Immune Biology of Acute Myeloid Leukemia: Implications for Immunotherapy

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INTRODUCTION

Immune surveillance of incipient tumor cells is important for defense against cancer development. However, active immune evasion is a cancer hallmark.[1] In acute myeloid leukemia (AML), a complex hematologic malignancy, AML blasts and leukemic stem cells (LSCs) evade and suppress host immune systems. Traditional AML therapies, such as allogeneic hematopoietic stem cell (HSC) transplantation (allo-HSCT) and donor lymphocyte infusions (DLIs), rely on T-cell–mediated effects, demonstrating AML cell sensitivity to functional immune cell cytotoxicity.[2,3] These observations support immunotherapy to evoke anti-AML immunity.

Clinical translation and AML immunotherapy development have been relatively slow. Intrinsic AML features complicate translation from basic immunobiology to effective immunotherapy. First, AML is not a single disease, but a family of unique malignancies; thus, genetic/epigenetic heterogeneity[4,5] and subclonality[6] contribute to biologic variation. Second, AML has two main compartments: peripheral blood (PB) and bone marrow (BM). BM is composed of endothelial cells, stromal cells (eg, mesenchymal stromal/stem cells [MSCs]), and most immune cell types, including cytotoxic T lymphocytes (CTLs), regulatory T cells (Tregs), natural killer (NK) cells, and myeloid subsets (eg, myeloid-derived suppressor cells [MDSCs]).[7] Global changes in BM immune cell profiles are associated with AML microenvironment immunosuppression.[8] Furthermore, the microenvironment protects LSCs, potential drivers of relapse, from treatment- or immune-mediated destruction.[9,10]

Increased knowledge of AML immune escape is needed to translate immunotherapy from bench to bedside. To date, a systematic analysis of basic science addressing this fundamental gap is lacking. We conducted this review to identify knowledge gaps and opportunities for AML immunotherapy development.

IMMUNE EVASION/SUPPRESSION IN AML

Mechanisms by Which AML Cells Form the Basis of Defective Immune Responses

AML cells evade or suppress the immune system through five main mechanisms: reduced expression of major histocompatibility complex (MHC) molecules, enhanced inhibitory ligand expression, reduced activating ligand/receptor expression, ligand shedding, and manipulation of soluble factors within the microenvironment (Fig 1).[2,7,11] Genetic mutation or immuno-editing reduces expression of HLA class II molecules and regulators required for T-cell AML recognition. Because endogenous or allogeneic immune cells eliminate high HLA/MHC-expressing cancerous cells, those with reduced or lost expression survive.[2,12] Without immunostimulation, little evidence exists of endogenous T-cell responses against AML. Reduced or lost HLA/MHC expression is predominantly observed after allo-HSCT.[13,14] In a study comparing samples from patients with AML obtained at diagnosis and relapse post–allo-HSCT, AML cells showed decreased expression of MHC class II proteins after transplantation in 17 of 34 patients. Interferon gamma (IFN-γ) administration reversed this downregulation, suggesting an epigenetic mechanism.[14] Another study of AML posttransplantation relapse samples reported transcriptional silencing of HLA class II molecules.[15] These findings suggest epigenetic mechanisms of immuno-editing may reduce HLA/MHC expression after allo-HSCT. Defective processing and loading of leukemia-associated antigens onto HLA class II proteins may also contribute to immune escape.[16]

Immune checkpoint pathways inhibit T- or NK-cell function. Enhanced expression of ligands for T-cell–regulating checkpoints, including cytotoxic T-lymphocyte antigen-4 (CTLA-4; surface protein expression),[17] programmed cell death protein 1 (PD-1; RNA and surface protein expression),[15,18] B7-H3 (surface protein expression),[19] and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3; RNA and surface protein expression)[20] were reported in AML and correlated with inferior outcomes.[21-23] In AML, the most extensively studied immune checkpoint pathway is PD-1/programmed death-ligand 1 (PD-L1). Several studies found absent or restricted surface protein expression of PD-L1 in de novo AML, but increased expression at relapse.[24-26] PD-L1 expression on AML blasts during disease progression could be adaptive for antitumor immunity and the associated inflamed microenvironment.[7] Supporting this hypothesis, ex vivo addition of IFN-γ and interleukin-6,

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CONTEXT

Key Objective

What are the current data and gaps in knowledge regarding the immune biology of AML, and what are the opportunities for translational research?

Knowledge Generated

Current data highlight the potential role for immunotherapy in AML. Gaps in knowledge include limited studies on the AML immune landscape and leukemic stem cell–specific mechanisms of immune escape, and lack of consensus in defining the AML tumor microenvironment.

Relevance

Addressing these knowledge gaps in AML immunobiology may translate to faster clinical development of immunotherapies for patients with AML.

inflammatory cytokines associated with activated T cells, upregulated PD-L1 on AML blasts.[24-26]

Downregulation of NK-cell receptor DNAX accessory molecule-1 (DNAM-1)[27] and NK group 2D ligand (NKG2DL), the ligand for the NK-cell immunostimulatory receptor NKG2D,[11] are potential AML mechanisms of NK-cell evasion. Although DNAM-1 cross-linking with its ligands on AML cells (CD112 and CD155) results in NK-cell–mediated killing, chronic cross-linking downregulates DNAM-1. Additionally, AML cells lacking NKG2DL because of intrinsically low expression,[28] ligand shedding,[29] and/or epigenetic silencing[30] escape NK cells.[11,28,31] Along with expressing immune checkpoint ligands, AML cells secrete or shed soluble factors, receptors, and ligands into the microenvironment to create an immunosuppressive milieu as summarized in Table 1.

Defective Immune Responses Created by AML Cells Foster an Immunosuppressive Microenvironment: Clinical Translation Opportunities

AML cell interactions with the immune system create an immunosuppressive microenvironment with reductions in population and/or function of CTLs and NK cells and accumulation of Tregs, macrophages, and MDSCs. This is significant because AML LSCs preferentially reside in BM where they are protected from the immune system.

LSC-specific mechanisms of immune escape. AML LSCs, or leukemia-initiating cells, were discovered in xenotransplantation experiments.[42,43] LSCs are capable of self-renewal and give rise to more differentiated bulk blast cells.[44] Analyses of LSC populations show that they are generally quiescent,[45] are chemotherapy resistant,[46] and evade immunosurveillance.[28,47] AML LSCs have elevated expression levels of CD47, a ligand for signal regulatory protein alpha located on macrophages and some dendritic cells (DCs). Activation via CD47 ligation inhibits phagocytosis. Thus, increased CD47 on LSCs enables evasion from macrophage-mediated phagocytosis.[47] Promising preclinical data showed that an anti-CD47 monoclonal antibody (mAb) induced macrophage-mediated phagocytosis of AML cells.[48] AML LSCs lack NKG2DL, resulting in escape from NK-cell–mediated lysis.[28] Poly(ADP-ribose) polymerase 1 (PARP1) is enriched in NKG2DL-negative AML cells, providing a possible therapeutic target for this population.[28]

A bioinformatics approach identified two LSC-specific immunosuppressive targets, galectin-1 and CD200, with enhanced expression on LSCs compared with normal HSCs.[49,50] CD200 positivity was associated with reduced immune-specific apoptosis and downregulation of inflammatory immune response-associated genes in AML cell lines.[50]

Clinical translation. These studies provide candidate targets for immune-mediated eradication of AML LSCs. Some LSC-directed agents are already under investigation. An anti-CD47 mAb is being evaluated in clinical trials for patients with relapsed/refractory AML (ClinicalTrials.gov identifiers: NCT02678338, NCT03248479).[51] A CD47×CD33 bispecific antibody (bsAb) is also being evaluated preclinically.[51]

In patient xenograft models, PARP1 inhibition induced NKG2DL expression on LSCs, sensitizing them to NK-cell–mediated clearance.[28] Another promising approach is disruption of AML-niche interactions (eg, E-selectin inhibition[52]) to free LSCs from the microenvironment and render them more vulnerable to immunosurveillance.

