



Immunotoxin therapy for hematologic malignancies: where are we heading?

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The identification of numerous unique targets in recent years has led to the development of various immunotoxins (ITs) for treating hematological malignancies. Some of these ITs have advanced to clinical trials and have resulted in a high response rate against leukemia. Newer targets with improved specificity are also being identified for targeting several leukemias. Currently, several modified versions of ITs with increased efficacy are being constructed and evaluated for cytotoxicity *in vitro* as well as *in vivo*. Here, we summarize recent advances in preclinical and clinical studies of recombinant ITs targeting diverse surface receptors.

Introduction

Q2 Innumerable therapeutic strategies for different types of cancer have emerged with improved specificity and potency while minimizing toxicity. ITs represent fusion proteins carrying a target molecule conjugated to a toxin molecule. The target moieties can be either antibody based, such as monoclonal antibodies (Mabs), genetically engineered single chain/double chain antibody fragments or ligands, cytokines, and growth factors targeting cell surface receptors [1,2]. After the initial success of monoclonal therapy for cancer, Mabs were linked to toxin molecules, which were more specific in targeting and more potent in destroying cancer cells. The careful design of target moiety and toxin is the key factor of a successful therapy because each type of cancer cell expresses a different set of surface antigens and responds differently to each toxin. Some ITs have been approved by the US Food and Drug Administration (FDA), such as denileukin diftitox (ONTAK[®]) for the treatment of cutaneous T cell lymphoma (CTCL). Here, we discuss the advances in antibody–toxin and ligand–toxin conjugates for targeting malignancies of myeloid and lymphoid lineages (Figs 1 and 2).

Antibody–toxin conjugates

In antibody–toxin conjugates, antibodies or their fragments are fused to a range of toxins, such as bacterial, plant, and fungal

toxins or human apoptotic proteins, which become internalized in the target cell and induce apoptosis. Mabs or single-chain variable fragments (ScFvs) against several target antigens have been developed and fused to toxins such as diphtheria toxin (DT), *Pseudomonas* exotoxin (PE), ricin, saporin, and gelonin, to construct ITs [3]. These target surface molecules are lineage specific and are being utilized for targeting specific types of leukemia or lymphoma, as discussed below (Table 1).

CD19

CD19 is expressed on the surface of B cells and acts as a B cell co-receptor in conjunction with CD21 and CD81. It is used to diagnose and target B cell lymphomas. The anti-CD19 Mab, B4, was conjugated to blocked ricin (anti-B4-bR) and exhibits cytotoxic activity in patients with lymphoid malignancies. In a phase I trial using anti-B4-bR IT, 11 out of 12 patients with B cell non-Hodgkin's lymphoma (B-NHL) remained in complete response (CR) to the treatment. HD37-dgA was effective in patients with B cell lymphoma in a phase I study. In a phase II study using adjuvant therapy in relapsed B cell NHL with anti-B4-bR, 26 out of 49 patients remained in CR [4].

A CD19-specific ScFv fused to a 38-kDa fragment of PE prolonged the survival of nonobese diabetic (NOD)/severe combined immunodeficiency (SCID) mice transplanted with Nalm-6 cells [5]. The conjugate showed synergistic toxicity along with valproic acid and cyclosporine, inducing apoptosis in 12 patients with B cell chronic

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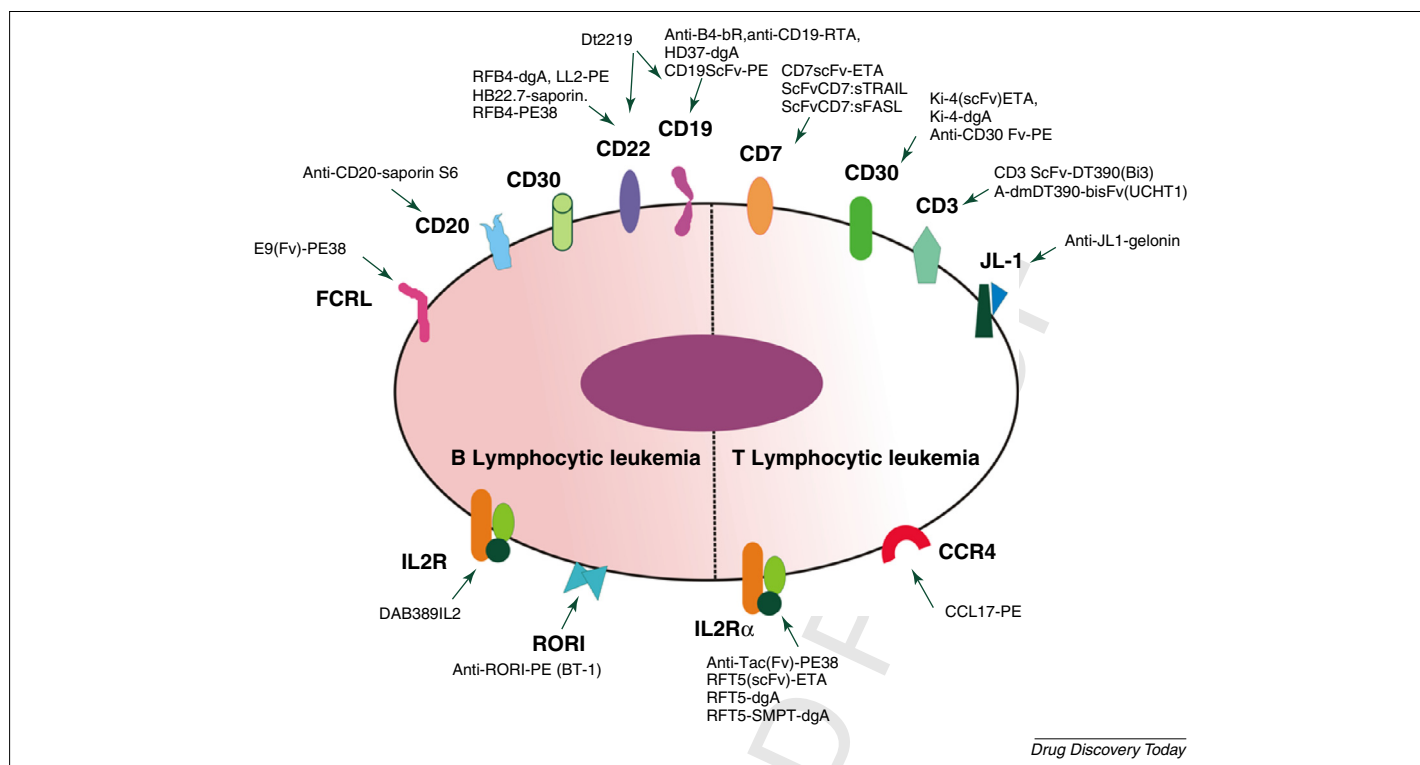


