Review article

CD123 and its potential clinical application in leukemias

Keqiang Liu a,b, Mengru Zhu c, Yao Huang d, Shuhua Wei d, Jingli Xie d, Yechen Xiao a,⁎

a Department of Biochemistry and Molecular Biology, College of Basic Medical Science, Jilin University, Changchun, China
b Department of Preventive Medicine, School of Public Health, Jilin University, Changchun, China
c School of Clinical Medicine, Jilin University, Changchun, China
d Department of Radiology, School of Public Health, Jilin University, Changchun, China

Abstract

The α chain of interleukin 3 receptor (IL-3Rα or CD123), together with the common βc subunit, forms a high-affinity IL-3R with biological function. In recent years, emerging research has found that CD123 is highly expressed on the surface of various cells (e.g., leukemia stem cells, LSCs), and it is associated with the initiation and development of many diseases, such as acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). As a novel biological marker, it has an attractive prospect in the diagnosis, targeted therapy, and evaluation of prognosis of many diseases. For these reasons, much attention has been attracted to the studies of the biological functions and potential value in the clinical application of CD123. In this review, the clinical prospects of CD123 will be discussed on the basis of information available.

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Introduction

The interleukin 3 receptor (IL-3R) system, including IL-3R, interleukin 5 receptor (IL-5R) and granulocyte–macrophage colony-stimulating factor receptor (GM-CSFR), regulates the proliferation, survival, and differentiation of hematopoietic cells, as well as immunity and inflammatory response by specifically binding respective ligands (IL-3, IL-5, and GM-CSF) [24]. IL-3R system comprises cytokine-specific α and common βc subunits which are shared by all three receptors.

The β subunit of IL-3R (IL-3Rβ or CD123) is a 75 kD glycoprotein and becomes 43 kD when hydrolyzed by N-glycosidase, and this molecule consists of three extracellular domains, a transmembrane domain, and a short intracellular domain [54]. The gene encoding CD123 spans approximately 40 kb and contains 12 exons, and it is mapped to the pseudo-autosomal region at the ends of the short arms of the X and Y

⁎ Corresponding author at: Department of Biochemistry and Molecular Biology, College of Basic Medical Science, Jilin University, 126 Xinmin Street, Changchun 130021, China.
Tel.: +86 431 85619474; fax: +86 431 85619303.
E-mail address: yechenxiao2400@126.com (Y. Xiao).
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chromosomes (Xp22.3 and Ypll.3), near the gene encoding the α subunit of GM-CSF [38,50].

CD123 binds IL-3 with low affinity and high specificity and forms high-affinity receptors with the βc subunits through receptor heterodimerization. The N-terminal domain of CD123 contributes significantly to IL-3 binding to IL-3R, while the C-terminal domain does not seem to be that important for the stability of the receptor/ligand complex, but is indispensable for intracellular signaling [3]. The βc subunit does not bind any cytokines by itself but it is involved in the formation of high-affinity functional receptors for IL-3, IL-5 and GM-CSF [24]. More importantly, the βc subunit plays a significant role in the transduction of intracellular signals and thereby triggers a range of biological functions, which are reviewed in references [7,26,28].

Expression of CD123 in cells

The βc subunit, shared by IL-3R, IL-5R, and GM-CSFR, is widespread on the surface of various cells while CD123 is more restricted to IL-3-responsive cells, including hematopoietic stem/progenitor cells (HSC/PCs), monocytes, megakaryocytes, B-lymphocytes and plasmacytoid dendritic cells (pDCs) [34,47,59,60]. After binding to IL-3, this molecule mediates the stimulation of the proliferation and multi-directional differentiation of hematopoietic cells [26]. The expression of CD123 is low or negative in primitive hematopoietic cells and erythroid progenitor cells; while relatively high in myeloid and B-lymphoid progenitor cells [34]. Along with the maturation of these cells, the expression of CD123 on the surface of cells gradually decreases and cannot be detected in mature granulocytes and lymphocytes [34]. In this review, our discussion will centre on the high expression of CD123 on leukemia stem cells (LSCs).

