

A Forecast of Targeting Leukemia Stem Cells by Nanomedicine

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Abstract

Leukemia Stem Cells (LSCs) are a subpopulation of leukemic cells that display characteristics of self-renewal, differentiation and tumor-initiating capacity. They are also thought to be responsible for Chemoradiotherapy resistance and the recurrence of leukemia. Recently, Nanomedicine has been widely used for cancer treatments with improved targeting efficiency and reduced side effects. In this review, we have summarized the studies of LSCs identification and therapeutic strategies with a commentary on recently developed cancer stem cell and LSCs targeting strategies by Nanomedicine.

Keywords: Nanomedicine; Nanocarrier; Cancer therapy; Leukemia stem cells; Cancer stem cells

Introduction

Cancer Stem Cells (CSCs) are a subset of cancer cells with self-renewal, differentiation and tumor-initiating properties. They are considered as the leading cause of tumor initiation, promotion, and relapse in most types of cancers [1]. The first experimental evidence for CSCs was given by Bonnet and Dick in 1997. They found that single CD34⁺CD38⁻ Acute Myeloid Leukemia (AML) cell was able to initiate AML in NOD-SCID mice [2]. Furthermore, this small subset population was found to be responsible for chemotherapy and radiotherapy resistance because CSCs have enhanced DNA repair ability, enriched anti-apoptotic proteins, improved drug efflux transporters, and are protected in specific microenvironment or niche [2]. Therefore, these leukemia initiating cells (LIC) or leukemia Stem Cells (LSCs) are considered as a critical target for leukemia therapy. Subsequently, CSCs in solid tumors have been identified from brain, prostate, breast, colon, and pancreas cancer [2].

Traditional cancer treatments, such as Chemotherapy and Radiotherapy, are cytotoxic to both normal and cancerous cells, which cause severe side effects, like bone marrow suppression, cardiomyopathy, and neurotoxicity. These side effects significantly limit their tumor therapeutic applications in clinic [3,4]. Recently, developed nanoscale devices have been used for drug delivery in clinic, because these nanoparticles are within 100 nanometers and can readily interact with biomolecules on the cell surface or within the cells. They can improve the drug delivery efficiency and stability *in vivo* [5]. This nanotechnology based drug delivery strategy has opened a novel avenue for cancer treatment and particularly improved the feasibility of CSCs targeting therapy *in vivo* [6].

Nanomedicine is the medical applications of nanotechnology. There are several applications of Nanomedicine by using nanomaterials in clinic inducing *in vivo* medical imaging for diagnosis and drug delivery for therapy [6]. In this review, we are focusing on the Nanomedicine involved targeted therapy particularly with a comment on the future applications of Nanomedicine in LSC treatment.

Leukemia Stem Cells

Like Hematopoietic Stem Cells (HSCs), LSCs are thought to reside at the apex of the leukemia hierarchy. LSCs give rise to leukemic progenitors and leukemic blasts with reduced capacity to self-renew and

differentiate [7-9]. Studies suggested that LSCs originate from HSCs or progenitor cells. For example, BCR/ABL1, an oncogenic tyrosine kinase in Chronic Myeloid Leukemia (CML), can be detected in several hematopoietic lineages [10,11]. DNMT3a mutations, common oncogenic mutation in AML are found in HSCs, progenitor and mature cell [12]. These studies indicated that leukemic genetic alterations might be initiated from stem cells and accumulate in committed progenitors and mature blood cells during differentiation, which eventually initiate leukemogenesis.

Identification of Leukemia Stem Cell Surface Markers

Identifying specific LSC specific markers is extremely helpful to develop new therapeutic strategies for LSC targeting therapy. However, previous evidence suggested that LSCs share similar cell surface markers with normal HSCs in mouse and human leukemia models [13]. Human LSCs were first identified as CD34⁺CD38⁻ clones, which overlap with normal HSCs [14]. Recent progresses have identified several novel surface markers, which can distinguish LSCs from normal HSCs, such as CD44 [15], CD123 [16], CLL-1 [17], TIM-1 [18], CD96 [19], CD47 [20]. In the following section, we will review several cell surface markers for LSC identification.