AML microenvironment: T-cell repertoire. Although spontaneous T-cell reactivity against defined AML antigens has been described,[53] no consensus has emerged regarding number, distribution, and functional status of T cells in the AML microenvironment (Table 2).[7] The contrasting findings may reflect underlying biologic differences between assessed AML compartments (PB or BM), disease heterogeneity, disease stage, prior therapy effects, limited patients evaluated, and/or patient differences.[7,54-56]

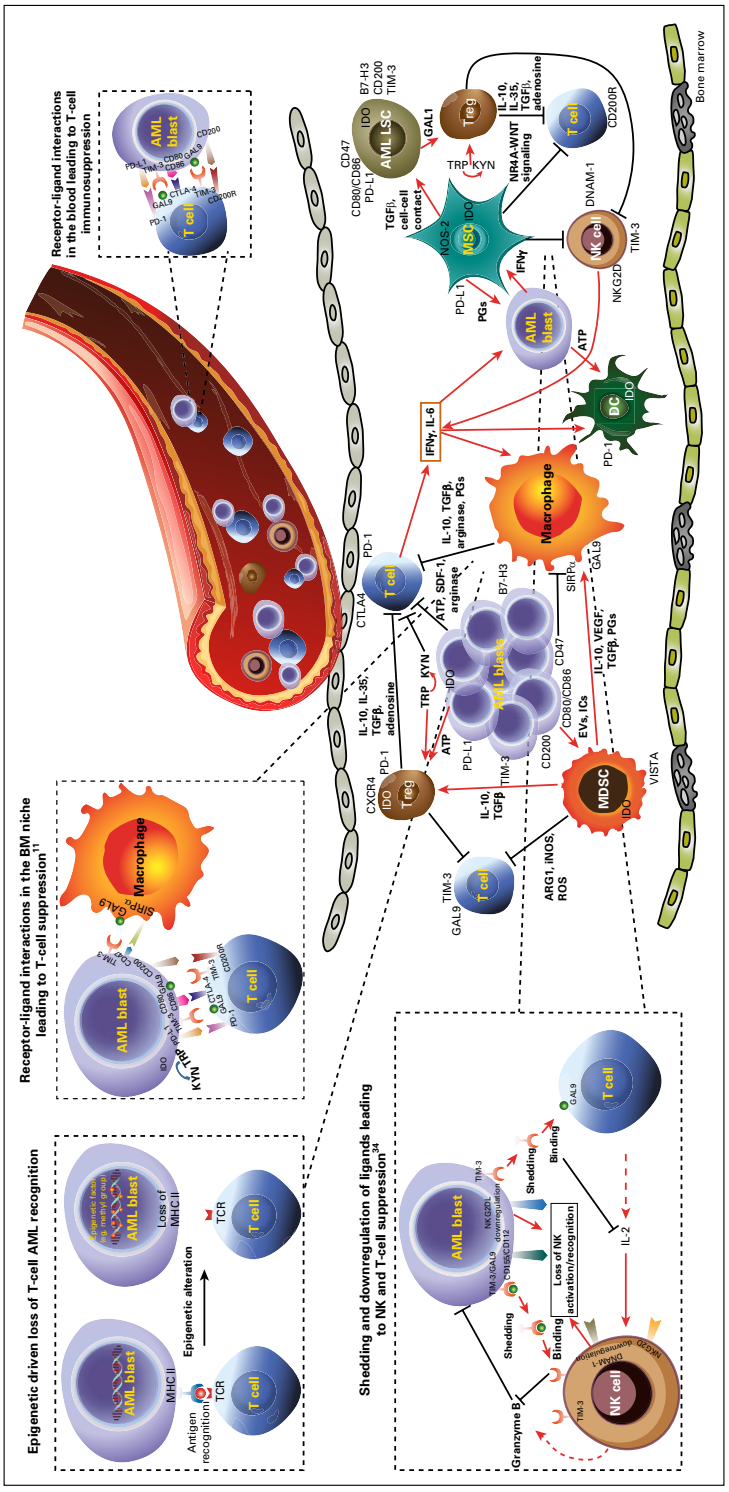

FIG 1. Cellular and molecular mechanisms of immune evasion in acute myeloid leukemia (AML) in the vascular and bone marrow microenvironments.[11,34] Cells that inhibit anti-AML immune function include regulatory T cells (Tregs), myeloid-derived suppressor cell (MDSCs), and mesenchymal stromal cells (MSCs). On the molecular level, activation of immune checkpoint pathways (eg, programmed death receptor-1 [PD-1], cytotoxic T-lymphocyte–associated protein 4 [CTLA-4]) and induction of immunosuppressive soluble factors (eg, kynurenine) by AML tumor microenvironment (TME) interactions fosters immune escape in AML. Additionally, under the pressure of allogeneic T cells, immuno-editing driven by epigenetic mechanisms may result in down-regulation of major histocompatibility complex (MHC) expression on AML cells, leading to immune escape and relapse in AML. ATP, adenosine triphosphate; CCR4, C-C chemokine receptor type 4; GAL9, galectin-9; IDO, indoleamine-2,3 dioxygenase; IFN-γ, interferon gamma; IL, interleukin; iNOS, inducible nitric oxide synthase; LSC, leukemic stem cell; MPS, metalloproteinases; NK, natural killer; NOS-2, nitric oxide synthase 2; ROS, reactive oxygen species; SDF1, stromal cell-derived factor 1; SIRPα, signal regulatory protein alpha; TCR, T-cell receptor; TGFβ, transforming growth factor beta; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; VEGF, vascular endothelial growth factor; VISTA, V-domain immunoglobulin suppressor of T-cell activation.

TABLE 1. Effects of Select Molecules Secreted or Shed by AML Cells on the Immune System

Name of Molecule	Effect of Molecule on the Immune System
Galectin-9/TIM-3	Myeloid cell lines and primary human AML cells (including LSCs) overexpress immune checkpoint TIM-3 and its ligand galectin-9 compared with normal hematopoietic stem and progenitor cells,[20,32-34] resulting in increased blood plasma levels of galectin-9 and soluble TIM-3[34]
	Galectin-9 inhibited NK-cell–mediated killing of AML cells by binding to TIM-3 on NK cells and blocking granzyme B transfer to AML cells[34]
	Soluble TIM-3 reduced the production and release of interleukin-2 from T cells, thereby preventing NK-cell and CTL activation[34]
Arginase II	AML cells secreted high levels of enzymatically active arginase II in culture medium, which mediated the inhibition of T-cell proliferation[35]
	The plasma of patients with newly diagnosed AML was found to have higher levels of arginase II compared with healthy donors. AML plasma inhibited T-cell proliferation, and this inhibition was reversed with arginase inhibition or arginine replacement[35]
	AML blasts promoted monocyte polarization into a T-cell suppressive M2 phenotype in an arginase-dependent manner[35]
IDO1	Tryptophan depletion and kynurenine production associated with IDO1 have been found to reduce proliferation and differentiation of T cells, increase levels of Tregs, and disrupt NK-cell activity[7,36]
	Constitutive expression of IDO protein in AML cells but not normal hematopoietic BM cells has been reported,[37] with higher expression levels correlating with poorer patient outcomes.[7,23,38,39]
SDF1	SDF1 secretion by AML cells induced CTL migration away from AML cells on coculture[40]
	In vivo, this mechanism may hamper CTL infiltration into the BM, fostering AML immune evasion
ATP	In vitro, ATP release from chemotherapy-treated dying AML cells was associated with the generation of PD-1– and IDO1-overexpressing Tregs and dendritic cells, respectively[41]

Abbreviations: AML, acute myeloid leukemia; ATP, adenosine triphosphate; BM, bone marrow; CTL, cytotoxic T cell; IDO, indoleamine 2,3-dioxygenase; LSC, leukemic stem cell; NK, natural killer; PD-1, programmed cell death protein 1; SDF1, stromal-derived factor 1; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; Tregs, regulatory T cells.

Increased inhibitory checkpoint molecule expression is consistently found on BM T cells[55,57-59]; however, the timing of increase (diagnosis or relapse) is unclear.[55,58,60] It is also unclear whether this reflects T-cell exhaustion or a population shift to differentiated effector T cells.[8,55,60]

In AML, Tregs dampen effector cell activity via secretion of cytokines and adenosine and increased adenosine triphosphate hydrolysis.[7,11] Higher PB and BM Treg frequencies were reported in patients with AML versus healthy controls, possibly because of increased indoleamine 2,3-dioxygenase 1 (IDO1) expression.[54,55,61] In AML, Tregs may preferentially accumulate in BM because of CXCL12/CXCR4 signaling.[7,62,63] Higher BM Treg frequencies were observed at diagnosis, with additional increases at relapse, suggesting Treg induction is an early event that is further modulated by the immunosuppressive AML microenvironment.[55]

Clinical translation. Functional T cells appear to infiltrate the AML microenvironment, but their efficacy is limited by immunosuppressive factors, including Tregs, impaired antigen recognition, and upregulation of immune checkpoints. Some therapies target immunosuppressive factors (eg, IDO1), whereas others are T-cell directed. Several immunotherapies have been developed to overcome AML immune evasion of T cells (Table 3).