Leukemia is a clonal malignancy of hematopoietic stem cells (HSCs). Steelman et al. [55] reported that CD123 which is strongly expressed on early hematopoietic cells could make these cells proliferate at the environment where IL-3 was below optimal concentration. This phenomenon suggests that the over-expression of CD123 can promote the proliferation of cells and accelerate the development of leukemia.

At the current time, research in leukemia focus on LSCs which is similar to HSCs and they both have high ability of self-renewal and proliferation. LSCs are regarded as the original cells promoting the initiation and development of leukemia and the root of leukemia’s relapse and drug resistance [6], Jordan et al. [36] carried out further study of LSCs by flow cytometry. They found that CD34+CD38− cells of 16 samples have plentiful CD123 expression in the total 18 samples of AML patients, while CD123 expression on normal CD34+CD38− cells from the marrow is nearly negative. The CD34+CD123+ leukemia cells transplanted into nonobese diabetic/severe combined immunodeficiency (NOD/SCID) mice can better establish and maintain leukemic populations in vivo. Collectively, these results suggest that CD123 is the characteristic marker of LSCs. So CD34+CD123+ cells have been the optimal immunophenotype of LSCs separated from AML patients [25]. What is more, CD123 has been a new target for acute leukemia (AL) on clinical diagnosis and targeted therapy.

The application of CD123 in disease diagnosis

CD123 was expressed at different levels in many diseases (Table 1), such as AL and hairy cell leukemia (HCL). The overexpression of CD123 makes it a valuable biomarker in the clinic diagnosis, treatment and evaluation of the prognosis of diseases.

CD123 and AML

AML is a clonal malignant disorder derived from a small population of CD34+CD38− AML cell with aberrant overexpression of CD123, namely LSCs. AML is characterized by the clonal expansion of myeloid precursor cells, which leads to their predominance in the bone marrow and blood and consequently the destruction of normal hematopoiesis. Since CD123 was found to be a unique marker for LSCs [62], the expression of CD123 in AML was studied at great length and these studies have recently showed the diagnostic value of this receptor. Muñoz et al. [51] reported a detailed analysis of CD123 expression on 45 AML specimens using flow cytometry, showing that CD123 was positive in 43 out of 45 (96%) AML patients. In this study, the authors found that all the AML cases except two patients with acute megakaryoblastic leukemia (M7) were CD123 positive [51]. Afterwards, Testa et al. [62] confirmed these findings by analyzing the expression of CD123 in primary blasts from 79 patients with AML for the aim of evaluating the relationship between the expression of this receptor chain, blast proliferative status, and disease prognosis. Compared with the expression levels in normal CD34 progenitors, CD123 was overexpressed in 45% AML patients. In terms of the biological level, these authors investigated peculiar properties of leukemic blasts with the relationship of elevated CD123 expression, finding that: 1) all the leukemic blasts with elevated CD123 expression exhibited higher cycling activity and increased resistance to apoptotic trigger elicited by growth factor deprivation; 2) spontaneous signal transducer and activator of transcription 5 (Stat5) phosphorylation was observed in 13% of AML patients, which exhibited high CD123 expression; and 3) the results also pointed out a possible relationship between the elevated CD123 expression and higher activation of the Stat5 signaling pathway in AML blasts [62]. In terms of the clinical level, the level of CD123 expression was associated with the number of leukemic blasts at diagnosis. Compared with patients exhibiting normal IL-3R levels, patients showing CD123 overexpression had a lower complete remission rate and survival duration. Importantly, the results reveal that the elevated expression of CD123 may lead to the proliferative superiority of the leukemic blasts and a negative prognosis [62]. Additionally, Vergez et al. [66] explored 111 patients under 65 years of age with de novo acute myeloid leukemia and treated with intensive chemotherapy, and observed a significant correlation between the percentage of CD34−CD38low/−CD123+ leukemic blast at diagnosis and response to treatment. More than 1% CD34−CD38low/−CD123+ leukemic cells had an adverse impact on disease-free and overall survival in AML patients, so the percentage of CD34−CD38low/−CD123+ leukemic blast represents a strong prognostic marker to identify patients at risk of treatment failure [66]. A study by Du and coworkers, with the aim to identify cell-surface markers for leukemia-initiating cells in Fanconi anemia (FA)-AML patients, provided evidence that CD123 is a useful marker as a leukemia-initiating cell-specific antigen for FA-AML [14].