CD44 is a transmembrane glycoprotein that acts as a receptor for hyaluronan acid (HA) and other receptors, including osteopontin, collagens, Matrix Metalloproteinases (MMPs) [21]. CD44 is highly expressed in CD34⁺CD38⁻ AML cells. Jin et al. reported that CD44 antibody could significantly reduce LSC numbers and prolong survival

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in AML xenograft mouse model. Furthermore, leukemic cells obtained from CD44 antibody treated mice failed to develop leukemia which indicates that CD44 is critical for the self-renewal maintenance of LSCs [15]. CD123 is known as interleukin 3 receptor, alpha (IL-3R α). Jordan et al. first found CD123 was highly expressed in CD34⁺CD38⁻ cells from AML specimens but not from normal BM derived CD34⁺CD38⁻ cells. Functionally, CD34⁺CD123⁺ cells have competitive leukemogenesis capacity [22]. Consistent with this, high CD123 expression was detected in AML and CML patients [23]. CLL-1 is a type II transmembrane glycoprotein and belongs to C-type lectin-like receptor family. CLL-1 was found specifically enriched in CD34⁺CD38⁻ LSCs in AML patients (77 out of 89 positive). CD34⁺CLL-1⁺ cells can initiate AML in immunocompromised mice and interestingly CLL-1 expression is completely absent on CD34⁺CD38⁻ cells from normal controls [24]. T cell immunoglobulin mucin-3 (TIM-3), is highly expressed in AML LSCs but absent in normal HSCs. Furthermore, TIM-3⁻ but not TIM-3⁺ AML cells can reconstitute human AML in immune-deficient mice [25,26]. Similarly, CD96 and CD47 are also highly expressed in CD34⁺CD38⁻ AML cells but weakly expressed in the normal HSCs [19]. Increased CD47 expression is correlated with poor survival in three independent cohorts of adult AML patients [20]. CD32 and CD25 were suggested to be associated with Chemotherapy-resistant capacity in human AML LSCs [27], however further LSC markers need to be developed for efficient LSC targeting. These data demonstrated that LSCs can be distinguished from normal HSCs basing on cell surface markers. We have summarized the reported LSCs markers with their LSCs targeting potential in Figure 1.

Therapeutic Strategies for LSCs Targeting Strategies

Because traditional cytotoxic chemotherapies often kill rapidly dividing normal cells, the primary goal of targeted therapies is to eliminate cancer and cancer stem cells more precision with less side effects. Besides all the targeted therapies, monoclonal antibody and small molecule therapies have achieved the most promising anti-tumor results

[28]. Monoclonal antibody treatments have remarkable specificity for target therapies and their side effects are well limited. Small molecular are more efficient and cost-effective compared to antibody therapies, however how to select and modify the best compound for targeting is still challenging in the field [29]. Targeting LSCs, which are maintained by self-renewal, is expected to eradicate leukemia and reduce recurrence [9]. With the increased understanding of LSCs, recently several promising therapeutic strategies have been developed to target LSCs, such as targeting cell surface antigens, signaling transduction and the niche of LSCs (Table 1).

Targeting Antigens on LSCs

Monoclonal antibodies are the best candidates for cell surface antigen targeting therapy [30]. Anti-CD44 and anti-CD123 monoclonal antibodies have been used for LSC targeting in AML mouse model, in which LSCs cannot home to their BM protective niche [15,16]. Anti-CD47 and Anti-Tim-3 can decrease LSC proliferation in AML xenograft models [25,31]. Notably, in most cases antibody based therapeutic strategies can specifically target LSCs but spare normal HSCs.

Targeting Signaling Transduction in LSCs

Both LSCs and normal HSCs are maintained by self-renewal, which is regulated by multiple key signals. How to distinguish the self-renewal signals between normal HSCs and LSCs is critical for developing novel LSCs targeting strategies [32,33].