Peptide- and cell-based vaccines induce expansion of AML-specific T cells via tumor-associated antigen recognition.[53,81] In a phase II study of patients with AML in first complete remission (CR) treated with a Wilms tumor 1 peptide vaccine (n = 22), 64% had an immunologic response, and median disease-free survival since first CR was 16.9 months; the vaccine was well tolerated.[82] Promising data were also reported in trials of DC-based vaccines and patient-derived AML cell vaccines, with some patients achieving prolonged remission.[51,83]

Although checkpoint inhibitors (CPIs) targeting PD-1 and CTLA-4 have been approved for various solid tumors, the activity of these inhibitors in AML seems to be relatively less potent based on available data. In a phase Ib study of ipilimumab (anti–CTLA-4) 10 mg/kg in patients with hematologic malignancies relapsing post–allo-HSCT (n = 22), the CR rate was 23% (AML, n = 4; myelodysplastic syndrome [MDS], n = 1). Immune-related adverse events and graft-versus-host disease were reported.[84] In a phase II study, patients with relapsed/refractory AML (n = 70) were treated with nivolumab (anti-PD-1) plus azacitidine. The rate of CR/CR with incomplete hematologic recovery (CRi) was 22%. Overall, the combination was safe, although immune-related toxicities were reported.[66] CPIs targeting other molecules are also under investigation.[51]

An antibody platform recently developed is the bsAb/antibody construct, which includes bispecific T-cell engager (BiTE) molecules and dual-affinity retargeting antibodies. BsAbs bind CD3 receptors on an endogenous T cell and a target antigen on a malignant cell. Simultaneous binding results in a cytolytic synapse with consequent lysis of the

TABLE 2. Studies of the T-Cell Repertoire and Function in AML

Reference	No. of Patients With AML Assessed	Technique(s) for Assessing T Cells	Compartment (PB or BM)	Patient Population	AML Treatment(s) Received (if any)	Main Finding(s)
Van Galen[54]	15	IHC	BM	AML	Not reported	Fewer T cells and CTLs for patients with AML *v* normal individuals (n = 15)
						Reduced CTL:T-cell ratio for patients with AML *v* normal individuals
						Increased proportion of Tregs for patients with AML *v* normal individuals
Williams[55]	107	IHC	BM	Newly diagnosed and relapsed/ refractory AML	Patients received different modalities of treatment, such as HMA-based, cytotoxic, targeted therapies, and investigational therapies	Comparable CD3+ T-cell infiltration in BM of relapsed/refractory AML (n = 13) *v* age-matched HD (n = 14)
		MFC (on BMAs)				Comparable CD8+ T-cell subset (HD *v* newly diagnosed AML [n = 39] *v* relapsed AML [n = 68]: 19.1% *v* 27.9% *v* 26.4%; *P* = .3)
						Increased proportion of Tregs (HD *v* newly diagnosed AML [n = 39] *v* relapsed AML [n = 68]: 1.7% *v* 2.1% *v* 3%; *P* = .02)
Le Dieu[56]	10-36	Flow cytometry (cell quantification)	PB	Newly diagnosed AML	N/A	Increase in the absolute number of PB (but not BM) T cells in AML (n = 36) compared with age-matched healthy controls (n = 17)
		Cell conjugation assays (immune synapse)				Both AML blasts and T cells from patients with AML exhibited impaired immune synapse formation in 10 independent experiments
		Microarray + qRT-PCR (gene expression)				Aberrant gene expression profile in AML (n = 10) *v* healthy control (n = 10); pathway analysis did not reveal specific affected pathways
Schnorfeil[60]	15-22	Immunophenotyping	PB and BM	Newly diagnosed and relapsed AML	Intensive chemotherapy or allogeneic SCT	Similar expression of inhibitory molecules on PB T cells for newly diagnosed AML *v* age-matched healthy controls
		Proliferation and cytokine production assays				Increased PD-1 expression on PB and BM T cells at posttransplantation relapse compared with diagnosis, which correlated with an increased proportion of effector memory T cells
						No proliferation defect in PB T cells for any group of patients with AML (n = 15) compared with healthy controls (n = 8)
						No cytokine (IFN-γ, TNF-α, IL-2) secretion impairment in PB T cells from any group of patients with AML (n = 22) compared with healthy controls (n = 20), except for reduced IFN-γ production of CD4+ T cells in newly diagnosed AML

(continued on following page)

TABLE 2. Studies of the T-Cell Repertoire and Function in AML (continued)

Reference	No. of Patients With AML Assessed	Technique(s) for Assessing T Cells	Compartment (PB or BM)	Patient Population	AML Treatment(s) Received (if any)	Main Finding(s)
Craddock[59]	AML (n = 24); MDS (n = 5)	Flow cytometry	PB	Relapsed AML or MDS after allo-SCT	Salvage therapy with lenalidomide and azacitidine at relapse after allo-SCT	Before lenalidomide/azacitidine therapy and compared with T cells from healthy donors, patient T cells were reduced in number, had an exhausted phenotype, and released fewer cytokines
						Among patients with a clinical response to salvage therapy (n = 7), no significant changes were observed in T-cell frequency, exhaustion phenotype, or cytokine profile after six cycles of salvage therapy

Abbreviations: AML, acute myeloid leukemia; BM, bone marrow; BMA, bone marrow aspirate; CTL, cytotoxic T cell; HD, healthy donor; HMA, hypomethylating agent; IFN, interferon; IHC, immunohistochemistry; IL, interleukin; MDS, myelodysplastic syndrome; MFC, multiparameter flow cytometry; N/A, not applicable; PB, peripheral blood; PD-1, programmed cell death protein 1; qRT-PCR, quantitative reverse-transcription polymerase chain reaction; SCT, stem cell transplantation; TNF, tumor necrosis factor; Tregs, regulatory T cells.

cancer cell. BsAb treatment was clinically validated for patients with B-cell precursor acute lymphoblastic leukemia (ALL).[85] In AML, bsAbs demonstrated promising antileukemic activity (including CRs) in phase I studies, supporting their potential role in this disease.[86-88] Their targets are primarily CD123, CD33, CLL1 (CLEC12A), and FLT3.

Adoptive transfer of T cells is another method of T-cell–mediated immunotherapy. Chimeric antigen receptor (CAR) T cells are modified T cells that express receptors engineered to engage target antigens on malignant cells[68] in an MHC-independent manner. CAR T-cell therapy has revolutionized treatment of hematologic malignances such as ALL and non-Hodgkin lymphoma. Translation to AML has been slower, with only early-phase data in small populations.[51,68] Slow uptake of CAR T-cell therapy reflects several challenges associated with this strategy in AML (Table 3). Alternative approaches, such as CAR NK cells and T-cell receptor (TCR) gene therapy, are being evaluated.[51,89] Activation of immunoregulatory checkpoints can hamper the efficacy of T-cell adoptive immunotherapy, and lack of costimulation is a TCR gene therapy limitation.[90] Studies to improve clinical translation of T-cell adoptive immunotherapy and TCR gene therapy are ongoing.[90] A phase I/II study of patients with high-risk relapsed AML, MDS, or chronic myelogenous leukemia previously treated with allo-HSCT is underway (ClinicalTrials.gov identifier: NCT01640301).

AML Microenvironment: NK Cells. NK cells from patients with AML often present with an unfavorable phenotype, including downregulation of natural cytotoxicity receptors,[31] reduced capacity to produce and secrete IFN-γ, and inhibited activity via Tregs and soluble factors in the microenvironment.

Clinical translation. Although AML cells are sensitive to NK-cell–mediated cytotoxicity, the immunosuppressive microenvironment fosters immune escape. Several strategies have been developed to overcome immune evasion of NK-cell surveillance.

Fragment crystallizable (Fc)-optimized antibodies are mAbs where the Fc region has been engineered to optimize therapeutic activity. In a recent phase Ib trial, an anti-CD33 Fc-optimized mAb (BI 836858) with azacitidine was evaluated in patients with previously untreated AML (n = 31). The combination demonstrated acceptable tolerability and was active, with five of 28 evaluable patients having CR/CRi.[91] Coengagement of AML target cells via CD33 and NK cells via CD16 through bispecific/trispecific killer cell engager antibodies are also promising strategies to enhance AML-specific targeting by NK cells.[51,92] Bispecific fusion proteins targeting NKG2DL on AML cells to activate NK cells are under investigation.[93]

NK-cell–mediated killing of cancer cells is not MHC presentation dependent. NK cells can be donor-derived haploidentical and transferred in conjunction with haploidentical transplantation. Promising efficacy and safety from phase I AML trials have been observed.[51]

AML microenvironment: Immunosuppressive MDSCs and macrophages. MDSCs, heterogeneous CD33+ immature myeloid cells, act as a major immunosuppressive factor, and MDSC expansion is linked with poor outcomes.[94,95] MDSCs exert their immunosuppressive activity via arginase-1, inducible nitric oxide synthase expression, and NOX2-derived reactive oxygen species (ROS) production.[96,97] Although the AML MDSC immunobiology is not well understood,[7] evidence suggests MDSCs accumulate in the AML microenvironment, contribute to immunosuppression, and could be immunotherapy targets.