<table>
<thead>
<tr>
<th>No. (%) of samples</th>
<th>Reference</th>
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<tbody>
<tr>
<td>AML 18 16 (98)</td>
<td>Jordan et al. [36]</td>
</tr>
<tr>
<td>45 (including 2 M7) 43 (96)</td>
<td>Muñoz et al. [51]</td>
</tr>
<tr>
<td>79 36 (46)</td>
<td>Testa et al. [62]</td>
</tr>
<tr>
<td>13 13 (100)</td>
<td>Muñoz et al. [51]</td>
</tr>
<tr>
<td>40 45 (89)</td>
<td>Hassanein et al. [27]</td>
</tr>
<tr>
<td>119 (95 pediatric and 24 adult) 98 (82)</td>
<td>Djikov et al. [13]</td>
</tr>
<tr>
<td>T-ALL 6 0 (0)</td>
<td>Muñoz et al. [51]</td>
</tr>
<tr>
<td>7 0 (0)</td>
<td>Testa et al. [62]</td>
</tr>
<tr>
<td>CLL 77 3 (4)</td>
<td>Muñoz et al. [51]</td>
</tr>
<tr>
<td>HCL 7 (including 1 CD25− variant) 6 (86)</td>
<td>Muñoz et al. [51]</td>
</tr>
<tr>
<td>23 22 (95)</td>
<td>Del Giudice et al. [12]</td>
</tr>
<tr>
<td>3 3 (100)</td>
<td>Fromm [22]</td>
</tr>
<tr>
<td>114 114 (100)</td>
<td>Venkataraman et al. [65]</td>
</tr>
<tr>
<td>HCL-variant 11 1 (9)</td>
<td>Del Giudice et al. [12]</td>
</tr>
<tr>
<td>20 8 (40)</td>
<td>Venkataraman et al. [65]</td>
</tr>
<tr>
<td>acute GVHD after HSCT 38 25 (66)</td>
<td>Lin et al. [45]</td>
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with the normal CD34+CD38− HSCs, CD123 was overexpressed in CD34+CD38− cells from FA patients with AML. They isolated CD34+CD38− cells from FA patients, and further sorted CD123 positive and CD123 negative subpopulations to transplant into irradiated recipient mice. The result displayed that only the CD123 positive population could initiate the development of a leukemic process. In addition, they found the FA CD34+CD123+ cells separated from leukemic mice showed higher sensitivity to IL-3 deprivation and Janus kinase 2 (JAK2)–STAT5 overactivation after IL-3 treatment. Under the treatment of a CD123-neutralizing antibody, IL-3-mediated proliferation and STAT5 activation was inhibited [14]. As mentioned above, CD123 not only owns remarkable prognostic and diagnostic significance, but also has become a valuable therapeutic target. In addition, CD123 was also applied in the diagnosis of myelodysplastic syndrome (MDS) [69]. The latest study showed that CD34+CD38− cells which highly expressed CD123 in MDS were associated with abnormal differentiation, decreased apoptosis and excessive proliferation, which were similar to AML [44].