Recently, several key signals have been identified for LSC self-renewal maintenance including Wnt, Hedgehog, and Notch signal pathways. The Wnt/ β -catenin pathway is hyper-activated in different forms of AML [34]. Loss of β -Catenin impairs self-renewal of LSCs in CML, with BCR-ABL fusion protein mutation [35,36], however, normal hematopoiesis was maintained in mouse models [37,38]. High level β -catenin was considered to be critical for leukemia initiation and drug resistance. Inhibition or deletion of β -catenin reduced the

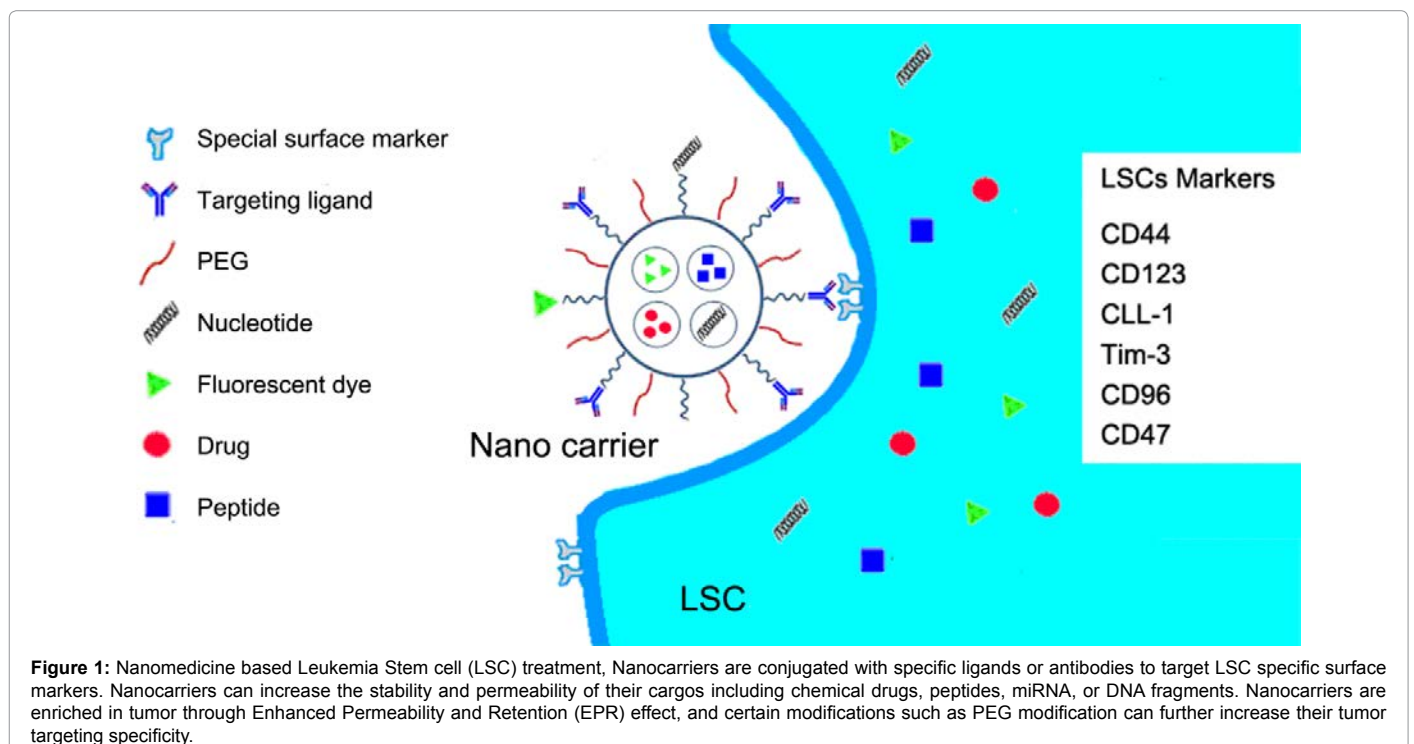


Figure 1: Nanomedicine based Leukemia Stem cell (LSC) treatment, Nanocarriers are conjugated with specific ligands or antibodies to target LSC specific surface markers. Nanocarriers can increase the stability and permeability of their cargos including chemical drugs, peptides, miRNA, or DNA fragments. Nanocarriers are enriched in tumor through Enhanced Permeability and Retention (EPR) effect, and certain modifications such as PEG modification can further increase their tumor targeting specificity.