TABLE 3. T-Cell–Directed Treatment Strategies in AML: Advantages and Limitations

Therapy Type/Strategy	Advantages	Challenges/Limitations	Strategies to Overcome Challenges/Limitations
Vaccine	Target antigen specificity Reduced off-target effects More favorable safety profile[51]	Depends on endogenous T-cell functionality, which may be impaired because of immunosuppressive microenvironments[7]	Combination approaches: vaccine + epigenetic agent[64] or CPI[7]
CPI	More widely studied compared with other cancer immunotherapies	Potentially serious immune-related toxicities[65]	Combination approaches: CPI plus epigenetic agent[66] or triplet combination with CXCR4 inhibition and chemotherapy (preclinical)[67]
	Actionable mutation is not required for their efficacy (may be useful in poor-risk AML)[65]	Limited single-agent activity[65]	
		Low mutation burden (CPI efficacy positively correlated with tumor mutation burden)[65]	
		May be less effective in immunologically "cold" or "immune-depleted" tumors[65]	
CAR T cells	Demonstrated success in other hematologic malignancies (eg, ALL, NHL)	Suitable antigen selection: candidate AML antigens also expressed on normal hematopoietic stem and progenitor cells with risk for myeloablation[68]	Identification of optimal antigen(s) and strategies to mitigate toxicity[68]
	MHC independent	Safety: CRS, neurotoxicity[51]	Conditional targeting and dual targeting[69]
		Logistics: complex, time-consuming, and expensive process of genetic modification and expansion of T cells	Adjunctive targeting of arginase activity[70]
		Mostly used as bridge to transplantation strategy when majority of patients need a treatment strategy to avoid transplantation	Preferential targeting of AML cells through the use of nanobodies[72]
		Low arginine microenvironment impairs CAR T-cell function and expansion[70]	Combine targeting of lineage-specific antigens overexpressed on AML cells with transplantation of gene-edited HSPCs lacking the target antigen[73]
		Lack of efficacy observed in early-stage human studies despite promising preclinical rationale[71]	
CD3 bispecific antibodies/ antibody constructs	Not affected by T-cell receptor activity, MHC presentation, or costimulation[74,75]	Depends on endogenous T-cell functionality	Combination approaches: bsAb + CPI,[78,79] epigenetic therapy (preclinical)[75]
	Use endogenous T cells (ie, overcome logistic challenges associated with ex vivo T-cell modification); off-the-shelf product[76]	Convenience: some current constructs require continuous infusion of the agent because of rapid clearance	CiTE molecule development[80]
	May be less sensitive than other therapies (eg, mAbs) to mechanisms of AML drug resistance[75]	Safety: CRS[77]	Preferential targeting of AML cells through the use of nanobodies[72]

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; bsAb, bispecific antibody; CAR, chimeric antigen receptor; CiTE, checkpoint inhibitory T-cell engaging; CPI, checkpoint inhibitor; CRS, cytokine release syndrome; HSPC, hematopoietic stem and progenitor cells; mAb, monoclonal antibody; MHC, major histocompatibility complex; NHL, non-Hodgkin lymphoma.

One study found increased BM MDSC frequencies in patients with active AML versus normal controls; engraftment of mice with AML led to MDSC expansion in BM and spleen.[97] Two other studies found increased BM and PB MDSC frequencies in newly diagnosed AML versus controls,[98,99] suggesting MDSC expansion occurs early. Interactions between AML cells and the microenvironment likely play a role. In one study, AML cells released c-myc–containing extracellular vesicles that trafficked to myeloid accessory cells in the BM microenvironment, resulting in MUC1-mediated upregulation of proproliferative cyclins E1 and D2 in MDSCs.[97]

MDSCs inhibit T-cell proliferation.[78,97,98] One study found this inhibition was partially mediated by immune checkpoint V-domain immunoglobulin suppressor of T-cell activation (VISTA). VISTA expression was greater on MDSCs from patients with AML versus healthy controls; VISTA knockdown reduced MDSC-associated T-cell inhibition. Furthermore, the proportion of VISTA-expressing MDSCs correlated with the proportion of PD-1–expressing T cells.[98] In another study, IDO upregulation in MDSCs through cell-to-cell contact with AML blasts was observed.[78]

One study reported increased frequency of immunosuppressive M2-like macrophages in BM and spleen of patients with AML versus healthy patients.[100] AML cells also polarized nonleukemic macrophages into an

AML-supporting state and induced their proliferation and infiltration into BM of human AML mouse models.[100]

Preclinical evidence shows that immunosuppressive MDSC populations are expanded in AML, supporting evaluation of MDSC-targeted therapies. CD33-directed therapies hold promise for MDSC elimination. In ex vivo studies, CD33-directed bispecific molecules engaged T cells to MDSCs to achieve antileukemic effects and restore immune homeostasis in AML[78] and MDS.[101] Immunodepletion of MDSCs was accompanied by T-cell expansion and activation and improved hematopoiesis.[101] Gemtuzumab ozogamicin, a CD33-directed antibody-drug conjugate, restored T-cell and CAR T-cell immunity against various cancers via MDSC targeting.[102]

Clinical translation. Phase 1 studies of the BiTE AMG 330 in AML (ClinicalTrials.gov identifier: NCT02520427) and the bispecific T-cell engager AMV564 in AML (ClinicalTrials.gov identifier: NCT03144245) and MDS (ClinicalTrials.gov identifier: NCT03516591) are currently underway, and multiple trials investigating gemtuzumab ozogamicin in AML are recruiting or completed. Another strategy relies on pharmacologic blockade of ROS production, an important mechanism of MDSC immunosuppression and differentiation into macrophages and DCs. In a phase III study, postconsolidation treatment with the NOX2 inhibitor histamine dihydrochloride in combination with interleukin-2 improved leukemia-free survival versus no treatment of patients with AML in CR.[103,104] Histamine dihydrochloride significantly reduced PB MDSCs in patients with AML, with strong reductions associated with longer leukemia-free survival.[96] Other strategies for selective targeting of MDSCs in AML include MUC1 inhibition,[97,105] granulocyte colony-stimulating factor therapy,[106] and HO-1 protein inhibition[107]; these treatments may synergize with CPIs.[98,107] Association of MDSC levels with clinical outcomes is unclear, because two small studies (N = 27 and N = 6) reported a correlation with minimal residual disease (MRD)[99] or relapse, respectively,[9] whereas one large study (N = 341) did not find a statistically significant relationship with MRD.[108]

AML microenvironment: Immunosuppressive MSCs. MSCs are fundamental BM regulators, with potent immunosuppressive functions that affect innate and adaptive cellular immunity; however, relatively little is known about their effects in hematologic malignancies.[109-111] This is likely because of a lack of standardized methods for isolating and characterizing MSCs, and the heterogeneity of AML and MSCs.[110,111] Preclinical data show a dynamic interplay among MSCs, AML cells, and the immunosuppressive microenvironment (Table 4).

Clinical translation. MSCs are critical BM components, supporting long-term maintenance and quiescence of LSCs[115,116] and protecting them from anti-AML therapy.[115-117] Future immunotherapy research should consider MSC-to-AML cell cross talk in shaping the immune microenvironment. Targeting individual pathways to reduce MSC-associated immunosuppression or interfering with MSC-to-AML cell cross talk may be effective strategies.

Defining AML immune microenvironments. Tumor immune microenvironments vary substantially between patients. In solid tumors, immunologically hot versus cold tumor microenvironments may have prognostic implications for CPI therapy. However, little is known about AML microenvironment heterogeneity.

There have been several attempts to define the AML immune microenvironment. Using the Cancer Genome Atlas, a pan-cancer Tumor Inflammation Signature (TIS) was developed to characterize the immune microenvironment in a variety of cancers. TIS includes 18 genes related to abundance of antigen-presenting cells, T- and NK-cell levels, IFN activity, and T-cell exhaustion. Higher scores indicate inflamed or hot tumors that may be more recognizable by the immune system. The TIS score for patients with AML was approximately 4—lower than the median of 5.5 observed in the entire cancer dataset, indicating AML tumor microenvironments are generally cold.[117a] Another AML study investigated T-cell repertoires at diagnosis and relapse and identified a dual checkpoint-positive T-cell population (PD-1+ and TIM-3+ or LAG3+).[55] The

TABLE 4. Preclinical Studies Assessing the Role of Immunosuppressive MSCs in AML

Reference	No. of Samples From Patients With AML	Patient Population	Main Finding(s)
Mansour[61]	12	De novo AML	BM-derived MSCs from patients with AML showed higher levels of IDO expression compared with control patients, which positively correlated with Treg frequency
Ciciarello[112]	61	AML	AML cells induced an upregulation of IDO1, PD-1, and NOS-2 on cocultured MSCs via secretion of IFN-γ
Wu[113]	Not reported	FA patients with AML	MSCs derived from patients with FA secreted high levels of prostaglandins, which resulted in upregulated NR4A-WNT/β-catenin signaling, Treg induction, and CTL inhibition
Vasold[114]	5	AML	Cell-to-cell contact between MSCs and AML blasts significantly reduced NK-cell–mediated lysis of AML cells compared with no MSCs in culture

Abbreviations: AML, acute myeloid leukemia; BM, bone marrow; CTL, cytotoxic T lymphocyte; FA, Fanconi anemia; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; MSCs, mesenchymal stromal/stem cells; NK, natural killer; NOS-2, nitric oxide synthase 2; NR4A, nuclear hormone receptor 4A; PD-1, programmed cell death protein 1; Treg, regulatory T cell.

