Principle and Progress of Treating Lymphoma with CD22 as Immunotherapy Target

Bosen Zhuang[1, *, †], Ruoxi Xu[2, †]

[1] College of Veterinary Medicine, Sichuan Agricultural University, Chengdu, Sichuan, 611100, China

[2] Beijing No.20 middle school, Beijing, 100084, China

* Corresponding Author Email: 202001000@stu.sicau.edu.cn

[†]These authors contributed equally.

Abstract. B-cell lymphoma is a type of lymphoid tissue tumour, which is usually caused by clonal proliferation of lymphocytes at different stages of differentiation. CD22 molecule is ubiquitous in normal B cells and B cell malignant tumours. It is a principal element in the B cell maturation and proliferation, and provides an important functional link to the adjustment of B cell surface and intracellular signaling and cell survival. Although the function of CD22 remains unclear, blocking the action of CD22 has been proved to inhibit the growth of malignant B cells and CD22 has become an important therapeutic target of B-cell lymphoma. We will also discuss the strategies for the treatment of B-cell lymphoma targeting CD22, including naked antibodies, bispecific antibodies, antibody-drug conjugate (ADC), antibodies conjugated to radioactive elements, and chimeric antigen receptor-based T-cell (CAR-T) cell immunotherapy.

Keywords: CD22, B-cell lymphoma, immunotherapy, ADC, CAR-T.

1. Introduction

In recent years, the role of B lymphocytes in regulating the immune system has been intensively studied. On the one hand, B cells are the source of all immunoglobulin production; B cells, on the other hand, can not only directly act as antigen-presenting cells (APC), but also indirectly affect other APCs, playing a key role in determining the response of immune cells to antigens. A large number of studies have shown that B cells play an vital role in the occurrence and development of B cell lymphomas and some autoimmune diseases. Therefore, immunotherapy targeting B cells may be a potential strategy for the treatment of these diseases. At present, B cell-targeted therapy is mainly divided into antibody therapy, antibody-drug conjugate (ADC) and CAR-T Immunotherapy. The most representative antibody therapy is monoclonal antibody therapy, which uses monoclonal antibody to specifically bind to the surface molecules of B cells to eliminate self-reactive B cells or malignant proliferating B cells. This treatment strategy has high specificity and selectivity, and does not affect other immune cells. The application of ADC therapy is not only because CD22 is a specific antigen target on the surface of many tumour cells, but also because of its endocytosis and internalization, which makes it an ideal target for ADC to deliver cytotoxic drugs. CAR-T can be redesigned in vitro to express a chimeric antigen receptor (CAR) that recognizes an antigen expressed on the surface of leukemia cells. In a clinical setting, CAR-T is activated, genetically modified, amplified, and then infused back into patients in order to re-establish a permanent anti-tumour immune system. Not only will it not be metabolized, but it will replicate, migrate, proliferate and kill target cells expressing cognate antigens in the patient's body, forming memory cells through its powerful in vitro expansion ability. This study briefly reviews CD22 and B-cell lymphoma, its mechanism, and the above three therapeutic strategies.

2. B-cell lymphoma

B cell development occurs at different stages of cell differentiation, which is characterized by the emergence of specific structures in the functional B cell receptor (BCR). The BCR consists of two

identical heavy chains and two identical light-chain Immunoglobulin (Ig) peptides, which are covalently linked by disulfide Bridges. The other components of BCR are CD79A and CD79B molecules, which contain cytosolic immunoreceptor tyrosine-based activation motifs (ITAM). These motifs transmit signals after the BCR is cross-linked. Activated B cells can be induced to proliferate or undergo further differentiation steps by modulating BCR signaling according to the differentiation stage of B-cell recognition antigens and activation of other B-cell surface receptors.[1]

Early B cells develop in the bone marrow and produce functional surface antigen receptors after successful rearrangement of Ig heavy and light chain genes. Cells expressing functional BCR differentiate into mature B cells and leave the bone marrow, whereas pre-B cells that fail to express BCR undergo apoptosis [1]. Mature B cells can be activated by antigen binding to BCR and participate in immune response. Because different stages of B-cell development and differentiation are characterized by specific BCR structures and expression patterns of differentiation markers, and because these processes often occur in specific histological structures, analysis of these features has been used to determine the origin of various human B-cell lymphomas. The rationale for this classification of B-cell lymphomas is based on the observation that malignant B-cells appear to be "frozen" at specific stages of differentiation, reflecting their origin. These studies' major concept is that most B-cell lymphomas originate from GC or post-GC B cells [2][3].

