Oligonucleotide Aptamer-Mediated Precision Therapy of Hematological Malignancies

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Precision medicine has recently emerged as a promising strategy for cancer therapy because it not only specifically targets cancer cells but it also does not have adverse effects on normal cells. Oligonucleotide aptamers are a class of small molecule ligands that can specifically bind to their targets on cell surfaces with high affinity. Aptamers have great potential in precision cancer therapy due to their unique physical, chemical, and biological properties. Therefore, aptamer technology has been widely investigated for biomedical and clinical applications. This review focuses on the potential applications of aptamer technology as a new tool for precision treatment of hematological malignancies, including leukemia, lymphoma, and multiple myeloma.

Currently, chemotherapy is the mainstay treatment for hematological malignancies.1 Although chemotherapy is effective in many cases, it can cause severe side effects in patients due to a lack of specificity. Therefore, cancer cell- or oncogene-selective therapeutic approaches have recently emerged, e.g., precision medicine, as a result of the advances in cancer genotyping and phenotyping studies. Precision medicine targets specific abnormalities within the cancer cell genome, proteome, and immunome and markers involved in cancer initiation, development, and growth.2,3 In contrast to conventional chemotherapy, precision medicine specifically targets the individual characteristics of each patient’s cancer phenotypic profile, resulting in significantly increased therapeutic efficacy and decreased non-specific toxicity. To date, precision medicine has been extensively applied in various cancers, especially hematological malignancies. The major approaches of precision medicine include the following: (1) cell-targeted chemotherapy to specifically deliver chemotherapeutic agents to the cells of interest without affecting normal tissues,1,5 (2) gene therapy to specifically silence oncogenes,6,7 (3) immunotherapy to harness the power of the immune system in eliminating cancers,8,9 and (4) cell-specific biotherapies to inhibit cancer development by stimulating relevant cellular signaling pathways.10 Precision medicine has shown great potential and perspective in the clinical treatment of cancer as a result of the recent technological advances.

Aptamers are short, single-stranded oligonucleotides (RNA or single-stranded DNA [ssDNA], respectively), usually 20–80 nt in length with a tridimensional folded structure. Aptamers are highly specific and bind tightly to their targets after structural recognition (Figure 1), in a manner similar to antibodies binding to their antigens.11 In 1990, Ellington and Szostak12 coined the term aptamer for this unique class of nucleic acids; the term derives from the Latin word aptus, which means fit, and the Greek word meros, which means part. To date, aptamers have been developed for a wide range of targets, including small metal ions or molecules, peptides, proteins, bacteria, viruses, whole cells, and targets within live animals.13 Aptamers have been widely used in the diagnosis and treatment of various diseases.14–17 Oligonucleotide aptamers present the following significant advantages compared to protein antibodies:

(1) Higher tissue permeability. Aptamers have significantly smaller molecular weights (8–25 kDa) compared to antibodies (over 150 kDa);18 thus, they can penetrate tissue membranes and reach their target sites more efficiently in vivo compared to antibodies, with dissociation constants (Kd) in the pico- to nanomolar range.19,20 Nonetheless, the smaller molecular weights of aptamers render them susceptible to rapid excretion through renal filtration in vivo.21 During the last decade, chemical modification strategies to prevent renal clearance of aptamers have emerged, and they have significantly increased the half-life of aptamers in vivo.22 Da Pieve et al.23 reported that conjugation of the murine PD-1 aptamer to a high-molecular-weight polyethylene glycol (PEG) significantly limited the rate of renal filtration, and it increased the half-life of the aptamer from 1 to 24–48 hr in vivo. Thus, modified aptamers can exhibit high bioavailability in clinical applications, given that they readily reach their targets, and they can remain in the bloodstream for extended time periods in vivo.

