active targeting nanocarriers contain specific structures (targeting moieties) that bind to specific surface structures on target cells, thus significantly enhancing therapeutic results and minimizing off-target effects. Multivalence is another notable advantage of nanocarriers as it allows better targeting, enhanced internalization and changes in subcellular trafficking, as well as augmented therapeutic efficacy [29, 30]. Various types of molecules have been conjugated to nanocarriers for active targeting including peptides [31, 32], antibodies [33], antibody fragments [34] aptamers [35], affibodies [36, 37], and small chemical molecules such as receptor ligands [38]. Although nanomedicines are extensively used, the limitations are not to be ignored such as toxicity/drug leak into the blood stream of liposomes, difficulty to scale up for polymeric nanoparticles, low drug-loading efficacy due to crystalline structure for solid lipid nanoparticles and toxicities for nanoemulsions and metallic nanoparticles [39]. Here we

shall discuss the utilization of nanocarriers in B cell targeted therapy as B cells are essential in the development of adaptive immunity related to tumor microenvironment and chronic inflammation.

B cells initiate from hematopoietic stem cells (HSC) in mammalian bone marrow [40]. HSCs pass through sequential developmental stages such as pro-B cells, pre-B cells and grow into immature B cells in a stepwise manner, at which stage B cells are capable to recognize antigens [41]. The immature B cells subsequently migrate to secondary lymphoid tissues (such as spleen and lymph nodes) where they divide into mature naïve B cells [42]. Activation of mature naïve B cells happens when they bind with their respective antigen. Activated naïve B cells are selected and differentiated into plasmablasts depending on bound antigens followed by development of antibody producing plasma B cells [43]. More details of selected surface marker expression and disease association along with B cell development stages are summarized in Figure 1.

B cells contribute to immunity through antibody-independent functions and antibody-dependent functions.

There are two major antibody-independent functions B cells perform to affect T cell activity and other immune cells. Antigen-activated B cells could act as antigen-presenting cells (APCs), participating in the generation or regulation of immune responses by activating or tolerating T cells at even low antigen concentration [44]. There are three ways for APCs to internalize antigen: phagocytosis, pinocytosis and receptor-mediated endocytosis. Other APCs like macrophages and dendritic cells internalize antigens via phagocytosis and pinocytosis while B cells internalize antigens through B cell antigen receptor (BCR)-mediated biorecognition. Thus, B cells serve as APCs with high sensitivity and specificity in normal immunity and autoimmune diseases [45, 46].

As most antigens need to be processed before being presented to T cells, B cells - like other APCs - perform antigen processing and presentation with facilitation from major histocompatibility complex class II (MHCII) molecules [47]. Antigens internalized via BCR signaling are degraded into smaller fragments in the lysosomes. The MHCII molecule binds to desired antigenic peptide fragment and translocates it to the cell surface to present the antigen to T cells [48]. Human leukocyte histocompatibility complex DO (HLA-DO) is expressed on human B cell surface and serves as chaperone in this process [49]. It is also reported that B cells are related to the generation of ectopic germinal center (GC) in inflammatory tissues. The activation of B cells results in the activation of CD4⁺ T cells while non-B cell APCs cannot maintain T cell stimulation. Activated T and B cells promote development of ectopic GCs [50].

Another antibody-independent mechanism B cells are involved in relates to proinflammatory cytokine secretion. Activated B cells can produce chemokines CCL22 and CCL17, which are able to recruit CD4⁺ Th2 type T cells [51]. These T cells, in turn, initiate B cell differentiation towards cytokine secreting B cells. Cytokines secreted by B cells include TNF- α , lymphotoxin and IL-6; this enables B cells to modulate and amplify immune response [52]. On the other side, production of pro-tumorigenic cytokines from B cells can

also support neoplastic cells as well as suppress cytotoxic T cell proliferation. Regulatory B cells suppress effector T cells and NK cells by expressing immune checkpoints, such as programmed death ligand PD-L1 [53, 54].

In the antibody-dependent mechanism, plasma cells differentiated from B cells secrete autoantibodies which are present in the peripheral circulation. Autoantibody-mediated antigen uptake has been proved to be a pathogenic mechanism of T cell-mediated autoimmune diseases [55, 56]. Secreted autoantibodies could also activate or inhibit receptor functions. Autoantibodies to thyroid stimulating hormone (TSH) receptor can either inhibit the TSH receptor signaling pathway or activate different signaling cascades [57, 58].

In short, B cells execute anti-tumor effect through recognition of tumor-specific antigens, performance of antigen-activated B cells as APC and antibody production (IgG) by plasma cells. Secretion of effector cytokines by activated B cell promotes T cell responses in anti-tumor functions and B cells may mediate direct toxicity in cancer [59, 60]. Meanwhile, B cells could also have pro-tumor activities by involvement in solid tumorigenesis by multiple tumor-promoting mechanisms and activation of myeloid-derived suppressor cells (MDSCs). In addition, B cells also play important roles in progression of autoimmune diseases. Besides autoantibody secretion, production of inflammatory cytokines and APC function, more detailed mechanisms of B cells involved in autoimmune disease development and corresponding B cell targeting approaches have been summarized in [61].

Moreover, B cell targeting strategies show promise in the treatment of many other diseases such as cardiovascular diseases. As atherosclerosis is lipid-driven, plasma cholesterol level is a cornerstone treatment modality. However, even with optimal lipid-lowering, there is still a considerable risk of cardiovascular disease, which may be attributed to inflammation [62]. Conventionally, B cells play an overall protective role in atherogenesis [63]. However, there are increased data indicating depletion of B cells is beneficial for preventing atherosclerosis development/progression in mouse models [64, 65]. Improvement of lipid profiles was noticed in these patients treated with B cell depletion therapy [63]. B cell activation may enhance atherosclerosis by producing autoantibody and inflammatory cytokines as described above, depending on the B cell subsets [65, 66]. Thus, selective B cell depletion strategies could possibly be advantageous to atherosclerosis management.

As critical players in B cell malignancies, immunity in tumor microenvironment and development of autoimmune diseases, B cells have been progressively recognized as essential participants in therapies of cancer and autoimmune diseases [53, 67]. Based on the roles B cells play in pathogenic pathways, therapeutic strategies for targeting B cells can be generally categorized into direct B cell depletion [68], modulation of BCR signaling [69], targeting B cell survival [70], targeting B cell/T cell costimulation [71], and immune checkpoint blockade [72]. In this review, we summarize the main strategies employed in targeting B cells and corresponding applications of diverse nanocarriers (Figure 2 & Table 1).

2. DIRECT B CELL DEPLETION

Direct B cell depletion is one of the most used strategies targeting B cells to treat cancer and autoimmune diseases (Figure 2A) [67, 73, 74]. Monoclonal antibodies are the major agents used for B cell depletion such as rituximab (Rituxan®), obinutuzumab (Gazyva®) and ofatumumab (Kesimpta®) targeting CD20 [75], blinatumomab (Blincyto®) and inebilizumab (Uplizna®) targeting CD19 [76], inotuzumab ozogamicin (Besponsa®) targeting CD22 [77] and daratumumab (Darzalex®) targeting CD38 [78]. Depletion strategies targeting CD19 can kill plasma cells, which are responsible for antibody production, while those targeting CD20 and CD22 do not diminish plasma cells. CD38 targeting approaches can specifically reduce the number of plasma cells as CD38 is particularly expressed on plasma cells [79]. Patients with chronic inflammation usually require repeated B cell depletion treatment; adverse effects including infusion reactions, immune response to chimeric antibody and infections may happen. Following repeated depletion, B cells can be restored in up to 6 months as a passive process once treatment is terminated [80]. Different disease types also affect the repopulation process. The repopulation speeds after rituximab depletion of B cell are significantly differentiated between patients with rheumatoid arthritis, connective tissue diseases, and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) [81].

2.1. CD20

The CD20 receptor is widely expressed on the surface of most B cells except pro B cells and plasma cells. Rituximab (Rituxan®, RTX), the first clinical anti-CD20 monoclonal antibody (mAb) to be developed, was approved to treat B cell non-Hodgkin's lymphoma (NHL) by the FDA in 1997 [82]. Rituximab is a chimeric antibody with murine variable regions of α CD20. The second generation of anti-CD20 antibodies with fully humanized sequences and engineered Fc fragments, include ocrelizumab (Ocrevus®), velruxumab, obinutuzumab and ofatumumab, and are created to be more effective with higher tolerance and minimized immunogenicity [83].

The anti-CD20 mAbs are effective via three mechanisms: antibody-dependent cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and CD20 crosslinking-mediated apoptosis [84, 85]. Immune effector cells (macrophages, neutrophils, NK cells, eosinophils, etc) are required for all these three mechanisms to function [86]. Notably, the interaction between Fc fragments and Fc gamma receptors ($Fc\gamma R$) triggers effector functions mediated by neutrophils and results in infusion related reactions [87] and RTX-induced interstitial lung injury [88]. Due to the murine-derived variable regions in RTX, production of human anti-chimeric antibodies was reported in 27% of patients treated with RTX [89]. Moreover, intrinsic resistance to RTX in patients has been observed which may due to RTX internalization [90]. Blocking of $Fc\gamma RIIIb$ could efficiently inhibit the internalization of RTX, demonstrating that the absence of Fc fragment could impede the development of resistance to therapeutic antibodies [91]. CD20-negative B cells result from $Fc\gamma R$ mediated trogocytosis; they contribute to resistance development to CD20 mAb therapy [85]. Also, resistance to CDC induced by RTX can be initiated by depletion of necessary complement effector molecules due to RTX exposure [90].