authors proposed this population demarcated two types of patients with AML: those with and those without an exhausted immune microenvironment. The proportion of double-positive T cells increased from diagnosis to relapse, indicating greater immune system exhaustion at later stages.[55] Finally, transcriptomic and proteomic profiling identified two types of immune microenvironments in AML BM samples: an immune-enriched and IFN-γ dominant type (elevated expression of lymphocyte-associated genes, IFN-γ, and immune checkpoint molecules) and an immune-depleted type (elevated expression of mast cell function– and T-cell exhaustion–associated genes, low expression of T-cell and B-cell genes).[118] The immune-enriched profile was observed in approximately 30% of patients, indicating that most AML tumors are cold.[119]

Clinical translation. Future studies evaluating AML BM heterogeneity are important for personalized immunotherapy. Agent (eg, CPIs) efficacy may be compromised by immune-depleted microenvironments, whereas hot tumors may be more susceptible to CPIs. Combination therapies incorporating CPIs may thus be more effective for tumors with immune-enriched microenvironments. Understanding how immunotherapies can modulate the microenvironment immune signature represents an additional research avenue. A preliminary study reported that treatment with a bsAb shifted the AML BM microenvironment signature to a more inflamed type as evidenced by increased immune cell infiltration, a higher TIS score, and enhanced IFN-γ signaling.[120]

Effects of standard AML therapies on the immune landscape. To deliver optimal immunotherapy to patients relapsing after allo-HSCT or chemotherapy, it is important to understand immune-related effects of these treatments. Allo-HSCT efficacy depends on an immune-mediated graft-versus-leukemia (GVL) effect to confer anti-AML alloimmunity. The GVL effect is mediated primarily by alloreactive T cells, although there is increasing recognition of alloreactive NK-cell responses and tumor-specific T-cell and antibody responses.[121] Understanding immune escape mechanisms during post–allo-HSCT relapse can inform immunotherapeutic strategies. A comprehensive study of immune signatures from patients relapsing after allo-HSCT found that significant downregulation of HLA class II transcripts commonly occurred posttransplantation and may be driven by epigenetic mechanisms.[15] The same study described another modality of relapse after allo-HSCT, which was characterized by impaired T-cell costimulation by AML blasts.[15] These effects were not observed at relapse after chemotherapy only.[15] Another study showed that compared with healthy donors, patients with AML relapsing after allo-HSCT had reduced T-cell frequencies characterized by an exhausted phenotype and altered cytokine profile.[59] These studies assessed circulating T cells but not BM-infiltrating T cells. A recent study reported early-differentiated T memory stem cells and central memory T cells from the BM of patients relapsing after allo-HSCT had an exhausted phenotype characterized by expression of multiple inhibitory receptors.[122] These findings show systemic T-cell impairment and exhaustion present at relapse after allo-HSCT.

The percentage of donor-derived T lymphocytes (chimerism) after allo-HSCT is correlated with disease outcomes, with mixed chimerism predictive of relapse and shorter survival.[123,124] Mixed chimerism via residual host Tregs and DCs may inhibit activation of donor-derived DCs and alloreactive T-cell induction.[125]

Profound immunodeficiency occurs after T-cell–depleted HLA-haploidentical allo-HSCT (hHSCT).[126] Reconstitution kinetics of various immune cell populations may be related to post-hHSCT relapse. NK cells reconstitute early post-transplantation, and their rapid recovery is associated with lower relapse risk in certain hematologic malignancies.[127] Furthermore, transplantation from NK alloreactive donors has been associated with better outcomes.[128] Another immune cell population of interest is invariant NK T (iNKT) cells. One study found that patients with hematologic malignancies who maintained remission after hHSCT had full reconstitution of iNKT cells, whereas patients who relapsed did not.[126] IFN-γ production[126] or direct killing of AML blasts in a CD1d-dependent manner[129] may explain the role of iNKT cells in maintaining antitumor immunity after allo-HSCT.

Chemotherapy affects humoral immunity to a greater degree than cellular immunity. In one study, T-cell frequency and function recovered to normal levels after consolidation chemotherapy, whereas B-cell immunity was impaired.[130]

Clinical translation. The role of chimerism is well recognized, and chimerism analysis remains an important tool to predict relapse post–allo-HSCT.[131] Several ongoing clinical trials focus on chimerism in AML post–allo-HSCT, including early detection and treatment of mixed chimerism (eg, ClinicalTrials.gov identifiers: NCT03850418, NCT03128034, NCT02724163). MRD measurements in the posttransplantation period can be performed; however, MRD monitoring remains challenging because suitable molecular markers are not available for all patients with AML.[132]

AML immune evasion mechanisms post–allo-HSCT suggest epigenetic therapies that reverse HLA expression loss may be effective for posttransplantation relapse. In the phase II RELAZA trial, azacitidine (hypomethylator) treatment of MRD post–allo-HSCT led to long-term responses in patients with MDS or AML.[133] Azacitidine combined with immune therapy (DLIs or lenalidomide) was also effective for patients with AML relapsing post–allo-HSCT.[59,134] Given impaired T-cell costimulation observed at relapse post–allo-HSCT, CPIs may be beneficial.[15] The preserved T-cell population and function after chemotherapy suggests T-cell–directed immunotherapies, such as bsAbs and CPIs, will not be compromised by prior chemotherapy.

In conclusion, AML is a complex, heterogeneous disease, and fundamental understanding of its immunobiology is critical for immunotherapy. Immune dysfunction is important for AML pathogenesis, supporting the role of immunotherapies to restore local immunity to eradicate the disease. An improved understanding of how LSCs evade the immune system and how they can be eradicated is needed. Moreover, cellular components of the AML immune microenvironment, such as MSCs and B cells, have not been well characterized. These understudied populations may have important roles to play; for example, B cells from high-risk patients with durable GVL responses produce anti-AML antibodies.[135] Standardized methods for characterizing the tumor microenvironment are important for translational development of patient-specific immunotherapies.

Allo-HSCT remains a cornerstone of immune-mediated AML therapy. Development of optimal strategies should be informed by lessons learned from allo-HSCT and the mechanisms of AML immune dysfunction. Allo-HSCT findings suggest combination therapies targeting multiple pathways and cellular effectors (including T cells and NK cells) will likely be optimal for developing alternative immunotherapeutic strategies. Post–allo-HSCT, the GVL effect enables donor immune cells to eliminate host leukemic cells by engaging a multicellular (T cells, NK cells, antibodies, antigen-presenting cells) response against multiple antigens, including leukemia-associated antigens and nonleukemia-specific antigens overexpressed in leukemia.[136,137] This broad immune response is likely important in overcoming the multiple immunosuppressive mechanisms and clonal heterogeneity observed in AML.

The implications of allo-HSCT for target identification and cellular effectors are important. Allo-HSCT can target multiple intracellular (presented by HLA) and/or surface antigens, whereas current AML therapies can only target limited surface antigens. Furthermore, although minor histocompatibility antigen-specific T cells can induce a potent GVL effect, translating this observation into AML clinical trials is difficult.[138] Prognosis for patients with relapsed/refractory AML remains suboptimal even with allo-HSCT,[139] an important consideration when investigating combination therapies in relapsed patients.

Being cognizant of optimal early- and late-phase trial design with regard to endpoints and molecular inclusion criteria is critical.[140] The allo-HSCT experience provides rationale for personalized immunotherapy based on immunologic profiles. For example, the modes of immune evasion after allo-HSCT (genomic loss of HLA *v* loss of HLA class II expression *v* T-cell exhaustion) could be targeted by distinct salvage immunotherapies.[12,15] Early-phase trial endpoints can also include dose-dependent changes in immunity and stratification of responders versus nonresponders using immune readouts. For early- and late-phase trials, biomarkers should be collected and analyzed using modern platforms (eg, immunology panels), and retrospective stratifications should be made and published regardless of outcome. Given the prognostic significance of MRD in AML and the potential for immunotherapy to eliminate LSCs, MRD-negative CR could be a useful endpoint in late-stage anti-AML immunotherapy trials. Late-stage trials can implement findings from earlier phases to better identify responder populations and develop inclusion/exclusion criteria. Additional understanding of the optimal sequencing of immunotherapies—specifically, which immunotherapies can be reserved for later lines of therapy and retain activity in patients refractory to other agents—is also important.

Overall, the gaps and opportunities highlighted in this review reiterate the importance of a strong foundation in basic immune biology that can be harnessed for clinical translation. We expect current and future advances in our knowledge of immune escape mechanisms will translate to powerful immunotherapies for patients with AML.