Target		Targeting Strategy	Leukemia type	Reference
Surface marker antibody/ ligand	CD44	CD44 monoclonal antibody H90	AML	[21]
	CD123	CD123 monoclonal antibody 7G3	AML	[22]
	CLL-1	CLL-1 monoclonal antibody 1075.7	AML	[118]
	CD47	CD47 monoclonal antibody B6H12.2 and BRIC126	CML	[35]
	Tim-3	Tim-3 monoclonal antibody ATIK2a	AML	[31]
Self-renewal	Wnt/ β -catenin	β -catenin shRNA	MLL; CML	[39,40,43]
	Hedgehog	Cyclopamine (Hh signaling inhibitor)	CML	[44,45]
	Notch	Recombinant Dll4-Fc Notch ligand	AML	[46]
Signaling Transduction	NF- κ B	Parthenolide; MG-132; AS602868	AML	[47-49]
	PI3K/AKT/mTOR	Rapamycin (mTOR kinase inhibitor)	AML	[50,51]
	LAIR1	shRNA-226(shRNA specifically targeted <i>lair1</i> mRNA)	AML	[53]
Reactive oxygen species	ROS-related drugs	Parthenolide; Fenretinide; Auranofin	AML; CML	[48,54-56]
Heat shock proteins	HSP90	7-AAG (selective inhibitor of HSP90); PU-H71 (small-molecule Hsp90 inhibitor)	AML; CML	[58,59]
Epigenetic mechanism	Histone deacetylase	AR-42 (Histone deacetylase inhibitor); Brd4 (The epigenetic sensor)	AML	[61,119-121]
	miRNA	shRNAs or JQ1 (the small-molecule Brd4 inhibitor) antagomiR-126	AML	[116].
Microenvironment	CXCR4/CXCL12	CXCR4 neutralizing antibody 12G5; CXCR4 antagonist such as Plerixafor and AMD3465	AML	[69-72]
	VPS33B	shVPS33B (shRNA specifically targeting VPS33B)	AML	[74]

Table 1: Therapeutic approaches aiming at LSCs.

growth of human MLL leukemic cells or completely abolished the oncogenic potential of MLL-transformed cells [39]. Overall, these evidences indicate that Wnt/ β -catenin is required for LSCs in multiple types of leukemia but not for homeostasis hematopoiesis, which makes Wnt/ β -catenin pathway a potential candidate for LSCs targeting therapy. Hedgehog (Hh) signaling pathway plays an important role in sustaining stem cell self-renewal. Deletion of smoothened (Smo), a key transducer of the Hh pathway, or Hh inhibitor treatment can eliminate LSCs in CML. Consistently, constitutive activated Hh signaling leads to augmented LSCs and accelerated disease progress [40]. Conditional Smoothened (Smo) deletion or over-activation has no significant effects on adult HSC self-renewal and function [41]. Notch signaling is silenced in both human and mouse AML cells. Activated Notch signal can induce rapid cell cycle arrest, differentiation, and apoptosis of LSCs in AML models [42].

Several key survival pathways are involved in LSC maintenance by promoting proliferate and preventing apoptosis in LSCs. For example, survival pathway in cancer, NF- κ B, was found constitutively activated in LSCs. Blocking NF- κ B signaling pathway by chemical inhibitors resulted in rapid cell death in LSCs, however normal HSCs were much less effected [43-45]. These data indicated that NF- κ B signaling pathway could serve as a potential target for LSC targeting therapy in AML. The PI3K/AKT/mTOR signaling pathway is activated in most cancers including leukemia. Phosphatase and Tensin Homologue (PTEN), a negative regulator of the PI3K/Akt/mTOR pathway, maintains normal HSCs function and prevents the leukaemogenesis [46,47]. Tissue specific deletion of PTEN in hematopoietic cells led the mice to develop AML and Acute Lymphoid Leukemia (ALL), Rapamycin (mTOR kinase inhibitor) can significantly deplete LSC population in PTEN mutant leukemic mouse model [46,47]. Consistently, PI3K/AKT/mTOR pathway inhibitors such as wortmannin and LY294002 have achieved certain LSC targeting effects in animal models [48]. Recently, Kang et al. showed that The LAIR1-SHP-1-CAMK1-CREB pathway sustains the survival and self-renewal of LSCs in AML but is dispensable for normal hematopoiesis, which highlighted the potential therapeutic value of this pathway in eliminating LSCs *in vivo* [49].