To further enhance therapeutic outcomes of anti-CD20 mAbs, antibody or antibody derivate-decorated nanocarriers have been extensively investigated. *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymer-epirubicin (EPI) conjugate attached to RTX (RTX-P-EPI) presented superior anti-tumor efficacy in comparison with RTX combined with small molecule drug epirubicin (RTX+EPI) and RTX combined with polymer-EPI (RTX+P-EPI) in treatment of lymphoma in a mouse model [92]. Carboxylic acid-terminated biodegradable polymers, polylactic acid-*block*-polyethylene glycol-COOH (PLA-*b*-PEG-COOH) and polycaprolactone-COOH (PCL-COOH) modified with RTX were used for tumor diagnosis as well as treatment when loaded with hydroxychloroquine sulfate and chlorambucil [93, 94]. Poly(lactic-*co*-glycolic acid) (PLGA) nanoparticle core coated with poly-L-arginine layers and CD20/CD44 antibody dual-targeting outer layer was applied to deliver siRNA, which can silence the B-cell lymphoma 2 (Bcl-2) protein thus inducing cell apoptosis [95]. In addition to polymer-based nanocarriers, versatile caveospheres [96], albumin [97], chitosan/quantum dots (QD) [98], liposomes [99, 100] and micelles [101] have been conjugated with anti-CD20 mAbs to enhance targeting and therapeutic efficiency. Nanoparticles containing iron oxide conjugated with anti-CD20 antibody have been used to enhance imaging and diagnosis of tumors [102–104].

The Kopeček lab has been working on targeting CD20 utilizing polymer-based nanomedicines for more than 10 years. Drug-free macromolecular therapeutics (DFMT) is a new paradigm in nanomedicine. Apoptosis is induced by biorecognition at the cell surface and crosslinking of receptors; no small molecule drug is needed. DFMT platform has two components: 1) a bispecific engager, comprising of Fab'-MORF1 (Fab' fragment of α CD20 conjugated with designated morpholino oligonucleotide sequence MORF1), and 2) a crosslinking (effector) molecule, P-(MORF2)_X (*N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymer decorated with multiple copies of complementary MORF2). The hybridization of MORF1/MORF2 induces CD20 crosslinking due to the macromolecular character of the MORF2 containing effector. The B cell depletion efficacy of this DFMT platform has been proven *in vitro* [105–107], *in vivo* (lymphoma mouse model [105, 106, 108], collagen-induced arthritis mouse model [109]), and in cells from patients diagnosed with different subtypes of B cell malignancies [110, 111]. Chu *et al* investigated the effect of multivalency of DFMT on apoptosis and proved that high valency P-MORF2 containing 10 MORF2 per macromolecule showed significantly higher B cell apoptosis rate in DFMT system compared to low valency P-MORF2 containing 3 MORF2 [105]. The superior efficacy was likely due to higher avidity to B-cells as well as more effective CD20 clustering contributed by high valence of P-MORF2. To enhance the performance of DFMT in RTX resistant lymphoma cells, gemcitabine or HPMA copolymer-gemcitabine conjugate were used to pretreat cells or mice as gemcitabine was proven to increase CD20 expression levels by activating NF- κ B pathway as NF- κ B binds to the CD20 promoter to induce CD20 transcriptional activation [106, 112]. As gemcitabine could induce p53-dependent cell apoptosis by itself in cancer cells [113], the combination of gemcitabine with our DFMT system may have syngeneic effect in apoptosis induction of CD20-positive B cells. In addition to using a synthetic polymer backbone as crosslinking component, human serum albumin (HSA) was also evaluated and conjugated with MORF2 to provide the HSA-(MORF2)_X effector [114, 115].

As a large number of patients have experienced side effect induced by RTX due to chimeric components, fully humanized type II antibodies such as obinutuzumab (OBN) have been developed to be less immunogenic [116]. CD20 mAbs are categorized into Type I or Type II depending on their mechanisms-of-action (Figure 3A). Both of the two types could elicit antibody-dependent cellular cytotoxicity (ADCC). However, type I mAbs rearrange CD20 into lipid rafts and the Fc fragment efficiently trigger the complement cascade while type II mAbs induce homotypic adhesion and direct programmed cell death via a caspase-independent pathway [117, 118] (Figure 3B). Unlike type I antibodies (rituximab and ofatumumab) that work primarily via CDC, OBN induces enhanced apoptosis by lysosome disruption and actin remodeling and ADCC, with only weak CDC activity [83, 116, 119]. The superior efficacy of OBN compared to RTX in preclinical studies may be due to 1) OBN inducing less CD20 internalization compared to RTX and 2) Fc fragment of OBN demonstrating better binding to Fc γ RIIIa [85]. The design of second-generation DFMT aims to augment the therapeutic efficacy by combining the activation pathways of Type I mAb and Type II mAb [120] (Figure 3C). This new design is composed of two components: a) bispecific engager, OBN-MORF1 (designated morpholino oligonucleotide sequence MORF1 conjugated to OBN); and b) a crosslinking (effector) nanoconjugate HSA-(MORF2)_X (HSA decorated with multiple copies of complementary sequence MORF2). The binding of OBN to CD20 is not hampered by attachment of MORF1. Type II pathways are activated upon OBN-MORF1 binding to CD20. Subsequent exposure to multivalent crosslinking effector HSA-(MORF2)_X leads to clustering the OBN-MORF1-CD20 complexes into lipid rafts, which triggers the Type I pathway (Figure 3C). This new “clustered OBN (cOBN)” strategy integrates mechanism-of-actions of both Type I and Type II α CD20, contributing to enhanced apoptotic levels of tumor cells [120]. Recently, it was demonstrated that DFMT is effective in crosslinking of CD38 receptors with concomitant induction of apoptosis in lymphoma and multiple myeloma cells [121].

Similarly, the MacKay lab utilized a polypeptide-based system conjugated with antibody derivatives to initiate CD20 crosslinking [122]. The single chain variable regions (scFv) which can recognize and bind to CD20 receptors were expressed as a fusion with an elastin-like polypeptide (ELP), functioning as the crosslinking component. The ELP is a hydrophilic, stimulus-responsive biopolymers comprised of pentameric repeats of [Val-Pro-Gly-Xaa-Gly]_n, in which Xaa could be different amino acid. One important property of these polypeptides is that they undergo a reversible phase transition at certain temperature, which depends on Xaa and number of repeats [122, 123]. The therapeutic efficacy of this design was proven in lymphoma models [122]. In other studies, scFv fused with streptavidin (SA) was used to pre-target B cells, followed by fluorescent polystyrene-PEG-biotin [124] or chitosan-biotinylated PEG-coated iron oxide [125] nanoparticles which could bind to SA via biotin-SA interaction. Pre-targeting with CD20 specific fusion protein significantly increased tumor targeting of nanoparticles. Besides antibody or antibody fragments, the use of anti-CD20 aptamers was also studied to kill CD20⁺ melanoma stem cells with salinomycin-loaded lipid-polymer nanoparticles as the carrier [126].

In summary, crosslinking of CD20 receptors expressed on most B cell surface could induce apoptosis, leading to B cell death. Anti-CD20 antibodies, Fab', scFvs as well as aptamers

were utilized in nanotechnology to target CD20 as a B cell depletion strategy. Furthermore, this is a platform technology applicable to crosslinking of other receptors.

2.2. CD19

Compared to CD20, CD19 has a broader expression across the stages of B cell development, including pro-B cells where CD20 is absent [127]. Thus, a strategy designed to deplete CD19+ B cells can remove not only mature B cells but also antibody-secreting cells. Inebilizumab (Uplizna®) [128] and blinatumomab (Blinicyto®) [129] are two examples of clinical antibodies targeting CD19.

PEGylated recombinant hybrid α CD19 antibodies enhanced the binding of compounds to CD19+ cell lines but not to CD19- cell lines [130]. In most cases, α CD19 mAb was used as a targeting agent combined with small molecule drugs. PEGylated gold nanoparticles conjugated with α CD19 antibody achieved higher cytotoxicity compared to free antibody due to high oxidative stress as well as trapping cells in the growth phases [131]. Imatinib-encapsulated CD19-targeting liposomes attained excellent efficacy in killing cells from patients diagnosed with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL), overcoming the resistance and system toxicity of imatinib [132]. A similar idea was reported using CD19-targeting liposomes loaded with compound “C61”, a tyrosine kinase (SYK) P-site inhibitor to initiate apoptosis of B-precursor leukemia cells [133]. SYK phosphorylation is involved in activation of proliferation and survival. Inhibition of SYK suppresses anti-apoptotic pathways such as PI3K and STAT3 [134]. Modification of polymeric nanocarriers encapsulating doxorubicin (DOX) with α CD19 mAb significantly increased cellular uptake as well as cytotoxicity [135]. The Uckun lab developed a recombinant human CD19-ligand protein (CD19L). This ~54 kDa CD19L has a great potential to serve as the targeting moiety for nanoscale delivery [136].

As the strategy of chimeric antigen receptor T cells (CAR-T) targeting CD19 antigen has been approved by the FDA to treat acute lymphoblastic leukemia (ALL) in 2017, a three-segment amphiphilic copolymer, methoxy polyethylene glycol-branched polyethyleniminepoly(2-ethylbutyl phospholane) (mPEG-bPEI-PEBP), was reported to encapsulate DNA plasmids of CAR-T to overcome low transfection efficiency and loading capacity as well as biosafety issues [137]. Antigen loss or antigen-low escape has been recognized as one of the major mechanisms for ALL relapse, which is likely due to the down-regulation of antigen expression caused by therapeutic pressure of CAR T therapies [138]. Although antigen loss in lymphoma is less reported than in leukemia, sequential loss of tumor surface antigens was observed. A patient bearing DLBCL lost CD19, CD20 and CD22 expression after CD19 CAR T and CD22 CAR T treatment [139]. Dual or multi-targeted CAR T therapies may be needed to overcome such tumor immune issues. More discussion regarding strategies overcoming antigen loss could be found in [138].