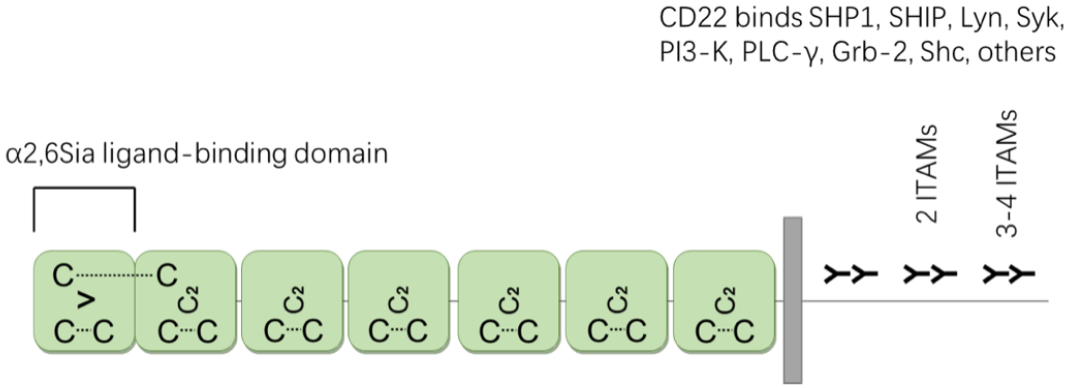

Figure 1. CD22 structure

At present, the drug treatment of B-cell malignancies mainly relies on immunosuppressive agents, such as cyclophosphamide, methotrexate, cyclosporine A and glucocorticoids. Despite the dramatic improvement in patient survival, none of these therapies can completely cure the tumour, and most are significantly toxic.

The emergence of therapies based on novel mab and CAR-T has made it possible to develop more specific, more effective therapies with lower systemic toxicity. Moreover, mab therapy can specifically reduce the number of B cells while being less toxic to other cells, such as the chimeric CD20 mab (Rituximab).

3. Expression and function of CD22

CD22, a member of the sialic acid-binding immunoglobulin type lectin family (Siglecs), is a type I transmembrane protein with a molecular weight of 135K and is a B-lymphocyte restriction antigen. It can specifically bind to sialic acid (Sia) -containing glycans and inhibit B cell receptor (BCR) signaling through its immunoreceptor tyrosine inhibitory motif (ITIM), which plays a role in maintaining humoral immune homeostasis.

CD22 is mainly expressed intracellularly during the early stage of B-cell development, making it a potential therapeutic target for B-cell lymphomas. CD22 antigen is present only in the cytosol during the pro and pre B-cell stages. When mature B cells differentiate into IgM+ and IgD+, this antigen is highly expressed on the cell membrane. CD22 was also highly expressed in follicular B cells, mantle cells and marginal B cells. CD22 antigen expression was down-regulated at the end stage when differentiated into plasma cells.

Although the function of CD22 is not fully defined, previous studies have shown that CD22 is an adhesion and signaling molecule involved in cell-to-cell interactions. After binding to CD22, its natural ligand can affect the phosphorylation of CD22 intracellular signaling region, inhibit B cell receptor (BCR) signaling, and thus lead to B cell activation. For example, studies in CD22-/- mice have shown that the interaction of CD22 and its ligands in vivo is essential for the survival of mature B cells, but has no significant effect on the development, maturation, or differentiation of early B cells. In addition, CD22 can also affect the proliferation, differentiation and homeostasis of B cells. For example, the inability of CD22-/- mice to express CD22 in vivo results in the inability of newly generated B cells to respond to BCR signals and thus fail to differentiate and mature when they enter the periphery. Thus, CD22 is a key factor for B cell growth and maturation.