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REFERENCES

1. Hanahan D, Weinberg RA: Hallmarks of cancer: The next generation. Cell 144:646-674, 2011
2. Teague RM, Kline J: Immune evasion in acute myeloid leukemia: Current concepts and future directions. J Immunother Cancer 1:1, 2013
3. Orti G, Barba P, Fox L, et al: Donor lymphocyte infusions in AML and MDS: Enhancing the graft-versus-leukemia effect. Exp Hematol 48:1-11, 2017
4. Roboz GJ, Guzman M: Acute myeloid leukemia stem cells: Seek and destroy. Expert Rev Hematol 2:663-672, 2009
5. Li S, Mason CE, Melnick A: Genetic and epigenetic heterogeneity in acute myeloid leukemia. Curr Opin Genet Dev 36:100-106, 2016
6. Bodini M, Ronchini C, Giacò L, et al: The hidden genomic landscape of acute myeloid leukemia: Subclonal structure revealed by undetected mutations. Blood 125:600-605, 2015
7. Lamble AJ, Lind EF: Targeting the immune microenvironment in acute myeloid leukemia: A focus on T cell immunity. Front Oncol 8:213, 2018
8. Ito S, Barrett J, Savani BN, et al: A suppressive microenvironment in acute myeloid leukemia induces global alteration of T and NK cell profiles - evidence for immune-editing effect by leukemia. Blood 124:1047, 2014
9. Przespolewski A, Wallace PK, Cronin T, et al: Increased monocytic myeloid-derived suppressor cells in the marrow of relapsed/refractory acute myeloid leukemia patients following induction chemotherapy. Blood 132:5270, 2018 (suppl 1)
10. Fracchiolla NS, Fattizzo B, Cortelezzi A: Mesenchymal stem cells in myeloid malignancies: A focus on immune escaping and therapeutic implications. Stem Cells Int 2017:6720594, 2017
11. Austin R, Smyth MJ, Lane SW: Harnessing the immune system in acute myeloid leukaemia. Crit Rev Oncol Hematol 103:62-77, 2016
12. Zeiser R, Vago L: Mechanisms of immune escape after allogeneic hematopoietic cell transplantation. Blood 133:1290-1297, 2019
13. Vago L, Perna SK, Zanussi M, et al: Loss of mismatched HLA in leukemia after stem-cell transplantation. N Engl J Med 361:478-488, 2009
14. Christopher MJ, Petti AA, Rettig MP, et al: Immune escape of relapsed AML cells after allogeneic transplantation. N Engl J Med 379:2330-2341, 2018
15. Toffalori C, Zito L, Gambacorta V, et al: Immune signature drives leukemia escape and relapse after hematopoietic cell transplantation. Nat Med 25:603-611, 2019
16. van Luijn MM, van den Ancker W, Chamuleau ME, et al: Impaired antigen presentation in neoplasia: Basic mechanisms and implications for acute myeloid leukemia. Immunotherapy 2:85-97, 2010
17. Costello RT, Mallet F, Sainty D, et al: Regulation of CD80/B7-1 and CD86/B7-2 molecule expression in human primary acute myeloid leukemia and their role in allogenic immune recognition. Eur J Immunol 28:90-103, 1998
18. Yang H, Bueso-Ramos C, DiNardo C, et al: Expression of PD-L1, PD-L2, PD-1 and CTLA4 in myelodysplastic syndromes is enhanced by treatment with hypomethylating agents. Leukemia 28:1280-1288, 2014
19. Lichtman E, Du H, Savoldo B, et al: Pre-clinical evaluation of B7-H3-specific chimeric antigen receptor T-cells for the treatment of acute myeloid leukemia. Blood 132:701, 2018 (suppl 1)
20. Kikushige Y, Shima T, Takayanagi S, et al: TIM-3 is a promising target to selectively kill acute myeloid leukemia stem cells. Cell Stem Cell 7:708-717, 2010
21. Chen X, Liu S, Wang L, et al: Clinical significance of B7-H1 (PD-L1) expression in human acute leukemia. Cancer Biol Ther 7:622-627, 2008
22. Graf M, Reif S, Hecht K, et al: High expression of costimulatory molecules correlates with low relapse-free survival probability in acute myeloid leukemia (AML). Ann Hematol 84:287-297, 2005
23. Folgiero V, Goffredo BM, Filippini P, et al: Indoleamine 2,3-dioxygenase 1 (IDO1) activity in leukemia blasts correlates with poor outcome in childhood acute myeloid leukemia. Oncotarget 5:2052-2064, 2014
24. Berthon C, Driss V, Liu J, et al: In acute myeloid leukemia, B7-H1 (PD-L1) protection of blasts from cytotoxic T cells is induced by TLR ligands and interferon-gamma and can be reversed using MEK inhibitors. Cancer Immunol Immunother 59:1839-1849, 2010
25. Krönig H, Kremmler L, Haller B, et al: Interferon-induced programmed death-ligand 1 (PD-L1/B7-H1) expression increases on human acute myeloid leukemia blast cells during treatment. Eur J Haematol 92:195-203, 2014
26. Tamura H, Dan K, Tamada K, et al: Expression of functional B7-H2 and B7.2 costimulatory molecules and their prognostic implications in de novo acute myeloid leukemia. Clin Cancer Res 11:5708-5717, 2005
27. Sanchez-Correa B, Gayoso I, Bergua JM, et al: Decreased expression of DNAM-1 on NK cells from acute myeloid leukemia patients. Immunol Cell Biol 90: 109-115, 2012
28. Paczulla AM, Rothfelder K, Raffel S, et al: Absence of NKG2D ligands defines leukaemia stem cells and mediates their immune evasion. Nature 572:254-259, 2019 [Erratum: Nature 572: E19, 2019]
29. Salih HR, Antropius H, Gieseke F, et al: Functional expression and release of ligands for the activating immunoreceptor NKG2D in leukemia. Blood 102: 1389-1396, 2003
30. Baragaño Raneros A, Martín-Palanco V, Fernandez AF, et al: Methylation of NKG2D ligands contributes to immune system evasion in acute myeloid leukemia. Genes Immun 16:71-82, 2015
31. Lion E, Willemen Y, Berneman ZN, et al: Natural killer cell immune escape in acute myeloid leukemia. Leukemia 26:2019-2026, 2012
32. Gonçalves Silva I, Rüegg L, Gibbs BF, et al: The immune receptor Tim-3 acts as a trafficker in a Tim-3/galectin-9 autocrine loop in human myeloid leukemia cells. OncoImmunology 5:e1195535, 2016
33. Haubner S, Perna F, Köhnke T, et al: Coexpression profile of leukemic stem cell markers for combinatorial targeted therapy in AML. Leukemia 33:64-74, 2019
34. Gonçalves Silva I, Yasinska IM, Sakhnevych SS, et al: The Tim-3-galectin-9 secretory pathway is involved in the immune escape of human acute myeloid leukemia cells. EBioMedicine 22:44-57, 2017
35. Mussai F, De Santo C, Abu-Dayyeh I, et al: Acute myeloid leukemia creates an arginase-dependent immunosuppressive microenvironment. Blood 122: 749-758, 2013
36. Della Chiesa M, Carlomagno S, Frumento G, et al: The tryptophan catabolite L-kynurenine inhibits the surface expression of NKp46- and NKG2D-activating receptors and regulates NK-cell function. Blood 108:4118-4125, 2006
37. Curti A, Aluigi M, Pandolfi S, et al: Acute myeloid leukemia cells constitutively express the immunoregulatory enzyme indoleamine 2,3-dioxygenase. Leukemia 21:353-355, 2007
38. Chamuleau ME, van de Loosdrecht AA, Hess CJ, et al: High INDO (indoleamine 2,3-dioxygenase) mRNA level in blasts of acute myeloid leukemic patients predicts poor clinical outcome. Haematologica 93:1894-1898, 2008
39. Fukuno K, Hara T, Tsurumi H, et al: Expression of indoleamine 2,3-dioxygenase in leukemic cells indicates an unfavorable prognosis in acute myeloid leukemia patients with intermediate-risk cytogenetics. Leuk Lymphoma 56:1398-1405, 2015