Similar to CD20, iron oxide nanoparticles conjugated with α CD19 mAb could be used for imaging, for example, to track B cells spreading from the bone marrow and spleen [140]. α CD3 and α CD16 are commonly used antibodies for dual targeting with CD19 [141, 142]. CD3 antigen can associate with T cell receptor (TCR). The use of α CD3 mAb was capable to stimulate T cell proliferation with tumor cells presence. Blinatumomab (a bispecific T

cell engager specific for CD19 and CD3) has been evaluated in several clinical trials for the treatment of NHL and ALL [143]. CD19 × CD3 × IL12 bispecific T cell engaging-cytokines transported by magnetic iron oxide nanoparticles were able to redirect T cells to leukemic B cells and co-deliver T cell-stimulating IL-12 simultaneously. The screened nanoparticles showed *ex vivo* lytic effect towards leukemia [144]. A similar strategy is described in [145]. CD16 also called FcγRIII is expressed on the surface of NK cells. The use of αCD16 mAb helped enrich NK cells to enhance the killing efficacy of CD19+ lymphoma cells [142]. Bispecific killer engagers (BiKE) containing a single variable portion (V_H and V_L) of αCD19 mAb and of αCD16 mAb linked together showed enhanced NK cell-mediated targeting of tumor cells [146]. CD19 can also be targeted by αCD19 scFV fusion protein as a B-cell based tumor vaccine treatment to induce anti-tumor immunity [147].

Anti-CD19 antibodies and CD19 ligand protein were commonly used as B cell targeting moieties. Dual targeting of CD19 with pathway inhibitors or receptor ligands such as αCD3 and αCD16 enhanced the therapeutic efficacy of nano-systems [141, 142].

2.3. CD22

CD22, a transmembrane protein which specifically binds to sialic acid, is a immunoglobulin-like lectin highly expressed on mature B lymphocytes as well as their malignant counterparts [148]. As a regulatory endocytic receptor, CD22 constitutively recycles between the cell surface and endosomes. Once the receptor is bound to the ligands, a rapid internalization happens and the ligands can be released in the acidic endosome. These superior properties favor CD22 to be a suitable molecular target for drug delivery [149].

Anti-CD22 mAb was conjugated to conjugate with superparamagnetic iron oxide nanoparticles to enhance the delivery efficacy of siRNA to treat ALL. The siRNA targeted the MAX dimerization protein 3 (MDX3) transcription factor, which is anti-apoptotic in pre-B ALL. Dual targeting of CD22 and MDX3 has great potential in the treatment of ALL [150]. Cadmium–tellurium quantum dots (CdTe QDs) conjugated with αCD22 mAbs and co-loaded with doxorubicin (DOX) and gambogic acid (GA) were developed as a nanoparticle-based strategy in combination with targeting moiety and chemotherapy. This delivery regimen can specifically target and preferentially deliver DOX and GA into B lymphocytic tumor cells [151]. Liposome loaded with doxorubicin derivative, AD198, was conjugated with anti-CD22 Fab' to target CD22 positive B malignant lymphocytes. The CD22 targeted liposomal formulation of the liposome was more specific and effective when compared to untargeted formulation [152]. Sialic acid (SA) has been also used to initiate the receptor-mediated internalization into CD22-expressing cells. Kwon's group utilized adeno-associated virus (AAV) with an acid-degradable, siRNA-encapsulating polyketal shell, producing core-shell viral/nonviral chimeric nanoparticles (ChNPs) to treat B cell lymphoma. The ChNPs were modified with SA on the surface to enhance the siRNA release in the cytoplasm of target cells [153]. Besides using SA and αCD22 mAb as targeting moieties, the Paulson lab developed a chemically distinct natural N-linked glycan scaffolds which showed high affinity to CD22 glycan ligand. These glycan scaffolds can efficiently deliver auristatin and saporin to kill B lymphocytic cells via CD22-mediated internalization [154].

As CD22 could mediate internalization once bound to ligands, various targeting moieties such as α CD22 mAb, sialic acid as well as natural N-linked glycan scaffolds have been used to enhance nanocarrier endocytosis, along with subsequent drug release in acidic endosomes for killing B cells.

2.4. CD38

CD38 is a transmembrane glycoprotein expressed on the surface of many immune cells including T cells, B cells and nature killer (NK) cells. While the high and uniform expression of CD38 is observed on multiple myeloma (MM) cells, much lower expression levels of CD38 are observed on normal lymphoid cells, myeloid cells, red blood cells and platelets [155]. The α CD38 mAb including daratumumab, isatuximab (Sarclisa®) and MOR202 function via multiple mechanisms: Fc-dependent immune effector mechanisms including ADCC, CDC and ADCP, inhibition of ectoenzymatic function, direct apoptotic induction and immunomodulatory effects by the depletion of CD38+ immune suppressor cells (regulatory T cells, regulatory B cells, and MDSCs) [155]. CD38 is involved in calcium homeostasis by acting as cyclic ADP ribose hydrolase. Antibodies such as isatuximab inhibit the cyclic ADP-ribosyl cyclase activity by binding to CD38 [156]. Similar to CD20-targeting therapy in NHL, α CD38 mAb has been applied as a combination strategy with standard chemotherapy to treat MM.

The first study to utilize CD38 as a target for nanomedicine drug delivery system to treat MM was reported by the Azab lab in 2017. They decorated bortezomib (BTZ) loaded polymeric chitosan nanoparticles with α CD38 mAb to enhance targeting efficacy and therapeutic results. BTZ is a proteasome inhibitor used to treat MM. The advantages of using chitosan nanoparticles include large drug loading capacity, superior adsorption capabilities and long shelf life. Conjugation of α CD38 mAb provides a better tumor penetration of the nanoparticles. The acidic tumor environment accelerates drug release from chitosan nanoparticles and enhances proteasome activity inhibition [157]. A similar study reported utilizing α CD38 mAb to conjugate with STAT3 (signal transducer and activator of transcription 3) inhibitor loaded poly(ethylene oxide)-*block*-poly(α -benzyl carboxylate- ϵ -caprolactone) (PEO-*b*-PBCL) backbone [158]. To avoid the NK cell killing side effect of daratumumab, F(ab')₂ fragments derived from daratumumab were used to pre-block NK cells to augment the anti-tumor effects [159]. A more detailed summary of anti-CD38 mAbs was provided in [156].

CD38 is mainly selected as a targeting receptor in therapies of multiple myeloma. α CD38 mAb were utilized with polymeric nanoparticles in this field.

2.5. Other Potential Targets

Besides the receptors mentioned above, there are other potential targets under investigation which have not been extensively utilized in nano-delivery systems for B cell depletion strategies.

The surface antigen signaling lymphocytic activation molecule-F7 (SLAMF7; CD319) is a marker of normal and malignant plasma cells. Besides plasma cells, SLAMF7 is also expressed on NK cells, CD8+ T cells and mature dendritic cells [160]. The humanized

anti-SLAMF7 mAb elotuzumab (Empliciti®) has been investigated in clinical trials to treat MM [161] and approved by the FDA in 2017 [162]. The function of elotuzumab includes two mechanisms. One is the Fc-mediated ADCC on MM cells and NK cells. The other one activates natural cytotoxicity of NK cells, from which IFN- γ is secreted to stimulate other immune cells [163]. In addition, the strong expression of SLAMF7 on CD20- plasmablast and plasma cells in RA synovium makes it a promising target for RA treatment. Humanized monoclonal antibody PDL241 could inhibit IgM production by depleting SLAMF7+ plasmablast and plasma cells in CIA mouse models [164].

One special target of B cell lymphomas is idiotypic sequences, which are specific to the hypervariable regions of immunoglobulin expressed by malignant B cells. Tumor-specific idio type vaccines have been developed to induce anti-idiotypic immune activation as the lymphoma idio type vaccines are the first-in-class to show prominent anti-tumor efficacy in human cancer [165]. Tumor associated, poorly immunogenic self-antigen expressing plasmid DNA (pDNA) has been used as DNA vaccine to treat B cell lymphoma [166]. Several clinical trials have been performed with limited therapeutic effect due to low transfection efficiency [166, 167]. To optimize the delivery strategy, synthetic polymer was utilized as a carrier. Branched polyethylenimine (PEI) conjugated with PLGA has been proven to enhance adjuvant effects in phagocytic cells and protect the anti-tumor effect in B cell lymphoma animal models [168]. PEI loaded with pDNA has been evaluated in patients with non-Hodgkin's lymphoma (NHL). The cationic polymer PEI enhanced the transfection efficiency of pDNA [169].

There are also cholesterol depletion strategies reported in the literature. Scavenger receptor type B-1 (SCARB1), highly expressed on the surface of diffuse large B cell lymphoma (DLBCL) cells, is significantly involved in cholesterol and cholesteryl ester homeostasis. Cholesterol-poor high-density lipoprotein (HDL)-like NPs (HDL NPs) targeting SCARB1 reduced cellular cholesterol levels, ultimately leading to lymphoma cell death [170].

Most of the targets discussed in this section are receptors expressed on B cell surfaces. The mechanisms of action include ADCC, CDC, crosslinking-mediated apoptosis, receptor-mediated internalization, etc. Corresponding antibodies and their derivatives as well as natural or synthetic ligands were applied as targeting/therapeutic moieties combined with nanotechnology to enhance therapeutic outcomes.

3. MODULATION OF B CELL ANTIGEN RECEPTOR (BCR) SIGNALING

The B cell antigen receptor signaling pathway is involved in B cell survival. The BCR complex is comprised of a membrane-bound immunoglobulin associated with CD79a(Ig α)/CD79b(Ig β) (Figure 2B). CD79a and CD79b comprise a heterodimeric signal-transduction component of the B cell receptor. The immunoreceptor tyrosine-based activation motif (ITAM) within the cytoplasmic domain of CD79a/79b complex is vital for signal transduction. Functional BCR is essential for B cell maturation, activation, development and maintenance [171]. Once bound to the antigen, the CD79a/b recruits the Src family kinases Lyn, Blk, Fyn, which phosphorylate the tyrosine residues in ITAM. The phosphorylation mediates recruitment of various kinases and adaptor proteins including the spleen tyrosine

kinase (SYK) and Bruton tyrosine kinase (BTK), initiating the formation of signalosome complex [172]. BCR aggregation is stimulated by the costimulatory receptor CD19 and activation of BTK [171]. The signalosome is responsible to activate three main downstream pathways: BTK, phospholipase C- γ 2 (PLC- γ 2) and phosphatidylinositol-3-kinase (PI3K). The mitogen-activated protein kinase (MAPK) and AKT pathway contribute to the BCR-induced survival and proliferation [173, 174]. Along with activation of these pathways, multiple effectors are activated including NF- κ B, Jun and nuclear factor of activated T cells (NFAT). Activation of NF- κ B signaling pathway protects B cells from apoptosis and is critical for mature B cell survival [175]. Thus, modulation of BCR signaling is another commonly used method to treat B cell-related diseases. Inhibitors targeting SYK, BTK, PI3K, Lyn, etc. have been well studied.