4. The mechanism of CD22 in B-lymphocyte treatment

CD22 provides an important functional link between surface and intracellular signaling regulation and cell survival, suggesting that blocking its interaction may inhibit the survival of malignant B cells. It has been reported that about 70% of B-cell line lymphoma and leukemia cells express CD22 molecule, especially in follicular, mantle and marginal zone B lymphoma cells, which provides an effective target for the treatment of B-cell lymphoma. In addition, CD22 is selectively expressed only in normal and malignant mature B lymphocyte lines. Other cells, such as non-B lymphocytes, bone marrow cells, hematopoietic stem cells, and non-hematopoietic cell lines, do not express CD22. Therefore, CD22-targeted therapy does not affect any non-CD22-expressing tissues and does not inhibit the generation of new B cells [4]。

With the clinical success of therapeutic antibodies in vivo, CD22 has been used as a target for antibody therapy. And act as potential regulators of immune responses. Several characteristics of the Siglec family make it a potential immunotherapy. The selective expression of CD22 by B lymphocytes and its membrane kinetics are favorable for rapid endocytosis after antibody ligation, which makes CD22 a good target for cytotoxic delivery. In addition, their ability to regulate cell signaling may also depend on the immunomodulatory effects of CD22.

The endocytosis and signal transduction functions of Siglces are related to their roles in immune cell responses. In B cells, CD22 is a circulating endocytic receptor, mainly distributed on the cell surface and endosomal compartments, and shared with Toll like receptors (TLRs), leading to strong inhibition of TLR signaling. The endocytosis mechanism of CD22 and its sub-cellular localization also play a key role in the regulation of TLR signaling pathway by CD22 [5][6][7]。

Antibodies specific for human CD22 are designed to treat most B-cell lymphomas and many types of acute B-cell lymphomas. As a receptor that can be rapidly internalized by binding to antibodies, CD22 can act as a toxic carrier to enter cells. Thus, antibody immunotoxins can target tumour cells using CD22 as a means of entry.

5. Specific advances in the treatment of B-cell lymphoma by targeting CD22

5.1. Antibody therapy

5.1.1 Naked antibody

Epratuzumab (IMMU-103, AMG-412, IMMU-hLL2, LymphoCide^{TM}) is a humanized monoclonal antibody (mAb) that is a CD22 inhibitor. The drug inhibits B cells from producing anti-autoprotein antibodies by binding to CD22. It was originally developed by Immunomedics company for the treatment of Waldenström macroglobulinemia, Sjögren's syndrome, systemic lupus erythematosus (SLE) (which entered phase III clinical trials), CD22-positive pediatric acute lymphoblastic leukemia (which entered phase I/II clinical trial) and non-Hodgkin's lymphoma (NHL). [8]

Epratuzumab is used in studies of NHL patients, including small lymphocytic leukemia (SLL), follicular lymphoma (FL), and diffuse large B-cell lymphoma (DLBCL). Multiple early studies have

shown that Epratuzumab is safe in combination with rituximab for the treatment of relapsed and refractory NHL. In a phase II trial, 49 NHL patients (49 FL and 7 SLL) were recruited to evaluate the efficacy of the combination of Epratuzumab and Rituximab. The patient received Epratuzumab and Rituximab once a week for 4 weeks. 24% of patients with follicular lymphoma (FL) had a complete response (CR) and 54% had an objective response (OR). The median progression-free survival (PFS) was 10 months. Among patients with CR, the median duration of response (DoR) was 29 months, and the best treated patients had CR for more than 4 years. Patients with small lymphocytic leukemia (SLL) had an objective response (OR) rate of 57%, a complete response (CR) rate of 57%, and a median progression-free survival (PFS) of 20 months. Among SLL patients with CR, the median duration of response (DoR) was 20 months. The combination of Epratuzumab and rituximab, in which no patient stopped treatment due to side effects, was well tolerated. [9]