40. Shafat MS, Abdul-Aziz AA, Marlien C, et al: Abstract 3131: Acute myeloid leukemia derived SDF1 repels tumor infiltrating lymphocytes in the bone marrow microenvironment. Cancer Res 78:3131, 2018 (suppl; abstr 3131)
41. Lecciso M, Ocadlikova D, Sangaletti S, et al: ATP release from chemotherapy-treated dying leukemia cells elicits an immune suppressive effect by increasing regulatory T cells and tolerogenic dendritic cells. Front Immunol 8:1918, 2017
42. Bonnet D, Dick JE: Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med 3:730-737, 1997
43. Lapidot T, Sirard C, Vormoor J, et al: A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature 367:645-648, 1994
44. Thomas D, Majeti R: Biology and relevance of human acute myeloid leukemia stem cells. Blood 129:1577-1585, 2017
45. Pollyea DA, Jordan CT: Therapeutic targeting of acute myeloid leukemia stem cells. Blood 129:1627-1635, 2017
46. Mabrey FL, Chien SS, Martins TS, et al: High throughput drug screening of leukemia stem cells reveals resistance to standard therapies and sensitivity to other agents in acute myeloid leukemia. Blood 132:180, 2018 (suppl 1)
47. Majeti R, Chao MP, Alizadeh AA, et al: CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. Cell 138:286-299, 2009
48. Liu J, Wang L, Zhao F, et al: Pre-clinical development of a humanized anti-CD47 antibody with anti-cancer therapeutic potential. PLoS One 10:e0137345, 2015
49. Herbrich S, Ruvolo PP, Ruvolo V, et al: Robust bioinformatics approach for identifying novel AML LSC targets: Putative role of galectin-1 in the immune-microenvironment. Blood 130:3962, 2017 (suppl 1)
50. Herbrich S, Baggerly K, Alatrash G, et al: CD200 is a stem cell-specific immunosuppressive target in AML. Blood 132:2768, 2018 (suppl 1)
51. Liu Y, Bewersdorf JP, Stahl M, et al: Immunotherapy in acute myeloid leukemia and myelodysplastic syndromes: The dawn of a new era? Blood Rev 34: 67-83, 2019
52. Rashidi A, DiPersio JF: Targeting the leukemia-stroma interaction in acute myeloid leukemia: Rationale and latest evidence. Ther Adv Hematol 7:40-51, 2016
53. Scheibenbogen C, Letsch A, Thiel E, et al: CD8 T-cell responses to Wilms tumor gene product WT1 and proteinase 3 in patients with acute myeloid leukemia. Blood 100:2132-2137, 2002
54. van Galen P, Hovestadt V, Wadsworth MH II, et al: Single-cell RNA-seq reveals AML hierarchies relevant to disease progression and immunity. Cell 176: 1265-1281.e24, 2019
55. Williams P, Basu S, Garcia-Manero G, et al: The distribution of T-cell subsets and the expression of immune checkpoint receptors and ligands in patients with newly diagnosed and relapsed acute myeloid leukemia. Cancer 125:1470-1481, 2019
56. Le Dieu R, Taussig DC, Ramsay AG, et al: Peripheral blood T cells in acute myeloid leukemia (AML) patients at diagnosis have abnormal phenotype and genotype and form defective immune synapses with AML blasts. Blood 114:3909-3916, 2009
57. Brück O, Dufva O, Blom S, et al: Quantitative multiplex immunohistochemistry identifies immunosuppression in the AML bone marrow and NK-cells as prognostic biomarker in intermediate-risk patients. Blood 132:2774, 2018 (suppl 1)
58. Willier S, Rothaemel P, Wilhelm J, et al: Bone marrow T cells are driven into exhaustion by acute leukemia in pediatric patients based on protein and transcriptome analysis. Blood 132:3722, 2018 (suppl 1)
59. Craddock C, Slade D, De Santo C, et al: Combination lenalidomide and azacitidine: A novel salvage therapy in patients who relapse after allogeneic stem-cell transplantation for acute myeloid leukemia. J Clin Oncol 37:580-588, 2019
60. Schnorfeil FM, Lichtenegger FS, Emmerig K, et al: T cells are functionally not impaired in AML: Increased PD-1 expression is only seen at time of relapse and correlates with a shift towards the memory T cell compartment. J Hematol Oncol 8:93, 2015
61. Mansour I, Zayed RA, Said F, et al: Indoleamine 2,3-dioxygenase and regulatory T cells in acute myeloid leukemia. Hematology 21:447-453, 2016
62. Shenghui Z, Yixiang H, Jianbo W, et al: Elevated frequencies of $CD4^+$ $CD25^+$ CD127lo regulatory T cells is associated to poor prognosis in patients with acute myeloid leukemia. Int J Cancer 129:1373-1381, 2011
63. Zou L, Barnett B, Safah H, et al: Bone marrow is a reservoir for CD4+CD25+ regulatory T cells that traffic through CXCL12/CXCR4 signals. Cancer Res 64: 8451-8455, 2004
64. Nahas MR, Stroopinsky D, Rosenblatt J, et al: Hypomethylating agent alters the immune microenvironment in acute myeloid leukaemia (AML) and enhances the immunogenicity of a dendritic cell/AML vaccine. Br J Haematol 185:679-690, 2019
65. Alfayez M, Borthakur G: Checkpoint inhibitors and acute myelogenous leukemia: Promises and challenges. Expert Rev Hematol 11:373-389, 2018
66. Daver N, Garcia-Manero G, Basu S, et al: Efficacy, safety, and biomarkers of response to azacitidine and nivolumab in relapsed/refractory acute myeloid leukemia: A nonrandomized, open-label, phase II study. Cancer Discov 9:370-383, 2019
67. Hwang HS, Han AR, Lee JY, et al: Enhanced anti-leukemic effects through induction of immunomodulating microenvironment by bLOCKing CXCR4 and PD-L1 in an AML mouse model. Immunol Invest 48:96-105, 2019
68. Sauer T, Rooney CM: Current challenges for CAR T-cell therapy of acute myeloid leukemia. Transfusion 59:1171-1173, 2019
69. Petrov JC, Wada M, Pinz KG, et al: Compound CAR T-cells as a double-pronged approach for treating acute myeloid leukemia. Leukemia 32:1317-1326, 2018
70. Mussai F, Wheat R, Sarrou E, et al: Targeting the arginine metabolic brake enhances immunotherapy for leukaemia. Int J Cancer 145:2201-2208, 2019
71. Baumeister SH, Murad J, Werner L, et al: Phase I trial of autologous CAR T cells targeting NKG2D ligands in patients with AML/MDS and multiple myeloma. Cancer Immunol Res 7:100-112, 2019
72. He X, Feng Z, Ma J, et al: Bispecific and split CAR T cells targeting CD13 and TIM3 eradicate acute myeloid leukemia. Blood 135:713-723, 2020
73. Borot F, Wang H, Ma Y, et al: Gene-edited stem cells enable CD33-directed immune therapy for myeloid malignancies. Proc Natl Acad Sci USA 116: 11978-11987, 2019
74. Frankel SR, Baeuerle PA: Targeting T cells to tumor cells using bispecific antibodies. Curr Opin Chem Biol 17:385-392, 2013
75. Laszlo GS, Gudgeon CJ, Harrington KH, et al: Cellular determinants for preclinical activity of a novel CD33/CD3 bispecific T-cell engager (BiTE) antibody, AMG 330, against human AML. Blood 123:554-561, 2014
76. Suryadevara CM, Gedeon PC, Sanchez-Perez L, et al: Are BiTEs the "missing link" in cancer therapy? OncoImmunology 4:e1008339, 2015
77. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al: Cytokine release syndrome. J Immunother Cancer 6:56, 2018
78. Jitschin R, Saul D, Braun M, et al: CD33/CD3-bispecific T-cell engaging (BiTE) antibody construct targets monocytic AML myeloid-derived suppressor cells. J Immunother Cancer 6:116, 2018
79. Krupka C, Kufer P, Kischel R, et al: blockade of the PD-1/PD-L1 axis augments lysis of AML cells by the CD33/CD3 BiTE antibody construct AMG 330: Reversing a T-cell-induced immune escape mechanism. Leukemia 30:484-491, 2016