3.1. CD79a/b

CD79a was reported to play a vital role in maintaining the immature, immune suppressive phenotype of myeloid derived suppressor cells (MDSCs) and in induction of protumorigenic cytokines secretion, resulting in tumor promotion effects. These functions make CD79a a novel target for cancer therapy [176]. High expression levels of CD79a were observed in most B lineage acute lymphoblastic leukemias (ALL) [177]. Compared to CD20 receptor, CD79a is expressed on a wider range of B cells from pre-B stage to the plasma cell stage of differentiation. However, expression loss of CD79b before differentiation of plasma cells has been reported [178]. Thus, CD79b could be considered as a potential anti-tumor target. Anti-CD79b mAb can be used as a component of antibody-drug conjugates to induce a prolonged depletion of proliferating B cells to treat NHL as it can be transported into the B cells [179, 180]. Antibody drug conjugate polatuzumab vedotin (Polivy®), an anti-CD79b-monomethyl auristatin E (MMAE) conjugate, has been approved by the FDA in 2019 for treatment of diffuse large B-cell lymphoma [181]. The anti-CD79b mAb also has great therapeutic efficacy in autoimmunity such as in mouse model of rheumatoid arthritis [182]. Those fundamental studies focusing on antibodies of CD79a/b indicate that this complex possesses great potential as an ideal target for nano-scale drug delivery system.

3.2. Bruton Tyrosine Kinase (BTK)

BTK is a non-receptor kinase which is essential for B cell proliferation and survival. Ibrutinib (Imbruvica®), a small molecule drug, the first-in-class BTK inhibitor, has been studied in the treatment of B cell malignancies. Clinical trials demonstrated the therapeutic efficacy of ibrutinib in CLL patients [183]. The FDA approved the use of ibrutinib in combination treatment of mantle cell lymphoma (MCL), CLL, small lymphocytic lymphoma (SLL), marginal zone lymphoma (MZL), Waldenström's macroglobulinemia (WM) and chronic graft versus host disease (cGVHD). Due to the poor water solubility and hepatic first pass effect of ibrutinib [184], formulation with nanotechnology has been investigated to enhance bioavailability. Chitosan/sulfobutylether- β -cyclodextrin nanoparticles were used to deliver ibrutinib to maintain the drug activity and prolong the drug release [185]. Other BTK inhibitors such as acalabrutinib, zanubrutinib, evobrutinib, tirabrutinib, SNS-062, etc. are also under investigation [186].

Besides BTK inhibitors, small interfering RNA (siRNA) are being investigated to silence BTK genes. PEG-*b*-PLGA was used to encapsulate siRNA targeting BTK genes in B cells and macrophages to treat rheumatoid arthritis in collagen-induced arthritis model. The systemic administration of siRNA loaded NPs significantly reduced expression of inflammatory cytokines and alleviated arthritis symptoms [187].

3.3. Spleen Tyrosine Kinase (SYK)

SYK is an intracellular cytoplasmic tyrosine kinase, which is important for immunoreceptor signaling in B cells, neutrophils and macrophages. Not limited to the crucial role in adaptive immune receptor signaling, SYK is also involved in multiple biological functions such as cellular adhesion, innate immune recognition, osteoclast maturation, platelet activation and vascular development [134]. The prodrug fostamatinib (Tavalisse®) as the first oral SYK inhibitor has been approved by FDA in 2019 for treatment of chronic immune thrombocytopenia (ITP) [188]. Entospletinib (GS-9973), cerdulatinib (PRT062070) and TAK-659 are also SYK inhibitors currently under investigation in clinical trials for various B cell lymphomas [189]. The Uckun lab did a wide range of research targeting SYK pathway. They developed C61 as an inhibitor for substrate binding targeting SYK P-site, which can inactivate SYK pathway and directly induce B cell apoptosis [190]. Interestingly, C61-loaded liposomal NPs demonstrated a promising pharmacokinetic and safety profile in mouse models and showed remarkable capacity to induce apoptosis in primary B-precursor ALL blast cells from patients [191, 192]. This formulation of C61 also significantly augmented the antitumor efficacy of low-dose total body irradiation (TBI) against B-precursor acute lymphoblastic leukemia (BPL) in mouse models [193].

3.4. Phosphatidylinositide-3-Kinase (PI3K)

Besides highly involved in B cells, the PI3K pathway is overactive in various cancer cells, such as breast cancer, colorectal cancer [194], glioblastoma [195] and lung cancer [196]. Activation of the PI3K pathway reduces apoptosis and enhances cell proliferation. Among various PI3K isoforms (α , β , γ , and δ), PI3K- γ is essential in immune suppression during inflammation and cancer and is also important for cellular activation and migration [197]. PI3K- γ is highly expressed in tumor-associated B cells. Eganelisib (IPI-549) was designed by Infinity Pharmaceuticals as a PI3K- γ inhibitor possessing clinical potential [198]. It can also be used in combination with checkpoint blockade antibodies to overcome treatment resistance [199]. The Huang lab has utilized IPI-549 embedded in poly(lactic-*co*-glycolic-acid) (PLGA) NPs modified with aminoethylanisamide (AEAA) to reshape the tumor immune microenvironment and mitigate immune suppression in desmoplastic tumors more effectively than free drug [200]. Similarly, the targeting carrier aminoethyl aminoethylanisamide-polyethylene glycol-polycaprolactone (AEAA-PEG-PCL) was used for co-treatment of breast cancer by combination of IPI-549 and silibinin [201]. AEAA is a ligand of sigma receptor, which is expressed on surface of many tumor cells, thus promoting tumor cell uptake [202]. Silibinin is an anti-tumor agent, which can significantly inhibit tumor-associated fibroblasts [203]. Co-treatment of IPI-549 and silibinin were proved to remodel the tumor microenvironment thus enhancing anti-tumor efficacy by decreasing myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) as well as change the stromal structure of tumor [201]. There are numerous other molecules

designed for different PI3K isoforms. Idelalisib (Zydelig®) is the first-in-class PI3K- δ inhibitor approved by the FDA for the treatment of multiple B cell lymphomas including CLL, relapsed FL and relapsed small lymphocytic lymphoma [204]. Pictilisib (GDC-0941) and AS101 are also general inhibitors of PI3K/Akt pathway; they are able to sensitize B lymphocytes to chemotherapy such as paclitaxel [205, 206]. Besides synthetic inhibitors, the natural product snake venom extracted from *Walterinnesia aegyptia* (WEV) was reported to inhibit the PI3K/AKT pathway. Silica NPs have been used as a carrier for the snake venom [207, 208].

In this section, some of the major components of the B cell signaling pathway are discussed including CD79a/b, bruton tyrosine kinase, spleen tyrosine kinase and phosphatidylinositide-3-kinase. For CD79a/b receptor, corresponding antibodies were used to deplete B cells. For those three kinases, inhibitors such as chemical drugs and siRNA were widely employed in nanotechnology to block those pathways.

4. TARGETING B CELL SURVIVAL

The tumor-necrosis factor (TNF) superfamily plays numerous roles in regulating cell functions including cell activation, apoptosis and tumor homeostasis [209]. B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) as two members of the TNF family, are responsible for B cell generation and preservation. BAFF can activate B cells and plasma cells via three transmembrane receptors: 1) transmembrane activator, calcium modulator, and cyclophilin ligand interactor (TACI), 2) B cell maturation antigen (BCMA), and 3) BAFF receptor (BAFF-R) (Figure 2C). TACI and BCMA can recognize and bind both BAFF and APRIL while BAFF-R only recognizes BAFF [210]. BAFF and APRIL are essential for the survival, proliferation, and differentiation of B cells and plasma cells. Overexpression of BAFF may cause expanded mature B cell compartment and autoimmunity in mice [211]. APRIL participates in augmentation of B-cell antigen presentation, stimulation of B cell proliferation and augmentation of B cell survival [212]. BAFF and APRIL are involved in B cell malignancies, including CLL [213], multiple myeloma [214], and non-Hodgkin's lymphoma [215]. Thus, inhibition of the BAFF/APRIL system has been investigated as a potential strategy in treatment of B-cell associated diseases.

4.1. B Cell Maturation Antigen (BCMA)

BCMA, a transmembrane glycoprotein, also known as tumor necrosis factor-receptor superfamily member 17 (TNFRSF17), recognizes BAFF and APRIL. It participates in regulation of B cell proliferation, differentiation and survival [216–218]. BCMA is preferentially expressed on mature B cells, especially highly expressed on all MM cells. It plays a vital role in transformation of plasma cell and progression of MM [219]. Overexpression of BCMA or APRIL binding to BCMA notably enhance MM cells growth and survival [220]. BCMA targeting strategies include antibody-drug conjugates (ADCs), bispecific T-cell engagers (BiTEs), chimeric antigen receptor T cells (CAR-T) and bispecific molecules [216]. Besides those treatment modalities, the Anderson lab has developed immunogenic heteroclitic peptides, BCMA_{54–62} (YILWTCLGL) and BCMA_{72–80}

(YLMFLLRKI), which are able to induce MM-specific immune responses with high anti-tumor abilities [221]. The highly effective peptide BCMA_{72–80} (YLMFLLRKI) was encapsulated into PLGA-based NPs to enhance its delivery to APCs. The presence of the BCMA_{72–80} peptide induced antigen-specific CD8⁺ cytotoxic T lymphocytes (CTL), which are capable of maintaining a long-lasting immunity against MM cells [222].