In another phase II study, 107 patients with diffuse large B lymphoma (DLBCL) were enrolled to investigate the efficacy of Epratuzumab in addition to first-line RCHOP therapy (rituximab, prednisone, doxorubicin, cyclophosphamide, and vincristine). All six cycles were successfully completed in 89% of patients, indicating that RCHOP combined with Epratuzumab was well tolerated. The objective response rate (ORR), partial response rate (PR) and complete response rate (CR) were 96%, 22% and 75%, respectively. The 3-year overall survival (OS) rate was 80%, and the 3-year progression-free survival (PFS) rate was 76%, which showed a trend of improvement compared with the historical cohort. [9]

Currently, Epratuzumab is not approved by the FDA, which may be due to the short duration of disease response in some patients, the lack of significant efficacy, and the availability of alternative therapies. The main toxicities of Epratuzumab include infusion reaction, febrile neutropenia, and myelosuppression. [9]

5.1.2 Bispecific antibody (Bsab)

JNJ-75348780 is a new bispecific antibody that acts on CD22/CD3. Its mechanism is to recognize CD22 antigen on the surface of malignant B lymphocytes and CD3 antigen on T lymphocytes, so as to recruit T cells to the vicinity of tumor cells, activate T cells to kill tumor cells. [9]

Since 2020, JNJ-75348780 has been undergoing a phase I, first-in-human dose-escalation clinical study in subjects with chronic lymphocytic leukemia (CLL)and non-Hodgkin's lymphoma (NHL). The purpose of this study was to investigate the safety of JNJ-75348780 and to determine the dosing regimen and recommended dose (RP2D) for phase 2 clinical use. The study is scheduled to last 2 years and will enroll 120 subjects.

5.2. ADC

5.2.1 Antibody conjugated toxin

Inotuzumab ozogamicin is an innovative ADC developed by Pfizer that consists of a monoclonal antibody targeting CD22 and the cytotoxic agent katchimycin. The CD22 antigen is ubiquitous on the surface of B cells, and inotuzumab ozogamicin can target cancer cells and bind to the CD22 antigen on their surface. These ADCs are then endocytosed into cancer cells, where katmycin can further exert its effects and cause cancer cell death. The drug was approved by FDA (U.S.), EMA (Europe) and NMPA (China) in 2017 and 2021, respectively, for the treatment of adult patients with relapsed or refractory precursor B-cell acute lymphoblastic leukemia (R/R B-ALL). This is the first antibody conjugated drug targeting CD22 to be approved by FDA.

Phase I/ II trials have shown that inotuzumab ozogamicin has a controlled safety profile and potential efficacy as monotherapy or in combination with rituximab for non-Hodgkin lymphoma (NHL). However, a phase III trial of Inotuzumab ozogamicin was discontinued in 2013. Patients with relapsed or refractory CD22+ aggressive non-Hodgkin lymphoma (NHL) who were ineligible for high-dose chemotherapy were enrolled. The trial was terminated because Inotuzumab ozogamicin plus rituximab did not achieve the primary endpoint and did not improve overall survival (OS) compared with the control group. [10]

Moxetumomab Pasudotox-TDFK (CAT-8015) combines the antigen-binding portion of CD22 antibody with a toxin, melt-PE38, to form a recombinant immunotoxin targeting CD22. After binding to CD22, it will be internalized by cells, processed and released the modified protein toxin, thereby inhibiting protein translation and leading to apoptosis [9]. In 2018, FDA (U.S.) approved the drug for the therapy of relapsed or refractory hairy cell leukemia (HCL) in adults who had received more than one previous systemic therapies, including purine nucleoside analogues.