(2) Easy to modify and low cost. Due to their simpler structures compared to antibodies, aptamers can be easily modified through chemical processes, enabling easier optimization of their clinical properties, such as resistance to nuclease degradation24–26 or
Leukemia is a broad term for a group of cancers originating from hematopoietic stem cells; it is characterized by uncontrolled proliferation of undifferentiated white blood cells in peripheral blood and bone marrow. As the abnormal cells cannot develop further, they accumulate over time to substitute normal blood cells; this causes various symptoms correlated with dysfunction of blood cells, including anemia, bleeding, bruising, fatigue, fever, and enhanced risk of infections. Leukemias are generally classified into four main categories, depending on the disease progression and type of blood cells that are affected: acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL). Currently, chemotherapy is the mainstream treatment for leukemia. However, chemotherapeutic agents lack selectivity between tumors and normal tissues, which results in serious side effects such as toxicity, limited drug concentration in cancer cells, and reduced therapeutic efficacy.

**Applications of Aptamers in Precision Medicine Therapy of Leukemia**

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**Aptamer-Mediated Therapies of AML**

AML is a type of malignant disorder originating from rapid clonal expansion of undifferentiated myeloid precursors, and it is currently treated with chemotherapy, despite the possibility of causing severe non-specific toxicity to normal tissues. Recent studies demonstrated that aptamer-mediated precision therapy has considerable efficacy in the treatment of AML. AS1411 is a DNA aptamer that specifically targets nucleolin, which is overexpressed in the cytoplasm and on membranes of various cancer cells, including AML. Chen et al. reported that AS1411 significantly inhibited cell growth and reduced viability of the AML cell line MV4-11 and AML patient cells. Additional experiments revealed the mechanism by which AS1411 interfered with bcl-2 mRNA, an important anti-apoptotic factor, playing a crucial role in the stabilization of nucleolin. The phase I clinical trial, completed in 2006, confirmed the safety and good tolerance of AS1411 with cytarabine in the treatment of AML, thus rendering it a promising candidate for AML therapy.

In addition to their role as direct, targeted biotherapeutics, aptamers can function as effective vehicles carrying drugs and target biomarkers on hematopoietic cells. Recently, Zhao et al. developed a DNA aptamer specifically targeting CD117, a biomarker highly expressed by certain AML cells. For the therapeutic study, the aptamer was conjugated with methotrexate (MTX) to generate Apt-MTX conjugates. This Apt-MTX conjugate showed significantly enhanced inhibition of cellular growth, triggered cell apoptosis, and induced G1 phase cell-cycle arrest of the AML cell line HEL and primary AML cells from patients, compared to MTX treatment alone, with negligible toxicity on off-target cells. Another well-characterized plasma membrane biomarker, CD123, which is highly expressed on 45%–95% of AML cells, has been associated with increased...
Aptamer-Mediated Therapies of ALL

ALL is an aggressive neoplasm stemming from uncontrolled proliferation of immature T or B lymphoblasts in bone marrow. Conventional chemotherapeutic treatments for ALL have shown limited efficacy. However, to date, non-specific toxicity toward normal tissues and relapses in one-fifth of the cases still remain big challenges for ALL patients. In recent years, the applications of aptamer-mediated targeted therapies have increased exponentially.

An important milestone in the field was the development of Sgc8c-7, an ssDNA aptamer that Shangguan et al. developed in 2006. Aptamer Sgc8c-7 specifically targets protein tyrosine kinase 7, which is highly expressed on the membrane of T-ALL cell line CCRF-CEM, thus providing excellent possibilities for more effective and precise treatment of ALL. Pioneering work by Huang et al. showed that conjugation of Dox to aptamer Sgc8c-7 resulted in highly efficient targeted delivery of Dox to CCRF-CEM cells, with minimum uptake by off-target cells; the aforementioned results show the advantages of aptamers in clinical applications. Besides linking to chemotherapeutic drugs, aptamer conjugates with new anticancer agents have also been extensively used in cancer treatment. Recently, photosensitizers emerged as a new group of anticancer agents because they can be activated by light irradiation to generate reactive oxygen species. However, photosensitizers showed insufficient localization at the target sites in vivo due to a lack of cellular specificity. Wang et al. successfully overcame this limitation by linking aptamer Sgc8c-7 with photosensitizer C66; the conjugate aptamer significantly increased selective binding and death of CCRF-CEM cells.