Reactive oxygen species (ROS), Heat shock proteins (HSP) and Epigenetic modifications have also been suggested in LSC regulation.

High ROS level results in compromised DNA repair system, increased mutation rates and nuclear damage. Interestingly LSCs have higher ROS level compared to the bulk of leukemia cells and normal HSCs, these ROS tolerance allow LSCs are able to accumulate more mutations for their survival [50]. Several ROS generators, such as Parthenolide, Fenretinide and Auranofin, are used in leukemia therapy. Parthenolide can induce robust apoptosis in primary human AML cells and blast crisis CML cells by increasing their ROS level and repressing their NF- κ B activation, however normal hematopoiesis is not effected [44]. Fenretinide and Auranofin, other ROS generators, were proven to eliminate LSCs in CML by selectively increasing their cellular ROS level [51,52]. Chaperone protein, Hsp90, can sustain BCR-ABL activity and promote pathogenesis in CML [53]. Hsp90 is also highly expressed in CD34+ LSCs in AML which sustain Bcl2 protein for anti-apoptosis and enhanced survival of LSCs in AML [54]. Therefore, HSP90 inhibitors hold anti-LSCs potential as they do in solid tumors [55]. Many epigenetic modifiers such as histone deacetylase (HDAC) and DNA methyltransferase (DNMT) inhibitors have been widely used for leukemia treatment [56]. AR-42, a novel histone deacetylase inhibitor, can selectively induce apoptosis of LSCs in AML by inhibiting NF- κ B activity and Hsp90 interaction with its various associated proteins [57]. Overall, the current advances in LSCs studies will develop better therapeutic strategies for leukemia treatment.

Targeting the Niches of LSCs

The bone marrow microenvironment or niche has provided a protective shelter for normal HSCs [58,59]. However, recent studies suggested that LSCs can share or hijack this refuge for their own survival [58,60]. Furthermore, LSCs can even remodel the bone marrow niche for better proliferation and chemotherapy evading [60]. Since LSCs reside in their own protective niche in the BM, theoretically expelling LSCs from their protective niche would significantly improve the traditional chemotherapy efficiency [61-64]. Therefore, HSC homing signal CXCR4-CXCL12 has been studied for their leukemia treatment effect [58]. Brault et al. found that CXCR4 expression is associated with poor prognosis in AML patients and the interaction between CXCR4 and CXCR12 is critical for the survival and retention of AML cells within the BM niche [65]. CXCR4 up-regulation is associated with increased

migration and G0-G1 arrest and survival in LSCs of CML [66]. CXCR4/CXCL12 neutralizing antibodies, CXCR4 antagonist such as plerixafor and AMD3465 were developed for leukemia therapy. Pretreatment of primary human AML cells with neutralizing CXCR4 antibodies or CXCR4 inhibitors blocked AML cell homing to the BM niche in transplanted NOD/SCID mice [65-68]. Recently, researchers found that LSCs can metabolically adapted to adipose tissue niche to evade chemotherapy, which suggested another promising target for LSCs treatment [69]. Autocrine signals are critical for stemness maintenance. Recently, Gu et al. have shown that HSC secreted exosomes promote HSC maintenance and leukemogenesis via VPS33B mediated GDI2/RAB11A/RAB27A pathway [70]. Overall, current understanding of LSC maintenance mechanisms provides us with opportunities to integrate our theoretical achievements to LSC treatment in pre-clinical practice.