CAT-3888 (BL22) is a first-generation product that is similar to CAT8015 in that it has the same toxin fraction and the similar anti-CD22 antibody. In its early phase I clinical study, 46 patients were recruited, including hairy cell leukemia (HCL) (n= 31)，chronic lymphocytic leukemia (CLL) (n=11), and non-Hodgkin's lymphoma (NHL) (n= 4). The results showed that the drug had the best effect on HCL, achieving a partial response rate (PR) of 19% and a complete response rate (CR) of 61%. There was also significant activity against CLL, but there was no complete response. [11]

The literature also reports that two anti-CD22 ADCs are in the clinical evaluation stage and have not yet received FDA approval. The immunotoxin IgG-RFB4-SMPT-DGA links the de-glycosylated ricin A chain to an CD 22 antibody. In an early-stage clinical study, a total of 18 B-cell lymphoma patients were recruited. Partial response (PR) was achieved in 4 patients, but no complete response (CR) was achieved. DT2219 is a bis-specificity antibody-coupled toxin that fuses the diphtheria toxin (DT) catalytic domain with a single-chain variable region (scFV) targeting human CD19 and CD22 antibodies. A study that enrolled 18 non-Hodgkin's lymphoma (NHL) patients showed treatment benefit in 3 patients. [9]

5.2.2 Antibodies conjugated to radioactive elements

5.2.2.1 ^{90}Y-epratuzumab tetraxetan

^{90}Y-epratuzumab tetraxetan uses 1, 4, 7, 10-tetraazacyclic dodecane-N, N', N'', N''' -tetra-acetic acid chelate as a linker, linking epratuzumab (anti-CD22 antibody) to Yttrium 90(^{90}Y). By B-cell endocytosis, radioactive isotopes are allowed to enter the cell and lead to cell death by β decay. [9]

A phase I and II trial of 90Y-epratuzumab tetraxetan enrolled 64 relapsed and refractory non-Hodgkin's lymphoma (NHL) patients. The objective response rate (ORR), complete response rate (CR) and median progression-free survival (PFS) were 62%, 48% and 9.5 months, respectively. Because of the radiation two patients developed grade 4 cytopenia as a side effect. In another trial, 18 relapsed and refractory aggressive Hodgkin's lymphoma (NHL) patients were treated with ^{90}Y-epratuzumab tetraxetan and veltuzumab (an anti-CD20 antibody). The objective response rate (ORR), partial response rate (PR) and complete response rate (CR) were 53% ,35% and 18%, respectively. A total of 13 patients had serious side effects, mainly grade 3-4 thrombocytopenia or neutropenia. [9]

Recently, another clinical trial enrolled 71 diffuse large B-cell lymphoma (DLBCL) patients who had received R-CHOP plus chemotherapy and ^{90}Y-epratuzumab tetraxetan was used as consolidation therapy. Eight patients achieved improvement from partial response (PR) to complete response (CR). A 2-year overall survival rate (OS) and overall complete response rate (CR) were 83% and 68%. Therefore, CHOP combined with ^{90}Y-epratuzumab tetraxetan in the treatment of elderly patients with DLBCL is feasible. [12]

5.2.2.2 BAY1862864

BAY1862864 is a drug conjugated by Thorium-227 and an anti-CD22 antibody. ^{227}Th can emit α particles that cause DNA damage, which causes cell cycle arrest and cell death. In a first-in-human study that recruited 21 non-Hodgkin's lymphoma (NHL) patients, objective response rate (ORR), partial response (PR) and complete response (CR) were38%, 19% and 5%, respectively [9].

5.3. CAR-T

The approval of CD19-targeted chimeric antigen receptor (CAR)-based T-cell immunotherapy is a milestone in the treatment of relapsed/refractory large B-cell lymphoma (R/R LBCL). CD19-CAR-T cell immunotherapy significantly improved the efficacy and survival of these patients, but some patients failed after CD19-CAR-T cell immunotherapy. Less than 25% of these patients responded to subsequent therapy, and the mean overall survival (OS) was only 3.6 months.[13]