In addition, nowadays, the use of nanoparticles, a promising approach in targeted medicine, is gradually gaining momentum in the treatment of ALL. Nanoparticles have good biocompatibility, large surfaces for enhanced aptamer loading, and uniform size and shape for excellent biodistribution. These characteristics prolong nanoparticle half-life in vivo and increase payload capacity of linked agents. N-Heterocyclic carbene (NHCs) are a class of organic compounds that can stabilize metals in air, heat, water, and acid through strong bonding. In recent years, NHC conjugates with gold nanoparticles (NHC-Au) have attracted our attention as a new group of potential anticancer agents. NHC-Au complexes are physically stable, and they exhibit remarkable cytotoxicity because they can efficiently inhibit growth and induce apoptosis of cancer cells. However, a common disadvantage of metal-based drugs entails their non-selective interactions with normal cells or tissues. Improvement of the cellular selectivity of NHC-Au complexes prevented these undesired interactions. Recently, Niu et al. reported that covalent conjugates of aptamer Sgc8c-7 to NHC-Au complexes selectively bound to CCRF-CEM cell lines and were specifically internalized into cells, without interacting with off-target cells. Additionally, a significantly higher cytotoxicity was observed against CCRF-CEM cells when they were treated with Sgc8c-7 conjugated to NHC-Au as compared to treatment with NHC-Au complexes alone; this result indicates that Sgc8c-7 can mediate specific and efficient delivery of NHC-Au to target cells, thus killing cancer cells with high efficiency. In addition, Luo et al. developed a smart drug carrier by assembling Sgc8c aptamer, Dox, and hairpin DNA complexes on the surface of gold nanoparticles. The aptamer-functionalized nanoconjugates specifically bound to CCRF-CEM cells, released encapsulated Dox with hairpin DNA when exposed to laser illumination, and specifically killed cancer cells.

In conclusion, aptamer Sgc8c-7 functions as an important vehicle for targeted medicine therapy of ALL via conjugation to chemotherapeutic drugs, photosensitizers, and nanoparticles, thereby enhancing their selective cytotoxicity without damaging normal tissues.
Furthermore, it achieves highly specific synergistic anticancer effects when combined with other anticancer agents, which underscores the high potential of aptamers in future clinical applications to treat ALL.

**Aptamer-Mediated Therapies of CML**

CML is a slowly progressing myeloproliferative neoplasm that originates from abnormal pluripotent bone marrow stem cells, and it is consistently associated with BCR-ABL fusion gene located in the Philadelphia (Ph) chromosome.72 Currently, precision therapy blocking the activity of ABL tyrosine kinase with the tyrosine kinase inhibitor (TKI) Imatinib is the first-line treatment for newly diagnosed CML patients.23,74 However, in nearly 40% of CML patients, Imatinib exhibits inadequate efficacy or loss of previously obtained response;75 thus, new alternatives for treatment are necessary. Ping et al.76 recently developed an aptamer that can specifically target BCR-ABL fusion gene, and they linked it with small interfering RNA (siRNA) to induce gene silencing. The studies showed that this aptamer-siRNA nucleic acid chimera significantly inhibited cellular growth and induced apoptosis of CML cell line K562 only,76 indicating its potential therapeutic value in CML treatment.

Besides impacting typical genes, aptamers exhibit anticancer activity by interfering with signaling pathways. Beta-arrestins, a family of ubiquitous cellular scaffold proteins, are important signaling adaptors, facilitating activation of various pathways77,78 that are closely correlated to cellular proliferation, differentiation, or apoptosis79 and several tumorigenic events.80,81 It was demonstrated that β-arrestin 2, a member of the β-arrestin family, was critical in the initiation and progression of CML via modulation of the Hh/Smo and Wnt/Fz pathways; this indicates that β-arrestin 2 is a viable target in treating CML.82 Based on these findings, Kotula et al.83 screened an aptamer that can specifically bind to β-arrestin 2. The aptamer specifically disrupted β-arrestin 2-signaling complexes, and thus it inhibited the downstream signaling processes of both Hh/Smo and Wnt/Fz pathways; these effects finally led to impaired tumorigenic growth of CML cell line K562 and patient-derived samples.83 Aptamers targeting specific genes and signaling molecules, involved in the development of CML, showed considerable effects in precision medicine therapy of the disease. Given that use of TKIs presently remains the conventional treatment for CML, the combination of aptamers with TKIs is an important route to achieve enhanced therapeutic effects in the future.