**CD123 and acute lymphoblastic leukemia (ALL)**

ALL is a clonal hematologic malignancy arising from B-lymphoid progenitor cells or T-lymphoid progenitor cells, which always attacks 30–40% of children in acute leukemia. Muñoz et al. [51] revealed that in 19 ALL specimens (including 13 B-ALL and 6T-ALL), all the B-ALL samples were CD123 positive while normal lymphoid progenitors were CD123 negative. On the contrary, the entire T-ALL lacked CD123 expression. As mentioned above, Testa et al. [62] investigated the CD123 expression of 25 B-ALLs and 7T-ALLs, with the consequence that B-ALLs were CD123 positive, while T-ALLs were CD123 negative. In addition, Djokic et al. [13] confirmed these observations and demonstrated CD123 expression in 95 pediatric and 24 adult ALLs. Compared with normal B-cell precursors, 31% of precursor-B ALL specimens showed a high level expression of CD123, 61% appeared low CD123 expression and 8% were negative. Noteworthy, the expression of CD123 had a close relationship with B-ALLs’ karyotype. For example, the expression of CD123 was high in 81.5% of B-ALL with hyperdiploid karyotype. On the contrary, B-ALL with ETV6/RUNX1 (TEL/AML1) rearrangement showed weak CD123 expression. As a consequence, the study demonstrated that the overexpression of CD123 was an aberrant phenotype present in a subset of precursor-B ALL with hyperdiploid genotype, and an additional marker of good prognosis in pediatric precursor-B ALL [13].

Leukemia relapse is the main reason leading to treatment failure in ALL patients. Accumulating evidence indicates that minimal residual disease (MRD) had the significant prognostic value in pediatric and adult ALL [43,32,39,53,57,67]. Moreover, if we can find a unique marker that expressed steadily in residual ALL blasts, this unique marker may also provide useful clinical information. The study of Djokic et al. proved that B-cell precursors and mature B cells showed a weak CD123 expression either in normal or regenerating (post-chemotherapy) bone marrow samples, in a comparison that B-ALL cells displayed a steady overexpression in recrudescence leukemia. In addition, the remarkable expression of CD123 was very useful to monitor MRD [13].

**CD123 and hairy cell leukemia (HCL)**

HCL is an uncommon chronic lymphoproliferative disorder (CLPD) of mature B cells, which accounts for 2% of leukemia. Muñoz et al. [51] analyzed 7 HCL patients, showing that CD123 was strongly positive in 6 HCL cases. On the contrary, CD123 was negative in only one patient with a CD25+ variant form of HCL. Similarly, Fromm [22] reported that all 3 HCL cases in the research expressed CD123. Despite the small amount of cases evaluated, CD123 is expressed with a characteristic pattern in HCL cases and it could show the potential in the differential diagnosis of B-CLPD. Venkataraman et al. [65] also found all 114 HCL cases expressed bright CD123 and only 8 of 20 HCL-variant (40%) samples were CD123+ (partial or dim). Del Giudice et al. [12] confirmed these findings and, particularly, identified the diagnostic value of CD123 expression. The results revealed that CD123 was moderately to highly positive in 95% classic HCL (n = 24). On the contrary, most cases of HCL-variant (91%) and splenic lymphoma with villous lymphocytes (SLVL) (97%) lacked the expression of CD123 [12]. Consequently they concluded that the high-level expression of CD123 made it an effective marker to distinguish typical HCL with SLVL or HCL-variant with high sensitivity and specificity [12].

**CD123 and graft-versus-host disease (GVHD)**

Hematopoietic stem cell transplantation (HSCT) is the only effective way to cure leukemia, but its efficiency is restricted by GVHD and opportunistic infection. Early diagnosis is very important for early therapy of patients. But in some case (like cytomegalovirus (CMV) infection), it is difficult to distinguish them by the traditional immunohistochemical method. Interestingly, the study of Lin et al. [45] suggested that the level of CD123 expression of GVHD is higher than CMV infection. And this result points out that CD123 could be a useful marker to identify cases who suffer GVHD or opportunistic infection after HSCT in patients with leukemia.