In order to evaluate the safety and efficacy of CD22-targeted CAR-T immunotherapy in R/R LBCL patients who had failed CD19-targeted CAR-T cell immunotherapy, professor John Baird et al. conducted a dose-escalation phase I study. The study enrolled three R/R LBCL patients who had progressive disease (PD) after multiple systemic therapies, including CD19-CAR-T cell immunotherapy [13]. All patients achieved complete response (CR) after treatment. Two of these patients, who previously had a high tumor burden, had a partial response (PR) on day 28 after infusion of CD22-targeted CAR-T cells, followed by further improvement to CR at 6 and 3 months, respectively. All patients maintained a complete response (CR) during a mean follow-up of 7.8 months (range, 6-9.3). This study demonstrated that CD22-targeted CAR-T cell immunotherapy had good safety and antitumor activity in R/R LBCL patients who had failed CD19-targeted CAR-T cell therapy before. Therefore, CD22 may be an important target for CAR-T immunotherapy in large B-cell lymphoma (LBCL). [13]

Researchers at Stanford University School of Medicine conducted a phase I clinical trial of CD22-CD19 bi-specific CAR-T for the treatment of large B-cell lymphoma (LBCL) and acute B-lymphoblastic leukemia (B-ALL). A total of 38 patients received CD22-CD19 bi-specific CAR-T therapy, including 21 with large B-cell lymphoma (LBCL) and 17 with acute B-lymphoblastic leukemia (B-ALL). Of the 21 patients with LBCL, 13 (62%) had a response and 6 (29%) had a complete response. The trial indicates that the therapy has good efficacy and safety. [14]

These studies suggest that targeting tumor cells with multi-specific CAR T cells can reduce tumour antigen escape and improve therapeutic efficacy. In another new study, researchers developed a triple-specific duo CAR-T cell therapy and evaluated the ability of a triple-specific duo CAR-T cell therapy to solve the antigen escape problem in vivo and in vitro. In vitro testing of tumour cell lines REH and Raji (CD19+CD20+CD22+) showed that duo CAR-T cells could lyse REH cells and Raji cells more efficiently than mono CAR-T cells. In addition, in mice carrying a mixed B-cell lymphoma cell line consisting of parental triple-positive (CD19+CD20-CD22+), CD19-, CD20-, and CD22- variant cells, only the triple-specific duo CAR-T cells were able to rapidly and efficiently suppress tumours. None of the mono CAR-T cells prevented tumor growth [15]. Therefore, for the patients who have relapsed and refractory B-cell malignancies with antigen loss or down-regulation, multi-specific duo CAR-T cell therapy is a very prospective therapeutic strategy.

6. Conclusion

In B cell lymphomas mediated by antibodies, targeted B cell therapy is an ideal treatment strategy. The advantage of directly targeting B cells is that antibodies have high specificity and selectivity, which can directly eliminate B cells without affecting other immune cells. The disadvantage is that it can not distinguish between normal B cells, autoreactive B cells or dysfunctional B cells, which may affect the normal humoral immunity of the body. This clearance may not be complete, because the expression of certain surface molecules changes at different developmental stages of B cells, so monoclonal antibodies targeting these molecules cannot completely eliminate autoreactive B cells at different developmental stages.

For CAR-T therapy, the major toxic side effects include off-target effects, cytokine release syndrome (CRS), nervous system injury and secondary malignancy. Now the off-target effect can be ameliorated by introducing suicide gene, constructing inhibitory CAR-T cells and double target antigen CAR-T cells. To control CRS, excessive activated CAR-T cells were eliminated by knocking down GM-CSF gene in CAR-T cells or introducing suicide gene. Dasatinib reversibly inhibits the

cytotoxicity, cytokine secretion and proliferation of CAR-T cells, which can be used to reduce nervous system injury by penetrating the blood-brain barrier. Prospective, multicenter, observational studies should be conducted to assess long-term safety and the risk of secondary malignancy after treatment. However, since hematopoietic stem cell transplantation depends on the ability to find MHC-matched donors and avoid potentially life-threatening infections and complications such as graft-versus-host disease, most B-cell lymphatic cancers can achieve molecular remission with CAR-T therapy, and there are well-developed treatment regiments to deal with adverse reactions after CAR-T therapy. Double target antigen therapy solves part of the problem of recurrence after single target therapy. Therefore, dual targeting of two antigens on the surface of lymphatic cancer cells can reduce the possibility of antigen loss variants, which has entered clinical practice and achieved satisfactory efficacy, and is expected to become a new protocol for lymphatic cancer recurrence.