**Aptamer-Mediated Therapies of CLL**

CLL is a neoplasm composed of immune-incompetent and clones of self-renewing B cells,84 which relentlessly accumulate in the peripheral blood, bone marrow, spleen, and lymph nodes.85 It accounts for 25% of all leukemias, and it ranks as the most common lymphoid malignancy in western countries, with a highly variable clinical course and prognosis.86 Conventional chemotherapies only eliminate CLL cells in peripheral blood, whereas those in bone marrow remain unaffected, thus leaving CLL incurable. An important proliferation mechanism involves bone marrow stromal cells, which constitutively secrete a type of chemokine named CXCL12; it recruits immune cells via interaction with its receptor CXCR4, which is highly expressed on the surface of CLL cells.87 CXCL12 and CXCR4 signaling has been demonstrated to promote interaction between CLL cells and the bone marrow microenvironment, and it enhances homing and retention of CLL cells in bone marrow.87 Thus, the inhibition of such tumor-supporting pathways could potentially enhance the therapeutic effects of chemotherapy on CLL and totally eradicate CLL cells in bone marrow.

Taking into consideration the previous findings, the RNA aptamer NOX-A12 was developed; it comprises 45 ribonucleotides and acts as the specific antagonist of CXCL12.88 NOX-A12 disrupted binding of CXCL12 to CXCR4, and it mobilized CLL cells from the protective bone marrow microenvironments to peripheral blood, thus sensitizing CLL cells to chemotherapeutic attack and triggering cellular apoptosis.89 The phase IIa clinical study of NOX-A12 in combination...
Lymphomas comprise a group of neoplasms that develop from the lymphatic system, and they are characterized by uncontrolled proliferation of lymphocytes. Typical signs and symptoms of lymphoma include enlarged painless lymph nodes, fever, drenching sweats, unintended weight loss, and constant fatigue. Based on the cell histology, genetic mutations, expression of certain genes, and other characteristics, lymphomas can be generally classified into Hodgkin’s lymphoma and non-Hodgkin’s lymphoma (NHL) with T or B cell subtypes. In this review, we discuss the progress of published reports on aptamer-mediated precision medicine therapy of lymphoma.

Applications of Aptamers in Precision Medicine Therapy of Lymphoma

Lymphomas comprise a group of neoplasms that develop from the lymphatic system, and they are characterized by uncontrolled proliferation of lymphocytes. Typical signs and symptoms of lymphoma include enlarged painless lymph nodes, fever, drenching sweats, unintended weight loss, and constant fatigue. Based on the cell histology, genetic mutations, expression of certain genes, and other characteristics, lymphomas can be generally classified into Hodgkin’s lymphoma and non-Hodgkin’s lymphoma (NHL) with T or B cell subtypes. In this review, we discuss the progress of published reports on aptamer-mediated precision medicine therapy of lymphoma.

Aptamer-Mediated Therapy of T Cell Lymphomas

T cell lymphomas affect T cells at different stages, and they account for about one in ten cases of NHL. Anaplastic large cell lymphoma (ALCL) is an aggressive T cell lymphoma characterized by cohesive proliferation of large pleomorphic lymphoma cells, abnormal activation of anaplastic lymphoma kinase (ALK) oncogene, and high-level expression of CD30 molecules. CD30 is a transmembrane protein receptor of the tumor necrosis factor (TNF) family, and it is normally expressed in activated T cells. CD30 protein targeting appears to be an attractive and rational approach for the diagnosis and treatment of ALCL.