To utilize BCMA and SLAMF7 (described in subsection 2.5) dual targeting for whole-body MM detection, ultra-small, silica-comprised and gadolinium-containing nanoparticles were conjugated with α BCMA mAb or α SLAMF7 mAb to enhance MRI imaging contrast [223].

4.2. B Cell Activating Factor Receptor (BAFF-R)

BAFF-R is expressed on B cell surface and frequently overexpressed in B cell malignancies [213, 224]. Also, excessive BAFF-R initiates severe autoimmune disorders. Overexpression of BAFF-R in transgenic mice initiated emerging autoreactive B cells secreting rheumatoid factor and anti-DNA autoantibodies, resulting in lupus-like autoimmune manifestations [225]. BAFF/BAFF-R complex is rapidly internalized and translocated to lysosomes once bound to each other [226]. CAR T cells targeting BAFF-R were able to target acute lymphocytic leukemia (ALL) cells lacking CD19, which provides a potential therapeutic approach for patients with this tumor escape variant [227]. The use of anti-BAFF-R mAb selectively depleted mature B2 cells and enhanced atherosclerosis development in hyperlipidemic ApoE^{-/-} mice. Consequently, these data suggest a potential for management of cardiovascular diseases [228].

Besides strategies with antibodies or CAR T cells, gene therapies are also utilized in BAFF-R targeting. The clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 gene editing system has been extensively utilized for DNA deletion, insertion, and replacement [229]. A library of poly(ethylene glycol)-*block*-poly(lactide-co-glycolide) (PEG-*b*-PLGA)-based cationic lipid-assisted nanoparticles (CLANs) with different surface PEG density and zeta potential were used to encapsulate CRISPR-Cas9 for *in vivo* B cell targeting. The treatment decreased the number of B cells and possessed therapeutic efficacy in mouse model of rheumatoid arthritis [230]. mBAFF, a soluble BAFF mutant, is a competitor of BAFF. mBAFF can block BAFF's biological activities, suppressing lymphocyte activation and proliferation. PEGylated liposomes were used to deliver mBAFF and vincristine to treat NHL mouse models [231]. An RNA aptamer and siRNA targeting BAFF-R have been used as targeting agents. An anti-BAFF-R antibody was used to deliver siRNA against BAFF-R [232]. RNA aptamer of BAFF-R was utilized in combination with siRNA against signal transducer and activator of transcription 3 (STAT3) as a dual functional conjugate to provide enhanced effect in inhibiting B lymphocyte survival *in vitro* [233].

4.3. Transmembrane Activator and CAML Interactor (TACI)

Unlike BCMA and BAFF-R which are predominantly expressed on B cells, TACI is expressed on both B cells and activated T cells [234]. A TACI-Ig fusion protein was developed to block the BAFF/APRIL pathway. TACI-Ig was made by fusing the TACI extracellular domains to the Fc portion of human Ig heavy chain γ 1 (IgG1). Treatment with TACI-Ig significantly reduced B cell counts in systemic lupus erythematosus (SLE)

mouse model [235]. Another study using collagen-induced arthritis (CIA) mouse models also indicated that treatment with TACI-Ig could inhibit proliferation response as well as differentiation of T and B cells, along with the alleviation of arthritis scores and other clinical symptoms [236]. However, the fusion protein TACI-Ig named “atacept” failed to show superior efficacy in clinical trials of MM, rheumatoid arthritis and SLE [237]. In patients with SLE and multiple sclerosis (MS), atacept-led inflammation was observed [237, 238]. Besides TACI-Ig, antagonistic anti-APRIL antibody [239] and TACI-incorporating CAR-T cells [240, 241] were also developed to treat MM. TACI can be a potential cell surface marker for development of targeting strategies as a supplement to BCMA-targeted therapies [242].

To utilize the nano-strategies targeting B cell survival, BCMA could be targeted by antibodies and immunogenic heteroclitic peptides; BAFF-R was blocked with antibodies, gene therapies such CRISPR gene editing system, RNA aptamer and siRNA as well as BAFF mutant (mBAFF) in the literature; TACI were mainly targeted by TACI-Ig fusion protein [237].

5. TARGETING B CELL AND T CELL COSTIMULATION AND IMMUNE CHECKPOINT BLOCKADE

In addition to activation of antigen receptors, costimulation between B and T cells is essential to fully activate lymphocytes for sustaining proliferation and differentiation (Figure 2D). The first cell surface costimulatory molecule is CD28, which is the major molecule for the activation of T cells [243]. Another class of costimulatory receptors are members of the TNF receptor family such as CD40 and CD27. There are also inhibitory molecules in contrast to costimulatory molecules like cytotoxic T lymphocyte associated protein 4 (CTLA4) and programmed cell death protein 1 (PD-1) receptor. CD80 and CD86 on B cells interact with both of the costimulatory receptors, CD28 and CTLA4 on T cells [244]. Notably, CTLA4 and PD-1 inhibit T cell activation and proliferation [245, 246].

5.1. CD80/CD86

Binding of CD80/CD86 on APCs to CD28 on the surface of CD4⁺ T cells, stimulates T cell proliferation and cytokine release [244]. Tada *et al.* reported that CD28-deficient mice were resistant to collagen-induced arthritis (CIA) as their T cell activation was severely impaired [247]. Consequently, blockade of CD28 on T cells provides a potential target for rheumatoid arthritis therapy. CTLA4 inhibits T cells activation by associating to CD80/CD86 as it has a higher binding affinity of CTLA4-CD80/CD86 compared to CD28-CD80/CD86 [248]. Abatacept (CTLA-Ig) is a fusion protein of the extracellular domain of human CTLA4 and Fc region of human IgG1. Abatacept binds to CD80/86 on APCs and so scavenges the costimulatory signal from APCs to CD4⁺ T cells. This suppresses the proliferation and cytokine production of T cells [249]. Besides abatacept, antibodies specific for CD80/CD86 and combination with sirolimus can also be utilized to prolong allograft survival in cynomolgus monkey renal transplant recipients [250]. Treatment of ovalbumin loaded NPs can promote the maturation of dendritic cells by enhancing the expression level of costimulatory factors CD80/CD86 [251].

5.2. CD40

CD40 is located on APCs including B cells, macrophages and dendritic cells. Ligation of CD40 on dendritic cells enhances production of IL-12 and augments T cell stimulation. CD40 and its ligand CD40L, expressed on activated CD4⁺ T helper cells, can activate APCs to prime CD8⁺ cytotoxic T lymphocytes (CTLs) [252]. Thus, the CD40-CD40L interaction plays a vital role in regulation of both B cell and T cell immune responses. Blockade of CD40L inhibits CTL priming [253].

The agonistic CD40 mAb FGK45 could be used in combination with antigens or vaccines to promote immune responses [254]. As immunosuppressive tumor microenvironments can restrain antitumor efficacy, CD40 activation by CD40 agonist mAb can enhance T cell response and reverse the unfavorable condition in many cancer types such as pancreatic carcinoma and melanoma [255, 256]. In addition, CD40 agonist mAb elicits protective immune responses in the treatment of autoimmune inflammatory condition in CIA mouse models [257]. However, due to the high dose needed for antibody treatment, potentially lethal side effects could occur [258]. Luminescent porous silicon NPs conjugated with multivalent CD40 mAb have been developed to lower systemic toxicity and enhance APC activation. Polymer-based NPs allow the multivalent CD40 mAb to amplify the potency of immune responses [259]. The poly(lactic-*co*-glycolic acid) (PLGA)-based NPs loaded with ovalbumin and CD40 agonistic mAb have been evaluated in melanoma mouse model. CD40-targeting improves efficient *in vivo* delivery of these NPs via enhanced binding and uptake of NP to DC, resulting in significant tumor control [260].

Interactions of CD40 with other ligands are also under investigation. The CD40-CD40L interaction is involved in development of atherosclerosis, leading to cardiovascular diseases [261]. But the inhibition of CD40-CD40L can also cause immune suppression. When the interaction between CD40 and tumor necrosis factor receptor-associated factor (TRAF) in macrophages was blocked while the CD40-TRAF2/3/5 interactions remained intact, reduction in atherosclerosis but preservation of CD40-mediated immunity was observed [262]. More detailed discussion of CD40 B cells in development of cancer vaccines is covered in [263].

5.3. Programmed Cell Death Ligands 1 and 2 (PD-L1/L2)

PD-1 is expressed on activated T cells, B cells and myeloid cells [264]. PD-1 can bind to two different ligands PD-L1 and PD-L2. hPD-L1 and PD-L2 is not limited to APCs but are expressed also on nonlymphoid tissues such as heart, lung and pancreatic islets [265]. As PD-1-PD-L1/L2 interaction can suppress the activation of T cells, overexpression of PD-L1/L2 in cancers leads to progression of tumors, resulting in poor clinical outcomes.

Multiple immunotherapy strategies are based on blockade of PD-1 associated pathways. α PD-1 mAb or α PD-L1 mAb have been evaluated in different types of cancers including non-small cell lung cancer, melanoma, renal cell cancer or Hodgkin's lymphoma [266–269]. The FDA has approved pembrolizumab (Keytruda®), nivolumab (Opdivo®) and cemiplimab (Libtayo®) as α PD-1 mAbs as well as α PD-L1 mAbs atezolizumab (Tecentriq®), avelumab (Bavencio®) and durvalumab (Imfinzi®). Due to the off-target

effects and toxicity of mAb treatment [270–272], nanocarriers such as PLGA NPs [273], gold NPs [274] and liposomes [275] have been conjugated with α PD-1 or α PD-L1 mAb in order to enhance tumor suppression effects and minimize side effects.