Targeting LSCs by nanomedicine

Recently, nanomaterials, devices within 100 nanometers, have been used in medical research such as drug delivery and biosensor imaging, which are called Nanomedicine [71,72]. In this section, we will discuss how nanomaterial based drug delivery system, nanocarriers, is used in cancer treatment and its potential application in LSCs targeting.

Chemical drugs used in cancer chemotherapy often have less water solubility and targeting specificity [73]. Compare to traditional drug incorporation system, Nanomedicine based drug deliver can easily cross tight epithelial and endothelial barriers with better targeting specificities and less side effects. Nanomedicine can also help to increase drug stability and solubility, with controlled drug releasing and improved delivery capacities. All these can be helpful for improving current therapeutic strategies in multiple disease treatments [6,74]. For example, Layer-by-Layer (LbL) Nanocarriers can selectively target tumor by recognizing hypoxic tumor PH and hualuronan modification can recognize CD44 [75], a CSC surface markers. Thus, hualuronan modified LbL Nanocarriers significantly increased their tumor targeting efficiency [76]. Furthermore, Nanocarrier system has enhanced drug stability *in vivo*, because these nanomaterial capsules have improved biocompatibility, which can protect chemical drugs from degradation and clearance. For example, nanocarriers coated with PEG (polyethylene glycol), can effectively repress the endocytosis of mononuclear phagocyte and prolong the drug retention time in blood [77]. The nanocarrier based drug delivery system is especially useful for unstable biological drugs such as siRNA and plasmid DNA. Researchers found that lipopeptide modified nanoparticles can serve as siRNA carriers for gene silencing *in vivo* with wide therapeutic index [78]. Compared to traditional viral siRNA deliver system, this Nanocarrier system has much lower biosafety risk and improved efficiency with lower cost [34,78]. As a result, the nanocarrier encapsulated drugs have much improved stability compared to free drugs which dramatically enhanced their *in vivo* cancer therapy efficacy. For example, Doxil, a liposomal based nanocarrier for doxorubicin, exhibited more than 100 times longer half-life in blood circulation than that of doxorubicin alone, which dramatically reduced cardio toxicity caused by doxorubicin treatment [79]. Furthermore, multiple nanocarriers have enhanced drug accumulation in the bulk of tumor than normal tissues such as liver, spleen and heart via enhanced permeability and retention (EPR) effect. Because tumor vessels are usually poorly aligned defective endothelial cells, lacking a smooth muscle layer and effective lymphatic drainage, which lead to abnormal molecular and fluid transport dynamics, especially for macromolecular drugs. This phenomenon is referred to the EPR effect, especially occurred in most

solid tumors [80-87]. Because of their nano scale size, the nanocarrier based drug delivery system can pass through blood-brain barrier [88,89]. Investigators found that those carriers can either open up a tight junction or undergo endocytosis to cross the blood-brain barrier, which prevents the passage of most traditional drugs [90-95].

Recently, switchable nanocarriers have been developed, in which the drug unloading is controlled by the changes of temperature, pH, light, ultrasound, or magnetic field [96,97]. These advances will significantly improve the drug deliver efficiency and specificity for cancer therapy.

Although multiple LSCs targeting strategies have been developed, the way of efficiently delivering drug *in vivo* is still challenging. Therefore, Nanomedicine provides a great opportunity for CSC and LSC targeting in pre-clinic applications. CD44, a major receptor for Hyaluronan (HA), is highly expressed in CSCs and LSCs. Therefore, the HA/CD44 interaction can serve as a potential target for CSC and LSC targeting therapy [98,99]. HA incorporated nanocarriers can deliver traditional chemotherapeutic drugs, such as doxorubicin and cyclosporine, to successfully target CD44 expressing CSCs both *in vitro* and *in vivo* [75]. This Nanomedicine based CSC targeting strategies have achieved prolonged survival in multiple animal cancer models including AML [76, 100-103]. Antibody incorporated nanocarriers have also been used for CSC targeting. For example, anti-CD133 incorporated nanocarrier can deliver paclitaxel to destroy liver CSCs in animal models [104,105]. Interesting, some nanomaterials have high CSC affinity although the potential mechanisms are unclear. For example, graphene oxide can selectively induce CSC differentiation by inhibiting multiple key pathways for CSC self-renewal including WNT, Notch and STAT-signaling. Since graphene oxide is non-toxic, this therapeutic strategy is promising for CSC eradication [106]. The metallofullerenol nanomaterial, Gd@C82(OH)22, can block epithelial-to-mesenchymal transition with resultant efficient elimination of breast CSCs, potentially through a bi-potent inhibition of HIF-1 α and TGF- β activities [107].