In 2004, Mori et al. first developed an RNA aptamer that can specifically target CD30. Recently, in vivo RNA delivery tools, such as polyethyleneimine (PEI), showed high cellular transfection efficiency and high buffering capacity. Zhao et al. designed a PEI-citrarate nanocomplex, which was equipped with CD30 aptamer and loaded with siRNA of ALK oncogene. In general, chromosomal translocation of the ALK gene was observed in 50%–85% of ALCL patients, and the knockout of ALK gene significantly increased the death rate of ALCL cells. The in vitro studies revealed that the nanocomplex selectively bound to CD30(+) ALCL cells, effectively silenced cell ALK oncogene, and triggered growth arrest as well as apoptosis of ALCL cells. Also, Zhao et al. developed another nanoscale drug delivery system, comprising a hollow gold nanosphere equipped with RNA CD30 aptamer on the surface and Dox inside the nanosphere. This gold nanosphere was stable under normal biological conditions (pH 7.4), but it became ultrasensitive at low pH and rapidly released 80% of loaded Dox at pH 5.0. Upon intracellular delivery of Apt-NMed triggered rapid Dox release and intracellular ALK-specific siRNA delivery, resulting in the combined chemotherapeutic and oncogene-silencing effects. Animal model studies demonstrated specific accumulation of Apt-NMed in ALCL tumor sites, induction of higher inhibition of ALCL tumor growth, and improved survival of the treated mice; Apt-NMed did not affect off-target tumors in the same xenograft mouse, thus opening a new avenue for precision therapy of ALCL.

In addition, we investigated unique aptamer-equipped natural killer (NK) cells for immunotherapy of ALCL. The study showed that the aptamer-equipped NK cells specifically recognized and captured CD30(+) ALCCL cells by increasing NK cell recognition and captured CD30(+) ALCCL cells by increasing NK cell recognition and killing efficiency of target cells. To sum up, the CD30-specific aptamer functions as an excellent guiding tool to efficiently deliver anticancer agents or immune cells to target cells or to specifically trigger an intracellular signaling pathway by binding to its receptors on lymphoma cells. These results lead to a wide range of successful precision medicines to treat T cell lymphoma.

Aptamer-Mediated Therapies of B Cell Lymphomas

B cell lymphomas comprise a group of malignancies resulting from the clonal proliferation of mature B lymphocytes. They include most NHLs and are more prevalent than T cell lymphomas. In general, B cell lymphomas express specific surface biomarkers that are restricted to a single light-chain type and a specific variable region. These surface markers are considered tumor specific and distinguish tumors from normal cells. Recently, studies on precision therapy studies of B cell lymphomas based on cell-specific biomarkers were conducted. It is well known that B cell lymphomas express only one type of surface Ig light chain (kappa or lambda); these chains are considered the gold standard biomarkers for diagnosis and potential targets for precision therapy of lymphoma.
developed a ssDNA aptamer that can specifically target Maver-1 lymphoma (B cell lymphoma) cells and Ig lambda-like polypeptide. The functional studies revealed selective internalization of aptamers into Maver-1 lymphoma cells, triggering cell cycle S-phase arrest and cellular growth inhibition. Importantly, the aptamer-induced S-phase arrest and chemotherapeutic treatment with cytarabine had a notable synergistic effect on killing Maver-1 cells. These results demonstrate the importance of aptamers in synergistic biotherapy via cell cycle regulation and chemotherapy of lymphoma.119

Besides targeting surface-specific markers, aptamers can attack B cell lymphoma by modulating the immune system. In recent decades, substantial efforts have been made to promote the use of T cells in cancer immunotherapy by modulating immune checkpoints or costimulatory molecules. CD28 is the main costimulatory receptor constitutively expressed on T cells, and it interacts with its ligands B7-1 and B7-2 expressed on antigen-presenting cells (APCs), such as dendritic cells, macrophages, and B cells.127 Recently, it was demonstrated that the B7-1- or B7-2-CD28 pathway on APCs is the strongest costimulatory signal for the full activation of T cells.136 Pastor et al.138 developed an aptamer that activated CD28; the investigators demonstrated that it boosted T cell immune response against a murine B cell lymphoma model and considerably prolonged the overall survival of mice.

In summary, aptamer-mediated precision therapy of B cell lymphoma mainly interferes with cell-specific biomarkers or cellular molecules, and it also modulates the immune system, resulting in direct, remarkable cancer suppression effects.