Peptides have been developed as small molecule candidates for immunotherapy. PPA, a dodecapeptide antagonist to PD-L1, possesses binding affinity to PD-L1 high enough to disrupt the PD-1-PD-L1 pathway [276]. Interestingly, multivalent HPMA copolymer-PPA conjugates combine checkpoint inhibition with PD-L1 crosslinking (Figure 4). The latter results in the change of PD-L1 subcellular fate; instead of recycling, PD-L1 uses the lysosomal route resulting in its degradation and downregulation. The multivalent polymer-peptide PD-L1 antagonist demonstrated higher antitumor activity than anti-PD-L1 Abs in combination with chemotherapy (multivalent HPMA copolymer-epirubicin conjugate [277]) and immunotherapy [278, 279]. Sun *et al.* combined the PPA peptide with the tumor angiogenesis affinity molecule CGKRK producing a new molecule, named CD peptide. PEG-PCL NPs loaded with paclitaxel and decorated with CD possessed higher antitumor activity than controls [280]. Recombinant single-chain variable fragment (scFv) of α PD-1 fusion protein-expressed with an amphiphilic immune-tolerant elastin-like polypeptide (iTEP) can self-assemble into multivalent nanoparticles, which efficiently block the PD-1 immune checkpoint *in vitro* and *in vivo* [281]. The role of PD-L2 in PD-1/PD-L1 axis targeting was also explored. Co-expression of PD-L2 with PD-L1 could inhibit PD-1/PD-L1 binding as well as enhance CD3 and inducible T cell co-stimulator (ICOS) on T cells. Administration of soluble multimeric PD-L2-Fc fusion protein was able to regulate immune response thus enhancing mice survival rate [282].

Besides strategies using PD-pathway targeting antibodies, methods of gene editing are also under investigation. Dual-locking nanoparticles (DLNPs) were formed with 4-(hydroxyethyl) phenylboronic acid (HPBA)-modified polyethyleneimine (PEI_{1.8k}-HPBA) and decorated by PEG on the surface. Plasmid DNA (pDNA) encoding the CRISPR/Cas13a system targeting PD-L1 was encapsulated in the core of DLNPs. The CRISPR/Cas13a system can only be released when an acidic microenvironment and high H₂O₂ concentration are both present; these enhances accumulation and gene-editing efficacy of the CRISPR/Cas13a system at the tumor sites. Besides superior blood circulation stability, the pDNA-loaded DLNP showed significant tumor suppression and improved survival rates in mouse melanoma model [283].

Small RNA molecules such as siRNA and miRNA have been also utilized in PD-1/PD-L1 targeting strategies. SiRNAs targeting PD-1 and PD-L1 were delivered by lipid-based NPs. These therapies were proven to be effective to increase tumor infiltrating lymphocytes cytotoxicity to cancer cells by silencing PD-1 and PD-L1 [284, 285]. MicroRNAs (miRs) play an important role in regulating interaction of tumor cells with microenvironment. As overexpressed in diffuse large B-cell lymphoma (DLBCL), miR155 sensitized B lymphocytes to anti-PD-L1 antibody via PD-1/PD-L1 interaction [286].

In short, this section summarized the costimulation and immune checkpoint blockade between B cells and T cells. To block the interactions between B cells and T cells, antibodies against CD80/CD86 and fusion protein (CTLA-Ig) were reported to block the

CD80/CD86-CD28 pathway. CD40 ligand was applied to block CTL priming. On the other hand, CD40 agonist mAb can enhance T cell response. There are numerous studies targeting the PD-1-PD-L1 checkpoint pathway for cancer therapy; besides antibodies, dodecapeptide antagonist to PD-L1 (PPA-1), scFv of α PD-1 fusion protein, CRISPR gene editing systems as well as siRNA/mRNA have been extensively used with platforms of nanotechnology.

6. SUMMARY

B cells play vital roles in the development of numerous diseases, including B cell lymphomas, autoimmune diseases, diverse carcinomas and cardiovascular diseases. This review summarized the major targeting molecules of B cell therapies and corresponding applications of nanotechnologies.

B cell targeting strategies are widely studied based on diverse mechanisms. Direct B cell depletion, modulation of BCR signaling, targeting B cell survival factors, targeting the costimulation of B cells and T cells, and immune checkpoint blockade are the major strategies discussed in this review. Selected surface receptors, pathways and cytokine factors which can be targeted in B cell therapy have been included. In addition, the field of B cell targeting vaccines is developing rapidly. CD19 (section 2.2), idiotypic sequences (section 2.5) and CD40 (section 5.2) related conjugates are currently under investigation. As DNA, mRNA, peptide/protein are the common agents used for cancer vaccines, a wide array of biomaterials has been employed as carriers such as lipid nanoparticles, PLGA, gold nanoparticles, and liposomes. A more comprehensive summary of applications of biomaterials in vaccine-based cancer immunotherapy is provided in [287].

Targeting agents including antibodies and their derivatives, ligands, small molecular inhibitors, gene editing with the CRISPR technique, siRNAs and miRNAs are commonly used in B cell targeting. Applications of nanocarriers in delivery of these agents has shown enhanced blood circulating time, improved targeting efficacy, reduced adverse effects as well as improved therapeutic outcomes. These advantages are enabled by the biophysical properties of nanocarriers. The multivalence of functional molecules introduced by nanocarriers delivery augments the density of targeting moieties and enhances their performance. It is noteworthy that the emerging area of using nanocarriers with the thriving CRISPR techniques cannot be overlooked [283].

Furthermore, single targeting may not be strong enough to attain ideal outcomes. Dual or triple functional nanocarriers can be developed in a single composition to achieve better therapeutic results. The multi-functionality could be achieved by combination either with therapeutic agents such as chemotherapy or with multiple targeting moieties/ligands. As reported in the literature, dual targeting of CD20/CD37 [100] or CD19/CD3 or CD16 [129, 142] could enhance direct B cell depletion efficacy of CD20 and CD19, while dual targeting of TACI/BCMA [240] or BCMA/SLAMF7 [223] significantly augmented plasma cell clearance. Besides therapeutic applications, nanomedicines provide advantages for tumor diagnosis and imaging [93, 102, 103, 223].

Table 1 provides a concise toolbox to locate a proper target for a variety of diseases. For example, multiple myeloma is a plasma cell disorder; consequently, receptors over-expressed on plasma cells such as BCMA, CD38 and SLAMF7 may have a great potential serving as targets. Regarding each specific receptor, the frequently used targeting agents and nanocarriers can be located. The current first-line treatments in clinical or in clinical trials are also provided as references.

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Statement of Significance

As B cells are engaged significantly in the development of many kinds of diseases, utilization of nanomedicines in B cell depletion therapies have been rapidly developed. Although numerous studies focused on B cell targeting have already been done, there are still various potential receptors awaiting further investigation. This review summarizes the most relevant studies that utilized nanotechnologies associated with different B cell depletion approaches, providing a useful tool for selection of receptors, agents and/or nanocarriers matching specific diseases. Along with uncovering new targets in the function map of B cells, there will be a growing number of candidates that can benefit from nanoscale drug delivery.

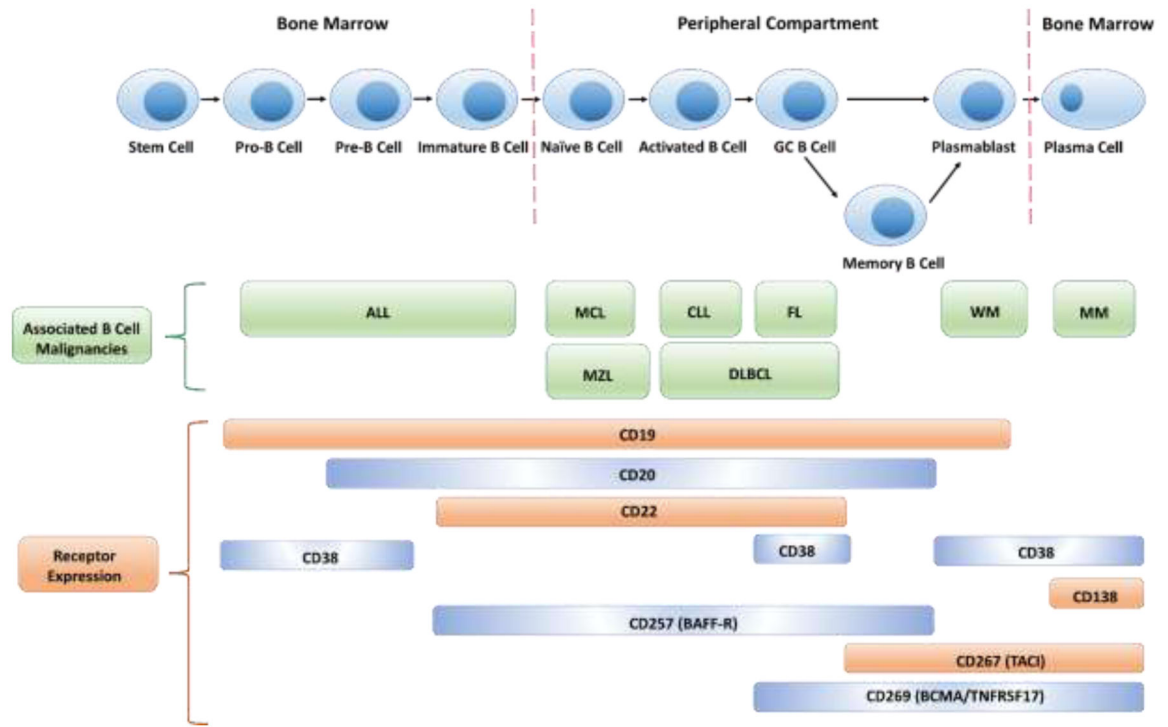


Figure 1. B cell lineage development along with corresponding biomarker expression and associated B cell malignancies. GC: germinal center; ALL: acute lymphocytic leukemia; MCL: mantle cell lymphoma; CLL: chronic lymphocytic leukemia; FL: follicular lymphoma; MZL; marginal zone lymphoma; DLBCL: diffuse large B-cell lymphoma; WM: Waldenstrom macroglobulinemia; MM: multiple myeloma.