**CD123-based therapies targeting LSCs in AML**

Treatments with traditional chemotherapy in AML patients often proved to be not curative. Emerging researches indicated that a small population of CD34+CD38− AML cell with aberrant overexpression of CD123, namely LSCs, may be responsible for drug resistance and relapse. LSCs were reported to be resistant to cell cycle-specific cytotoxic agents because most of them are in G0 phase of the cell cycle [23]. Additionally, LSCs were resistant to many toxins for the expression of ATP-associated transporters [11] and to apoptotic stimuli for the over-expression of anti-apoptotic genes, Bcl-Xl and Bcl-2 [37]. For these reasons, LSCs play the key roles in the initiation, development, drug resistance and relapse of AML [30]. Only LSCs are selectively eliminated, can AML be cured completely without relapse. As described earlier, CD123 is overexpressed on AML-LSCs, while normal HSCs have much lower levels of CD123 expression, even no CD123 expression in some cases [36], so CD123 has been considered as a unique marker for AML-LSCs. Hopefully, novel chemotherapeutic agents directly targeting CD123 may effectively mediate the elimination of AML-LSCs while sparing normal HSCs. Interestingly, Chen et al. [10] demonstrated that a new isoform (SP2) of IL3Rx, which lacks domain 1 of the extracellular region, was also expressed in a variety of human leukemia lines, indicating that IL3Rx SP2 might be a potential target for anti-leukemia therapy. Noteworthy, van Rhenen et al. [64] reported that there was a strengthened density of CD123 (median, 60%) on the surfaces of normal HSCs in patients who had received routine chemotherapy. This finding suggests an increased CD123 expression on the surface of regenerative normal HSCs in the bone marrow after hematopoietic system suffering serious damage, such as canceration or chemotherapy. Therefore, the therapy which eliminates LSCs selectively by targeting CD123 is likely to have certain limitation in AML patients received routine chemotherapy in view of its bad effect on regenerative normal HSCs. However, up to now, there are few studies on whether CD123 will maintain high level expression on the surfaces of normal HSCs in such patients in a long run. Further studies on this issue are warranted. As the α chain of IL-3R, CD123 can be targeted by two main approaches, either using specific antibodies or its natural ligand.

**Targeting LSCs with natural ligand**

One approach to target CD123 highly expressed on the surface of leukemic cells could be achieved through the use of the natural ligand
IL-3. Toxins fused to IL-3 may be the “magic bullet” binding directly to this molecule, resulting in LSC death or differentiation. One such “magic bullet” was DT388IL3, a recombinant toxin consisting of the catalytic and translocation domains of diphtheria toxin (amino acid residues 1–338, DT388) with a Met-His linker fused to human IL-3 [18]. This fused toxin showed potent and selective killing to IL-3R expressing AML cell lines and leukemic progenitors from patients in vitro and in vivo [25,16,19] while quite a few AML cell lines and samples from patients were not killed and showed resistance to DT388IL3. To solve this problem, the researchers fused the DT388 to a variant of human IL-3, resulting in a new fusion toxin DT388IL3[K116W] with enhanced binding affinity for IL-3R [46]. And this variant recombinant toxin was shown to be more potent than DT388IL3 in cytotoxicity against acute myeloid leukemic progenitors [31]. It is worth mentioning that the potency of both DT388IL3 and DT388IL3[K116W] in mediating leukemic cell killing was associated with the expression level of IL-3R (IL-3Rα, and particularly IL-3Rβ) on the surface of leukemic blasts [31,61]. As reported by Li [43], oncolytic adenoviruses containing IL-3 fused with manganese superoxide dismutase (MnSOD) or mannose-binding plant lectin significantly suppressed leukemia cell proliferation in vitro and prolonged the survival of HL60/Luc xenograft NOD/SCID mice model. Together with the selection of patients who are most likely to benefit from these agents according to the expression level of CD123, these targeting agents may be a promising targeted therapy for AML.