Applications of Aptamers in Precision Medicine Therapy of MM
MM is a plasma cell neoplasm characterized by clonal proliferation of malignant plasma cells in the bone marrow, monoclonal Ig accumulation in blood or urine, and associated organ dysfunction.140 Despite conventional therapeutics such as Bortezomib,141 MM still remains an incurable disease with poor prognosis for the majority of patients, and ongoing research is required to find additional therapeutic approaches.142

In recent years, aptamer-based precision medicine has shown promising results in the treatment of MM. CD38, a type II transmembrane glycoprotein that is widely expressed on plasma cells, is considered an
| Disease | Biomarker | Development | Therapy | Application |
|---------|-----------|-------------|---------|-------------|
| AML | nucleolin | by nonantisense synthesis based on observations that guanosine-rich oligonucleotides possessed antiproliferative properties against cancer cells | biotherapy | synergetic anticancer effect of AS1411 with cytarabine in treatment of AML during phase II study (NCT00512083) |
| | CD117 | SELEX from whole cell | cell-selective chemotherapy | cellular growth inhibition, apoptosis, and cell-cycle arrest of AML cell line, and patient sample by Apt-MTX conjugates |
| | CD123 | SELEX from peptide | cell-selective chemotherapy | cellular cytotoxicity of AML cell line, tumor growth inhibition and prolonged survival of AML xenograft mouse model via Apt-MTX conjugates |
| ALL | PTK7 | SELEX from whole cell | cell-selective chemotherapy | specific enhanced cellular cytotoxicity of ALL cell line via Apt-Dox conjugates and Apt-photosensitizer Ce6 conjugates |
| CML | BCR-ABL | SELEX from purified protein | gene therapy | significant cellular growth inhibition and apoptosis of CML cell line induced by Apt-siRNA chimera |
| | β-arrestins | SELEX from purified protein | biotherapy | impaired growth of CML cell line and patient-derived samples via β-arrestin 2 aptamer |
| CLL | CXCL12 | SELEX from purified protein | biotherapy | sensitizing CLL cells to chemotherapy with enhanced apoptosis rates via aptamer targeting, increased complete remission rate of aptamer-treated relapsed CLL patients; aptamers used in combination with Bendamustine and Rituximab in phase IIa clinical study (NCT01486797) |
| T cell lymphoma | CD30 | SELEX from whole cell and purified protein | cell-selective chemotherapy and gene therapies | chemotherapy and oncogene silencing of target cell lines, tumor growth inhibition, and higher survival rate of xenograft mouse models achieved by Apt-siRNA-Dox conjugates |
| | Ig light chain | SELEX from whole cell and purified protein | biotherapy | increased capturing and killing efficiency of target cell lines induced by aptamer-equipped NK cells (S.Y., unpublished data) |
| | CD20 | SELEX from whole cell | biotherapy | cell-cycle arrest, growth inhibition, and synergistic killing effect of target cell lines by chemotherapeutics via aptamer targeting |
| | BAFF-R | SELEX from purified protein | biotherapy and gene therapy | inhibition of cellular proliferation of target cell lines by direct aptamer binding and oncogene silencing by Apt-siRNA conjugates |
| B cell lymphoma | Ig heavy chain | SELEX from whole cell | cell-selective chemotherapy | induction of target cell line death upon illumination of the Apt-photosensitizer chimera |
| | CD28 | SELEX from purified protein | immunotherapy | enhanced cellular immune response against lymphoma and prolonged survival of mice |
| nucleolin | by nonantisense synthesis based on observations that guanosine-rich oligonucleotides possessed antiproliferative properties against cancer cells | biotherapy | facilitated chemotherapy against target cell lines via aptamers |