FIGURE 1

Surface receptors and their respective immunotoxins being used to target lymphocytes for hematological malignancies, such as acute lymphoblastic leukemia (ALL), chronic LL (CLL), cutaneous T cell lymphoma (CTCL), Hodgkin's disease (HD), non-Hodgkin's lymphoma (NHL), and other lymphomas. For additional definitions, please see the main text.

lymphocytic leukemia (B-CLL). An anti-CD19 Mab conjugated with ricin A toxin (rRTA) was cytotoxic in pre-B acute lymphoblastic leukemia (pre-B-ALL) and Burkitt's lymphoma cells [6]. The combination of two ITs, known as Combotox, contains anti-CD19 (HD37-dgRTA) and anti-CD22 (RFB4-dgRTA) conjugated to deglycosylated

RTA (dgRTA). Combotox showed improved survival in SCID mice injected with a NALM-6-UM1 cell line [4]. A phase 1 study of Combotox in pediatric patients with refractory B-ALL resulted in three CR and seven partial responses (PRs) out of a total of 17 children [7]. A recent multi-institutional Phase I trial in refractory B-ALL showed decreased blast counts in 17 patients in the study and partial remission in an additional patient [8]. A combination of Combotox and cytarabine (Ara-C) was used in an advanced ALL murine xenograft model using a NALM/6 cell line and exhibited longer median survival [9]. Anti-CD19 IT BU12-Saporin showed higher activity and, along with anti-CD20 Mab (rituximab) and its F(ab)2 derivative, induced apoptosis in Ramos cells and was effective in SCID-Ramos mice [10].

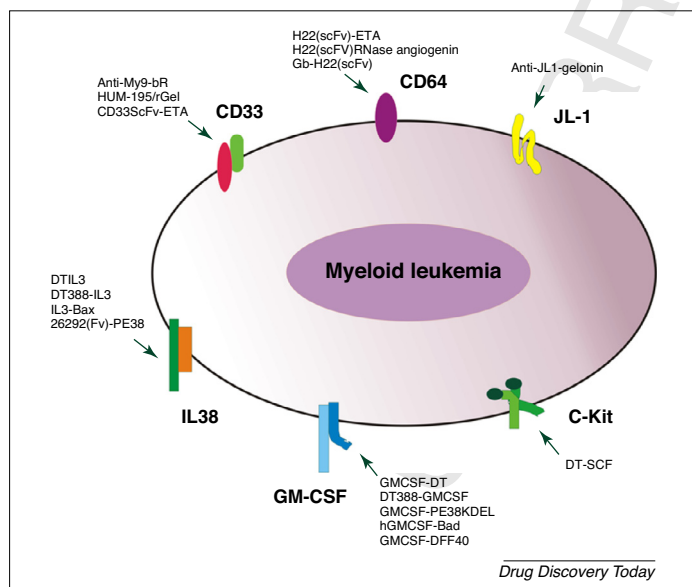


FIGURE 2

Surface receptors and their respective immunotoxins being used to target myeloid cells in leukemic conditions, such as acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and other myeloid leukemias. For additional definitions, please see the main text.

CD20

CD20 is a 35-kDa protein expressed on normal B cells and abundantly expressed in hairy cell leukemia (HCL). Rituximab was developed to carry mouse variable and human constant regions targeting CD20, and was highly effective in patients with relapsed B-NHL and mantle cell lymphoma (MCL) [11]. A rituximab-saporin-S6 conjugate showed cytotoxicity in Raji and D430B cell lines, enhanced toxicity along with fludarabine, and induced apoptosis in 80% of lymphoma cells from patients with NHL [12].

CD22

CD22 is expressed on B cells in most B cell leukemias and lymphomas. Initially, chemical conjugates with dgA using Mabs H6 and RFB4 or Mabs HD6 and HD39 linked to saporin were used. RFB4-dgA resulted in two CRs and ten PRs out of 41 patients with

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