Currently, a phase I clinical trial with SL-401 (a CD123-targeting agent comprised a truncated diphtheria toxin fused to human IL-3) for a subset of AML patients heavily pretreated is initiated [17]. In this study, there were 2 durable complete responses and 5 partial responses to the SL-401 treatment with improved overall survival, and this SL-401 treatment was well tolerated [17]. At the same time, this fusion toxin was introduced in a phase I clinical trial to evaluate its safety and therapeutic effect in a group of patients with blastic plasmacytoid dendritic cell neoplasms (BPDCN) [20]. After one single cycle of SL-401 most patients achieved a complete response and the SL-401 administration was well tolerated [20]. Recently, a new report indicates SL-401 could eradicate CD34+CD138−BCR-ABL−CML stem cells which highly expressed CD123 by inducing apoptosis and inhibiting cell growth [21]. These promising findings demonstrated the attractive opportunity for this fusion toxin SL-401 in the prospective treatment of AML, BPDCN and CML.

Targeting LSCs with therapeutic antibodies

Cytokine-toxin fusion proteins target LSCs based on the high affinity of IL-3R complex (IL-3Rα and IL-3Rβ), but cannot bind leukemic cells in which only a single component of IL-3R expressed. High affinity antibodies reacting with CD123 will allow the selective elimination of leukemic blasts without the help of IL-3Rβ, and may efficiently avoid the agonist effect. Sun et al. [58] first characterized a neutralizing monoclonal antibody against CD123, mAb 7G3, which specifically bound to CD123 and antagonized leukemic cell proliferation stimulated by IL-3. By targeting CD123, mAb 7G3 impaired AML-LSCs in vivo while had lesser effects on normal HSCs [35]. Interestingly, the IL-3-mediated proliferation and survival of both the CD34+CD38−leukemic subpopulations and the unsorted AML cells were inhibited by mAb 7G3 in vitro [35].

Subsequently, researchers humanized and affinity-matured mAb 7G3, and optimized the cytotoxicity against AML cells by engineering the Fc-domain [8]. This Fc-engineered antibody, CSL362, possessed stronger affinity for CD16 on NK cells, which led to greater antibody-dependent cell-mediated cytotoxicity (ADCC) against CD123+ leukemic cell lines compared to CSL360, a non-Fc-engineered anti-CD123 mAb. It is important to note that both primary AML blasts and CD34+CD38−CD123+ LSCs were killed by NK cell-mediated ADCC when treated with CSL362, and even samples resistant to ADCC by CSL360 were susceptible to CSL362-induced ADCC [8,9]. A non-clinical program was conducted in non-human primates to evaluate the general safety and toxicity profile as well as the pharmacokinetic and pharmacodynamic properties of CSL362 [29]. The results from this non-clinical safety program demonstrated an excellent tolerance and favorable safety profile of CSL362 [29]. Furthermore, the antileukemic effect of cytarabine/daunorubicin treatment was significantly extended by the addition of CSL362 in AML xenografts established in NOD/SCID or NOD-SCID IL2Rγ null (NSG) mice [42]. A Phase I study of CSL362 is underway in CD123 positive AML patients (ClinicalTrials.gov identifier: NCT01632852).

Interestingly, it is recently reported that CSL362 effectively targeted leukemic stem and progenitor cells in patients with chronic myeloid leukemia (CML) based on the high expression of CD123, the level of which is increasing upon disease progression [52]. And the combination of tyrosine kinase inhibitors (TKIs) and CSL362-induced ADCC caused greater reduction of CML progenitors and further augmented their preferential elimination over normal HSCs [52]. Additional studies are required to evaluate the role of CSL362 in the treatment of CML.

Single-Chain Fragment Variable (ScFv) antibody consists of variable regions of heavy (VH) and light (VL) chains from one IgG, which are joined together by a flexible linker [1]. Although the generating molecule lacks the constant regions of the antibody, it retains antigen-binding specificity and can be applied in the construction of immunotoxins and gene delivery system [1,33]. Recently, Du et al. [15] fused the anti-CD123 ScFv region to a 38-kD fragment of Pseudomonas exotoxin A (PE38), resulting in a neoteptide immunotoxin (26292Fv−PE38), which bound CD123 expressing cell line TF-1 specifically in vitro. Interestingly, researchers mutated the REDKX sequences at the C-terminal to KDEL (26292Fv−PE38−KDEL), causing greater cell toxicity especially to cells expressing CD123 highly [15]. Similarly, in the experiments of Stein and coworkers, the protein originating from the fusion of an anti-CD123 ScFv and a truncation of Pseudomonas exo-toxin A induces potent apoptosis in AML-derived cells [56].