(Continued on next page)
Important biomarker for diagnosis and a promising target for precision therapy of MM.\textsuperscript{143} Wen et al.\textsuperscript{144} developed a CD38-specific ssDNA aptamer, capable of targeting MM cells with high affinity. The authors conjugated this aptamer with Dox to form Apt-Dox conjugates (ApDCs); they observed specific internalization of ApDCs in MM cells and continuous trafficking into lysosomes, where the low pH microenvironment triggered structural changes, leading to the rapid release of Dox. The released Dox (from ApDCs) specifically killed MM cells without affecting off-target cells.\textsuperscript{144} The therapeutic potential of ApDCs was also demonstrated by tumor growth inhibition and the lack of toxicity in xenograft mice.\textsuperscript{144} Furthermore, a ssDNA aptamer specifically binding to Annexin A2 (ANXA2), the protein closely related to proliferation and adhesion of MM, has been developed.\textsuperscript{145} The binding specificity of the aptamer was confirmed in vivo in nude mouse xenografts with MM cells and MM bone marrow aspirates. It was demonstrated that the aptamer blocked MM cell proliferation induced by ANXA2, thereby providing a promising candidate for MM diagnosis and treatment.\textsuperscript{145} In summary, aptamer-mediated therapeutic approaches, via targeting cell proliferation pathways or specific surface markers, have shown promising effects in the precision treatment of MM.

**Conclusions**

The newly developed aptamer technology has shown promising results in precision medicine therapy of hematological malignancies (summarized in Table 2). Currently, patients diagnosed with hematological malignancies are primarily treated by standard chemotherapy.\textsuperscript{1} However, the clinical outcomes of chemotherapeutic treatments showed only minimal improvement over the past three decades due to unavoidable side effects induced by chemotherapeutic agents; these include toxicity to normal tissues, limited drug concentration, and high relapse rates.\textsuperscript{44}

Aptamer-mediated precision therapy showed superior outcomes in clinical applications as compared to chemotherapy. First, aptamer-mediated therapies cover a vast spectrum of targets, including extracellular tumor-specific markers, intracellular oncoproteins, dysregulated proteins, or signaling pathway-related factors, thus providing more options to treat and cure cancers. Given the complex pathogenesis of leukemias, lymphomas, and MM, the development of treatments based on widespread targeting is very valuable. Second, aptamers can be easily modified by the conjugation of different anticancer agents, such as chemotherapeutic drugs, nanoparticles, siRNAs, and guiding immune cells. The flexibility of modifying aptamers coordinate well with their wide spectrum of targets, and it leads to enhanced anticancer effects as compared to chemotherapeutic drugs. Finally, aptamers are small oligonucleotides with high affinity and specificity for their targets and fewer side effects to normal tissues. The high safety and tolerance of aptamer-mediated treatments are of great importance, especially in the treatments of leukemia where cancer cells are diffusely distributed in the tissues.

Aptamer-mediated treatments provide an advantageous approach compared to conventional therapies, and they present a promising perspective in clinical applications given their aforementioned unique properties and development potential. However, several challenges remain to be addressed. Unmodified RNA aptamers are vulnerable to nuclease-mediated degradation in the bloodstream, and thus methods to improve the in vivo biostability of aptamers are urgently needed. Despite chemical modifications of RNA aptamers, including changes to the phosphodiester backbone or PEGylation to improve their stability in vivo,\textsuperscript{46,47} their effectiveness has remained limited. Moreover, aptamer-drug conjugates may display different pharmacokinetics, biodistribution, and tolerability in vivo. Therefore, maintaining the same efficiency of aptamer-drug conjugates from bench to bedside remains a considerable challenge. Also, aptamer-based products initially had limited commercial success in the markets because aptamer technology was new, and relevant systematic academic studies on pharmacokinetics and pharmacodynamics were not available.\textsuperscript{18} The aforementioned issues should be addressed prior to the future application of aptamers as dominant therapeutics in the clinic.

In summary, aptamers have opened an attractive and promising venue of precision medicine in cancer treatment. Next-generation aptamer-based therapeutics with superior biological functions will emerge as new aptamers are developed. Additional aptamer-based therapeutic approaches, such as treatment of leukemia or lymphoma in combination with stem cell transplantation or CAR-T cell adoptive transfer, may be explored and applied in the future. As new clinical improvements are achieved, the number of successful aptamer-based applications in cancer therapy will certainly increase, thereby providing a strong incentive to further develop this promising class of cancer therapeutics.

**AUTHOR CONTRIBUTIONS**

S.Y. wrote the manuscript. Y.Z., H.L., L.X., and Z.D. revised the manuscript. W.H., Y.L., and W.J. drew the figures and summarized the tables.
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