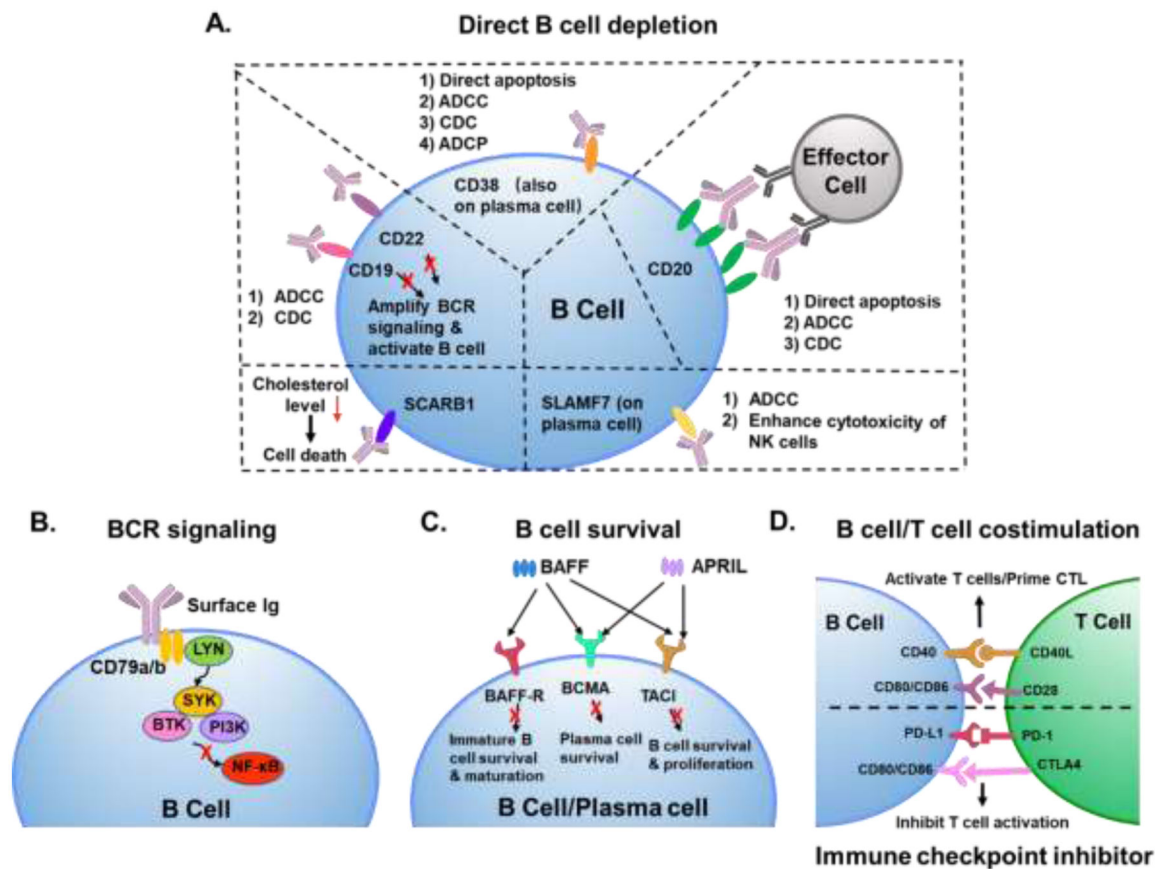


Figure 2.

B cell targeting approaches. **A.** Mechanisms for direct B cell depletion. ADCC: antibody-dependent cellular cytotoxicity; CDC: complement-dependent cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; BCR: B cell antigen receptor signaling; SCARB1: scavenger receptor type B-1; SLAMF7: surface antigen signaling lymphocytic activation molecule-F7; NK cells: natural killer cells. **B.** Through BCR signaling. LYN: tyrosine-protein kinase; SYK: spleen tyrosine kinase; BTK: Bruton's tyrosine kinase; PI3K: phosphoinositide 3-kinase; NF- κ B: nuclear factor kappa B. **C.** Targeting B cell survival. BAFF: B cell activating factor; APRIL: a proliferation-inducing ligand; BAFF-R: B cell activating factor receptor; BCMA: B cell maturation antigen; TACI: transmembrane activator and CAML interactor. **D.** Targeting B cell/T cell costimulation and immune checkpoint inhibition. CTL: cytotoxic T lymphocyte; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; CTLA4: cytotoxic T lymphocyte associated protein 4.

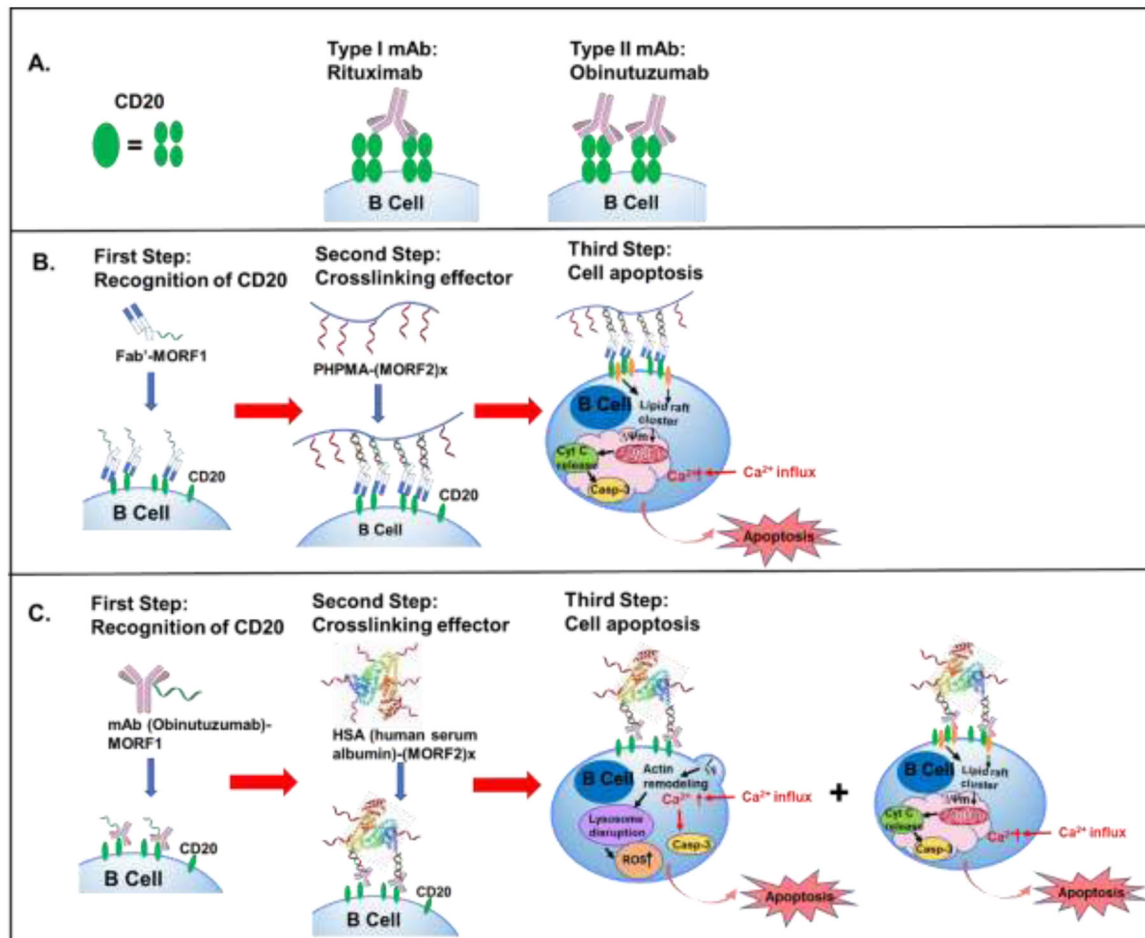


Figure 3.

A. CD20 receptor is composed as a tetramer. Type I antibody like rituximab (RTX) binds to two different tetramers (inter-tetramer binding), inducing CD20 redistribution in lipid rafts. Type II antibody like obinutuzumab (OBN) binds within the same tetramer (intra-tetramer binding), which doesn't cause CD20 redistribution. **B.** Treatment of Fab'-MORF1 followed by P-(MORF2)x causes rearrangement of CD20 complexes in lipid rafts, leading to calcium influx and caspase activation and finally cell apoptosis. **C.** Second generation of DFMT: binding to CD20 of OBN-MORF1 conjugate initiates actin remodeling, thus trigger lysosome disruption and reactive oxygen species (ROS) production, resulting in onset of Type II apoptosis. In addition, crosslinking of the CD20-OBN-MORF1 complex with HSA-(MORF2)X leads to clustering the CD20 complexes in lipid rafts thus triggering Type I apoptotic effects.