A bispecific antibody, one member of artificial antibody, is engineered by linking two ScFvs with specificity for two different antigens. Such a genetic engineering antibody opens a vast foreground in tumor immunotherapy because of its capacity of building the bridge between target cells and functional molecules or cells, endowing the immune reaction with guidance quality and other fine characteristics. Recently, in the studies on targeted therapy for AML, researchers fused anti-CD123 ScFv to three other (anti-CD16, anti-CD33, anti-CD3) ScFvs, generating three bispecific antibodies [40,41,56]. These bispecific antibodies all induced potent lysis of AML blasts in ADCC reactions and showed attractive prospects for future clinical testing.

CD123 chimeric antigen receptor (CAR) redirected T cell therapy

Chimeric antigen receptors (CARs) are synthetic molecules consisting of an extracellular antigen-binding domain and intracellular signaling domains via a spacer region [48]. CAR-expressing T cells selectively kill tumor cells by targeting cell surface antigens. Many groups have developed specific CAR T cells for different antigens, including CD19 [68], EGFR [49], TCR-like chimeric receptor [70].

The most recent report on CD123 CAR cells came from Tettamanti’s study [63]. They generated cytokine-induced killer (CIK) cells expressing CD123 CAR, and proved that anti-CD123 CAR-redirected CIK cells were able to strongly kill CD123+ cell lines, as well as primary AML blasts [63]. Five months later, the other paper about CD123 CAR T cells was published in Blood journal. They developed two CARs containing a CD123-specific single-chain variable fragment, in combination with the other two domains from CD28 and CD3, targeting different epitopes on CD123 [48]. These CD123-CAR-redirected T cells displayed an effective activity against primary AML patient samples and antileukemic activity in vivo against a xenogenic model of disseminated AML [48]. Besides, the CD123-scFv-based CAR T cells also exhibited more stronger antileukemia activity against a CD123+ cell line compared with
previous mentioned CD123-scFv-based immunotoxin [15,48]. Note-worthily, Ehninger and his co-worker found that the modified T cells express chimeric antigen CD123 and CD33 are more efficient in reducing leukemia burden in vivo compared with those of CD123 CAR alone [71]. In a recent preclinical study, Gill et al. reported human CD123-redirected T cells eradicate primary AML in immunodeficient mice [72]. Given that the anti-CD123 CAR has less impact on normal HS/PCs and granulocyte/macrophage and erythroid colony formation [73]. CD123 CAR T cells will be a very promising immunotherapy for the treatment of high-risk AML.

Conclusions
Numerous research has been carried out studying the potential clinical application of CD123 in the past two decades since it was reported to be a novel biological marker of LSCs. The overexpression pattern of CD123 in many diseases, including AML, B-ALL, and HCL, makes this molecule a useful marker in the auxiliary diagnosis of these diseases. And CD123 might be a prognostic marker easily adopted in clinical practice to rapidly identify AML patients at risk of treatment failure. Furthermore, the high expression of CD123 on the surface of LSCs makes it a wonderful target to kill them selectively while spare the normal HSCs, which leads to a complete cure without relapse. A variety of targeting agents have been developed to achieve this goal, and some of them displayed an attractive opportunity and entered phaseclinical trials. Additional studies on the use of this membrane receptor in the diagnosis, prognosis, and targeted therapy of hematologic malignancies are warranted. And in the treatment for these leukemia diseases using CD123-targeting medications, further attention is required to be paid on the combination with traditional chemotherapy and patient selection in order to maximize efficacy and minimize side effects.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

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References