Besides traditional chemotherapy, Nanomedicine can also improve the therapeutic efficiency of recent developed cancer treatment strategies such as hyperthermia therapy and Photodynamic Therapy (PDT). For example, gold-coated nanoshells can increase the sensitivity of CSCs to hyperthermia therapy in breast cancer xenograft model [108-110]. Barth et al. reported Calcium Phosphosilicate Nanoparticles (CPSNPs) can encapsulate nearinfrared fluoroprobe Indocyanine Green (ICG) for diagnostic imaging and drug delivery. For LSC targeting, ICG-CPSNPs reacted with antibodies to target CD117 or CD96 expressing LSCs. They found that their nanocomplexes accumulated in LSCs, dramatically improved PDT efficacy and resulted in 29% disease-free survival in mouse leukemia model [111].

Taking advantage of the protective role of nanorriers, unstable nucleotide drugs, such as siRNAs and miRNAs, can be applied for *in vivo* cancer treatment. siRNA has been considered as one of the most promising candidate for gene therapy in cancer treatment, however their instability significantly limited their clinical applications [112]. Recently, Dorrance et al. have successfully delivered antagomiR-126 into AML mouse models by using nanocarrier, in which LSCs were depleted [113]. Another advantage of nanocarrier based delivery system is that it can transport multiple drugs simultaneously. Palamà et al. have shown that nanocarriers can deliver Imatinibmesylate and doxorubicin simultaneously into CML cells. Such combo treatment achieved much improved efficacy than single drug treatment [114].

Future Perspective

Nanomedicine based LSC targeting strategies have opened a novel avenue for leukemia treatment. Nanocarriers can specifically deliver traditional chemotherapeutic drugs and gene therapy drugs such as siRNA and even Crip-Cas9 gene editing tools into LSCs. The accomplishment of these strategies will significantly reduce the risk of leukemia recurrence. Several research directions need to be further explored by us to achieve this ultimate goal.

The first aim is to distinguish normal HSCs with LSCs. Although in previous studies, LSCs are thought to share the similar cell surface markers and intrinsic regulatory signals with normal HSCs. Recent studies have uncovered several key signals that can distinguish LSCs with normal HSCs [115]. Those cell surface markers such as CD44 and CD133, and intrinsic molecules, like PTEN and β -catenin can be used as potential drug targets for LSC targeting therapy. In the future, how to develop better strategies to target these candidates would be critical, fortunately Nanomedicine has already shown its promising applicable prospects.

The second aim is to improve the *in vivo* targeting efficiency. Although accumulating studies have discovered critical drug targets for CSC self-renewal regulation, the complete cure of the cancer has not been achieved. The main reason is that most drugs, especially those unstable chemical drugs, cannot be efficiently delivered into tumor. To compromise the instability issue, physicians have to increase the drug dosage, which unfortunately leads to enhanced cytotoxicity to normal tissues in cancer patients. Therefore, nanocarriers provide one of the best solutions to solve this issue, which may remarkably improve cancer treatment in the near future.

The third aim is to improve the biological drug treatment efficiency. Biological drugs, such as special peptides, miRNA and siRNA, have been proved with great advantage for cancer treatment. However, their limited stability hindered their clinical applications. Recently several nanocarriers have shown promising results in biological drug delivery *in vivo* (Figure1) [113,116].

Overall, LSCs studies have discovered increasing LSC targeting candidates with great clinical potential. How to efficiently target those candidates for improving cancer treatment would be critical. Currently, Nanomedicine has been proved with promising success in CSC and LSC targeting treatments.

Author Contributions

XH wrote the manuscript. XK and MZ provided critical comments and revised the manuscript.

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