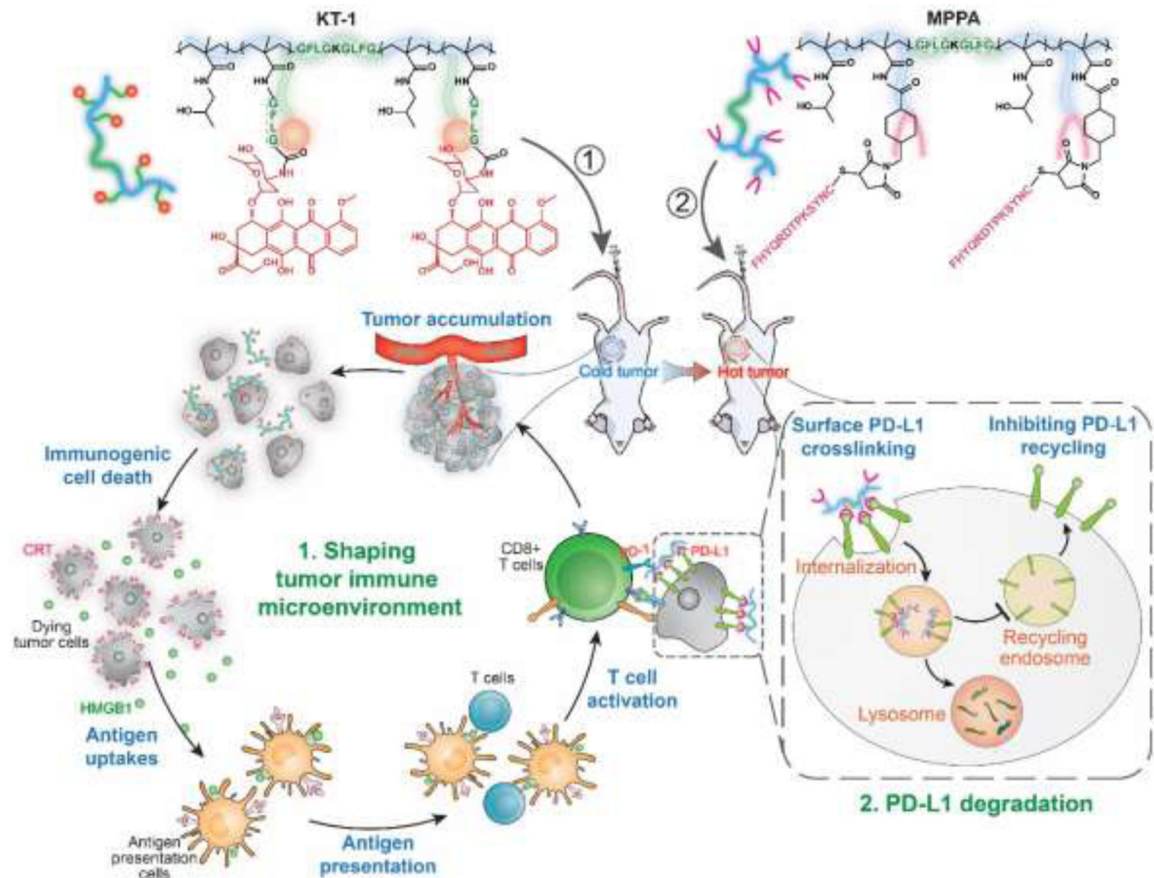


Figure 4.

Schematic illustration of the combination strategy targeting PD-L1. Degradable HEMA copolymer-epirubicin (EPI) conjugate (KT-1) [277] induces ICD and activates the immune response of tumor microenvironment. Sequentially, the multivalent polymer peptide PD-L1 antagonist (MPPA) mediates PD-L1 crosslinking; this redirects PD-L1 to lysosome degradation instead of recycling back to cell surface. This consecutive two-step treatment regimen activates and recruits the peripheral T cells into tumor microenvironment in a durable way. Reprinted from ref [278].

Table 1.1

Examples of nanomedicines for B cell targeting.

Mechanisms	Targets	Diseases/ Applications	Clinical Options	Targeting Moieties	Nano-strategies
Direct B cell depletion	CD20	Non-Hodgkin's lymphoma (NHL) [105–107, 114, 115, 120], chronic lymphocytic leukemia (CLL) [110, 111], rheumatoid arthritis (RA) [109], leukemia [125], melanoma [126], etc	mAb: rituximab (Rituxan®), obinutuzumab (Gazyva®), ofatumumab (Kesimpta®), ibritumomab (Zevalin®), ocrelizumab (Ocrevus®), etc. More details in [288].	Antibodies [92–104], Fab' fragment [105–115, 120], scFv [122, 124, 125], aptamers [126]	PLA- <i>b</i> -PEG-COOH, PCL-COOH [93, 94], PLGA [95], caveosphere [96], albumin [97], chitosan/quantum dots [98], liposome [99, 100, 126], micelles [101], iron oxide [102–104], PHPMA [105–111], HSA [114, 115, 120], ELP [122], polystyrene-PEG-biotin [124], PEG-coated iron oxide [125]
	CD19	Burkitt's lymphoma [130], acute lymphoblastic leukemia (ALL) [131–133, 135], rheumatoid arthritis [289]	mAb: inebilizumab (Uplizna®); BiTE: blinatumomab (Blincyto®); CAR-T therapies: axicabtagene ciloleucel (Yescarta®), tisagenlecleucel (Kymriah®), lisocabtagene maraleucel (Breyanzi®). More details in [290].	Antibodies [130–132, 135, 137, 140, 289], CD19L [136]	Liposome [130, 132, 133], gold NPs [131], PEG-PCL [135], mPEG-bPEI-PEBP [137], iron oxide [140]
	CD22	ALL [150], NHL [151], diffuse large B-cell lymphoma (DLBCL) [153]	mAb: epratuzumab in clinical trials [291, 292]; ADC: inotuzumab ozogamicin (Besponsa®) [293]; CAR-T therapy: moxetumomab pasudotox (Lumoxiti®) [294]	Antibodies [150, 151], Fab' fragment [152], sialic acid [153], N-linked glycan scaffold [154]	Iron oxide [150], quantum dot [151], liposome [152], ChNP [153]
	CD38	Multiple myeloma [157, 158]	mAb: daratumumab (Darzalex®); isatuximab-irfc (Sarclisa®) [155].	Antibody [157, 158]	Chitosan NP [157], PEO- <i>b</i> -PBCL NP [158]
	Surface antigen signaling lymphocytic activation molecule-F7	Multiple myeloma [161, 223]	mAb: elotuzumab (Empliciti®) [162]	Antibody [161, 223]	Silica/Gd NP [223]
	Idiotypic sequences	NHL [168, 169]	DNA vaccines failed several clinical trials [166, 167]	Immunogenic self-antigen expressing plasmid DNA [168, 169]	PEI-PLGA NP [168, 169]
	Scavenger receptor type B-1	DLBCL [170]	N/A	Cholesterol-poor high-density lipoprotein [170]	Lipoprotein-like NP [170]
Modulation of B cell receptor signaling	CD79a/b	NHL [179, 180], RA [182]	ADC: polatuzumab vedotin (Polivy®) [181]	Antibody [179, 180, 182]	N/A
	Bruton tyrosine kinase	CLL, mantle cell lymphoma, small lymphocytic lymphoma, marginal	Kinase inhibitors: ibrutinib (Imbruvica®), acalabrutinib (Calquence®),	Inhibitor (Ibrutinib) [186], siRNA [187]	Chitosan/sulfobutylether- β -cyclodextrin NP [185], PEG- <i>b</i> -PLGA [187]

Mechanisms	Targets	Diseases/ Applications	Clinical Options	Targeting Moieties	Nano-strategies
		zone lymphoma, RA [187]	zanubrutinib (Brukinsa®) [295]		
	Spleen tyrosine kinase	ALL [191], mantel cell lymphoma [192], B-precursor acute lymphoblastic leukemia [193], RA [296], CLL [297]	Kinase inhibitor: fostamatinib (Tavalisse®); entospletinib in clinical trials Phase I/II [189]	Inhibitors (C61 [191–193], R406 and R788 [296, 297])	Liposome [191–193]
	Phosphoinositide 3 kinase	Pancreatic adenocarcinoma [200], breast cancer [201, 207], multiple myeloma [208], etc	Kinase inhibitor: alpelisib (Piqray®), idelalisib (Zydelig®), copanlisib (Aliqupa®), duvelisib (Copiktra®), umbralisib (Ukoniq®). More information provided in [298].	Inhibitors (IPI-549 [200, 201], GDC-0941 [206], AS101 [207], Walterinnesia aegyptia venom [207, 208])	PLGA [200], PEGylated PCL NP [201], silica NP [207, 208]
Targeting B cell survival	B cell maturation antigen (BCMA)	Multiple myeloma [222, 223]	ADC: belantamab mafodotin (Blenrep®); CAR T therapy: idecabtagene vicleucel (Abecma®). More in [299].	BiTE, CAR-T, BCMA _{72–80} peptide [222], antibody [223]	PLGA NP [222], silica/Gd NP [223]
	B cell activating factor receptor (BAFF-R)	ALL [227], atherosclerosis [228], RA [230], NHL [231], myasthenia [232]	mAb: belimumab (Benlysta®); tabalumab/bortezomib/ianalumab in clinical trials [217, 300]; CAR-T therapy PMB-101 got IND (investigational new drug) clearance for ALL.	CAR-T [227], antibody [228, 229], CRISPR-Cas9 [230], BAFF competitor (mBAFF) [231], siRNA [232, 233], RNA aptamer [234]	(PEG-b-PLGA)-based cationic lipid-assisted NP [230], PEGylated liposome [231]
	Transmembrane activator and CAML interactor (TACI)	Systemic lupus erythematosus [235], RA [236], multiple myeloma [239–241]	Recombinant fusion proteins: ataccept failed in clinical trials [237]. More discussion in [242].	TACI-Ig [235, 236], anti-APRIL antibody [239], CAR-T [240, 241] (usually combined with BCMA-targeting)	N/A
Targeting B cell/T cell costimulation and immune checkpoint blockade	CD80/CD86	RA [249], renal transplant [251]	Recombinant fusion proteins: abatacept (Orencia®); FPT155 in clinical trial Phase Ia/Ib [301].	CTLA-Ig [249], antibody [251], ovalbumin (targeting dendritic cells) [252, 303, 304]	Liposome [302], carbon nanotube [303]
	CD40	RA [257], activate APCs [259], melanoma [260]	mAb: sotigalimab in clinical trials phase I/II. More discussion on CD40 targeting in [263].	Antibody [257, 259, 260, 303]	Silicon NP [259], PLGA NP [260], carbon nanotube [303]
	Programmed cell death ligand 1 and 2 (PD-L1/L2)	Various type of tumors including melanoma [273], colorectal cancer [274], breast cancer [275, 278, 284], glioma [280], melanoma [283], DLBCL [286], etc.	αPD-1 mAb: pembrolizumab (Keytruda®), nivolumab (Opdivo®), cemiplimab (Libtayo®); αPD-L1 mAb: atezolizumab (Tecentriq®), avelumab (Bavencio®), durvalumab (Imfinzi®), etc. More in [304].	Antibody [265–268, 272–274], peptide antagonist PPA [278, 280], scFv [282], plasmid DNA encoding CRISPR/Cas13a [283], siRNA [284, 285], microRNA [286]	PLGA NP [273], gold NP [274], liposome [275], PHPMA [278], PEG-PCL NP [280], iTEP [253], PEI-HPBA [254], lipid-coated calcium phosphate NP [284], lipid NP [286]