At present, for the treatment of some autoimmune diseases and B-cell lymphoma, a variety of drugs have been proved to be relatively safe and effective by clinical evaluation, and some have been successfully applied in clinical treatment. However, patients often have adverse reactions during or after treatment. How to balance the safety and efficacy of drugs has become a difficult problem in clinical practice. An ideal therapeutic strategy targeting B cells would eliminate autoreactive B cells without affecting the normal function of B cells, which may require further searching for specific surface components of autoimmune B cells or dysfunctional B cells in future studies.

Reference

[1] Rajewsky, K. Clonal selection and learning in the antibody system [J]. Nature, 1996, 381, 751–758.

[2] Küppers, R., Klein, U., Hansmann, M.-L. & Rajewsky, K. Cellular origin of human B-cell lymphomas [J]. N. Engl. J. Med, 1999, 341, 1520–1529.

[3] Stevenson, F. K. et al. The occurrence and significance of V gene mutations in B cell-derived human malignancy [J]. Adv. Cancer Res, 2001, 83, 81–116.

[4] Moek, K.L.; de Groot, D.J.; de Vries, E.G., Fehrmann, R.S. The antibody-drug conjugate target landscape across a broad range of tumour types [J]. Ann. Oncol, 2017, 28, 3083–3091.

[5] Tateno H, Li H, Schur MJ, Bovin N, Crocker PR, et al. Distinct endocytic mechanisms of CD22 (Siglec-2) and Siglec-F reflect roles in cell signaling and innate immunity [J]. Mol. Cell. Biol, 2007, 27: 5699–710.

[6] Kawasaki N, Rademacher C, Paulson JC. CD22 regulates adaptive and innate immune responses of B cells [J]. J. Innate Immun, 2011, 3: 411–19.

[7] Jellusova J, Wellmann U, Amann K, Winkler TH, Nitschke L. CD22 × Siglec-G double- deficient mice have massively increased B1 cell numbers and develop systemic autoimmunity [J]. J. Immunol, 2010, 184: 3618–27

[8] Yinhua Kang, Ming Fan. Anti-CD22 monoclonal antibody: Epratuzumab [J]. Progress in Pharmaceutical Science, 2009, 33, 3: 138-139

[9] Nikesh N Shah, Lubomir Sokol. Targeting CD22 for the Treatment of B-Cell Malignancies [J]. Immunotargets Ther, 2021,10: 225-236.

[10] Ilana R Yurkiewicz, Lori Muffly, Michaela Liedtke Inotuzumab ozogamicin: a CD22 mAb-drug conjugate for adult relapsed or refractory B-cell precursor acute lymphoblastic leukemia [J]. Drug Des Devel Ther, 2018, 12: 2293-2300.

[11] Kreitman, R. J., Squires, D. R., Stetler-Stevenson, M., Noel, P., et al. Phase I trial of recombinant immunotoxin RFB4(dsFv)-PE38 (BL22) in patients with B-cell malignancies [J]. Journal of Clinical Oncology, 2005, 23(27), 6719-6729.

[12] Loretta Sullivan-Chang, Robert T O'Donnell, Joseph M Tuscano. Targeting CD22 in B-cell malignancies: current status and clinical outlook [J]. BioDrugs, 2013, 27(4): 293-304.

[13] John H Baird, Matthew J Frank, Juliana Craig. CD22-directed CAR T-cell therapy induces complete remissions in CD19-directed CAR-refractory large B-cell lymphoma [J]. Blood, 2021, 137(17): 2321-2325.

[14] Jay Y Spiegel, Shabnum Patel, Lori Muffly, et al. CAR T cells with dual targeting of CD19 and CD22 in adult patients with recurrent or refractory B cell malignancies: a phase 1 trial [J]. Nat Med, 2021, 27(8): 1419-1431.

[15] Schneider D, Xiong Y, Wu D, et al. Trispecific CD19-CD20-CD22-targeting duoCAR-T cells eliminate antigen-heterogeneous B cell tumors in preclinical models [J]. Sci Transl Med, 2021, 13(586): eabc6401.