80. Herrmann M, Krupka C, Deiser K, et al: Bifunctional PD-1 × αCD3 × αCD33 fusion protein reverses adaptive immune escape in acute myeloid leukemia. Blood 132:2484-2494, 2018
81. Keilholz U, Letsch A, Busse A, et al: A clinical and immunologic phase 2 trial of Wilms tumor gene product 1 (WT1) peptide vaccination in patients with AML and MDS. Blood 113:6541-6548, 2009
82. Maslak PG, Dao T, Bernal Y, et al: Phase 2 trial of a multivalent WT1 peptide vaccine (galinpepimut-S) in acute myeloid leukemia. Blood Adv 2:224-234, 2018
83. van de Loosdrecht AA, van Wetering S, Santegoets SJAM, et al: A novel allogeneic off-the-shelf dendritic cell vaccine for post-remission treatment of elderly patients with acute myeloid leukemia. Cancer Immunol Immunother 67:1505-1518, 2018
84. Davids MS, Kim HT, Bachireddy P, et al: Ipilimumab for patients with relapse after allogeneic transplantation. N Engl J Med 375:143-153, 2016
85. Curran E, Stock W: Taking a "BiTE out of ALL": Blinatumomab approval for MRD-positive ALL. Blood 133:1715-1719, 2019
86. Ravandi F, Stein AS, Kantarjian HM, et al: A phase 1 first-in-human study of AMG 330, an anti-CD33 bispecific T-cell engager (BiTE) antibody construct, in relapsed/refractory acute myeloid leukemia (R/R AML). Blood 132:25, 2018 (suppl 1)
87. Westervelt P, Roboz GJ, Cortes JE, et al: Safety and clinical activity of AMV564, a CD33/CD3 T-cell engager, in patients with relapsed/refractory acute myeloid leukemia (AML): Updated results from the phase 1 first-in-human trial. https://amphivena.com/wp-content/uploads/2019-Amphivena-presentation-S877_Safety_and_Clinical_Activity_AMV564_Roboz_EHA_2019-Presentation.pdf
88. Uy GL, Rettig MP, Vey N, et al: Phase 1 cohort expansion of flotetuzumab, a CD123×CD3 bispecific Dart protein in patients with relapsed/refractory acute myeloid leukemia (AML). Blood 132:764, 2018 (suppl 1)
89. Chapuis AG, Egan DN, Bar M, et al: T cell receptor gene therapy targeting WT1 prevents acute myeloid leukemia relapse post-transplant. Nat Med 25: 1064-1072, 2019
90. Oda SK, Daman AW, Garcia NM, et al: A CD200R-CD28 fusion protein appropriates an inhibitory signal to enhance T-cell function and therapy of murine leukemia. Blood 130:2410-2419, 2017
91. Blum W, Ruppert AS, Mims AS, et al: Phase 1b dose escalation study of BI 836858 and azacitidine in previously untreated AML: Results from Beat AML S2. Blood 132:4053, 2018 (suppl 1)
92. Duell J, Lammers PE, Djuretic I, et al: Bispecific antibodies in the treatment of hematologic malignancies. Clin Pharmacol Ther 106:781-791, 2019
93. Märklin M, Hagelstein I, Koerner SP, et al: Bispecific NKG2D-CD3 and NKG2D-CD16 fusion proteins for induction of NK and T cell reactivity against acute myeloid leukemia. J Immunother Cancer 7:143, 2019
94. Filipazzi P, Huber V, Rivoltini L: Phenotype, function and clinical implications of myeloid-derived suppressor cells in cancer patients. Cancer Immunol Immunother 61:255-263, 2012
95. Toor SM, Elkord E: Therapeutic prospects of targeting myeloid-derived suppressor cells and immune checkpoints in cancer. Immunol Cell Biol 96:888-897, 2018
96. Grauers Wiktorin H, Nilsson MS, Kiffin R, et al: Histamine targets myeloid-derived suppressor cells and improves the anti-tumor efficacy of PD-1/PD-L1 checkpoint blockade. Cancer Immunol Immunother 68:163-174, 2019
97. Pyzer AR, Stroopinsky D, Rajabi H, et al: MUC1-mediated induction of myeloid-derived suppressor cells in patients with acute myeloid leukemia. Blood 129: 1791-1801, 2017
98. Wang L, Jia B, Claxton DF, et al: VISTA is highly expressed on MDSCs and mediates an inhibition of T cell response in patients with AML. OncoImmunology 7: e1469594, 2018
99. Sun H, Li Y, Zhang ZF, et al: Increase in myeloid-derived suppressor cells (MDSCs) associated with minimal residual disease (MRD) detection in adult acute myeloid leukemia. Int J Hematol 102:579-586, 2015
100. Al-Matary YS, Botezatu L, Opalka B, et al: Acute myeloid leukemia cells polarize macrophages towards a leukemia supporting state in a growth factor independence 1 dependent manner. Haematologica 101:1216-1227, 2016
101. Cheng P, Eksioglu E, Chen X, et al: Immunodepletion of MDSC by AMV564, a novel tetravalent bispecific CD33/CD3 T cell engager restores immune homeostasis in MDS in vitro. Blood 130:51, 2017 (suppl 1)
102. Fultang L, Panetti S, Ng M, et al: MDSC targeting with gemtuzumab ozogamicin restores T cell immunity and immunotherapy against cancers. EBioMedicine 47:235-246, 2019
103. Yang LP, Perry CM: Histamine dihydrochloride: In the management of acute myeloid leukaemia. Drugs 71:109-122, 2011
104. Brune M, Castaigne S, Catalano J, et al: Improved leukemia-free survival after postconsolidation immunotherapy with histamine dihydrochloride and interleukin-2 in acute myeloid leukemia: Results of a randomized phase 3 trial. Blood 108:88-96, 2006
105. Pyzer AR, Stroopinsky D, Rosenblatt J, et al: MUC1 inhibition leads to decrease in PD-L1 levels via upregulation of miRNAs. Leukemia 31:2780-2790, 2017
106. Chen J, Yang N, Liu H, et al: Immunological effects of a low-dose cytarabine, aclarubicin and granulocyte-colony stimulating factor priming regimen on a mouse leukemia model. Oncol Lett 16:3022-3028, 2018
107. Zhou Z, Fang Q, Ma D, et al: Knockout tumor microenvironment HO-1 neutralizes myeloid-derived suppressor cells and enhances the antitumor effect of PD-1 inhibition in murine models of acute myeloid leukemia. Blood 132:2782, 2018 (suppl 1)
108. Godwin CD, Fromm JR, Othus M, et al: Pre-transplant bone marrow monocytic myeloid-derived suppressor cell frequency is not associated with outcome after allogeneic hematopoietic cell transplantation for acute myeloid leukemia in remission. Bone Marrow Transplant 54:1511-1514, 2019
109. Ghobrial IM, Detappe A, Anderson KC, et al: The bone-marrow niche in MDS and MGUS: Implications for AML and MM. Nat Rev Clin Oncol 15:219-233, 2018
110. Lee MW, Ryu S, Kim DS, et al: Mesenchymal stem cells in suppression or progression of hematologic malignancy: Current status and challenges. Leukemia 33:597-611, 2019
111. Corradi G, Baldazzi C, Očadlíková D, et al: Mesenchymal stromal cells from myelodysplastic and acute myeloid leukemia patients display in vitro reduced proliferative potential and similar capacity to support leukemia cell survival. Stem Cell Res Ther 9:271, 2018
112. Ciciarello M, Corradi G, Simonetti G, et al: Up-regulation of immune tolerance genes in leukemic mesenchymal stromal cells is induced by acute myeloid leukemia cells through an IFN-gamma-dependent inflammatory signaling. Blood 132:2579, 2018 (suppl 1)
113. Wu L, Amarachintha S, Xu J, et al: Mesenchymal COX2-PG secretome engages NR4A-WNT signalling axis in haematopoietic progenitors to suppress anti-leukaemia immunity. Br J Haematol 183:445-456, 2018
114. Vasold J, Wagner M, Drolle H, et al: The bone marrow microenvironment is a critical player in the NK cell response against acute myeloid leukaemia in vitro. Leuk Res 39:257-262, 2015
115. Ito S, Barrett AJ, Dutra A, et al: Long term maintenance of myeloid leukemic stem cells cultured with unrelated human mesenchymal stromal cells. Stem Cell Res (Amst) 14:95-104, 2015

116. Wang W, Bochtler T, Wuchter P, et al: Mesenchymal stromal cells contribute to quiescence of therapy-resistant leukemic cells in acute myeloid leukemia. Eur J Haematol 99:392-398, 2017

117. Zhou X, Yuan B, Yan Y, et al: Bone marrow stromal cells induce ALDH+ stem cell phenotype and chemotherapy resistance in AML cells through TGF-β1 mediated signaling: Reversal by TGFβ inhibitor galunisertib. Blood 130:1163, 2017 (suppl 1)

117a. Danaher P, Warren S, Lu R, et al: Pan-cancer adaptive immune resistance as defined by the Tumor Inflammation Signature (TIS): Results from The Cancer Genome Atlas (TCGA). J Immunother Cancer. 6(1):63, 2018

118. Rutella S, Vadakekolathu J, Altmann H, et al: Capturing the complexity of the immune microenvironment of acute myeloid leukemia with 3D biology technology. J Clin Oncol 36:50-50, 2018 (suppl 5)

119. Davidson-Moncada J, Viboch E, Church SE, et al: Dissecting the immune landscape of acute myeloid leukemia. Biomedicines 6:110, 2018

120. Rutella S, Church SE, Vadakekolathu J, et al: Adaptive immune gene signatures correlate with response to flotetuzumab, a CD123 × CD3 bispecific Dart molecule, in patients with relapsed/refractory acute myeloid leukemia. Blood 132:444-444, 2018 (suppl 1)

121. Loke J, Malladi R, Moss P, et al: The role of allogeneic stem cell transplantation in the management of acute myeloid leukaemia: A triumph of hope and experience. Br J Haematol 188:129-146, 2020

122. Noviello M, Manfredi F, Ruggiero E, et al: Bone marrow central memory and memory stem T-cell exhaustion in AML patients relapsing after HSCT. Nat Commun 10:1065, 2019

123. Tang X, Alatrash G, Ning J, et al: Increasing chimerism after allogeneic stem cell transplantation is associated with longer survival time. Biol Blood Marrow Transplant 20:1139-1144, 2014

124. Lee HC, Saliba RM, Rondon G, et al: Mixed T lymphocyte chimerism after allogeneic hematopoietic transplantation is predictive for relapse of acute myeloid leukemia and myelodysplastic syndromes. Biol Blood Marrow Transplant 21:1948-1954, 2015

125. Kinsella FAM, Zuo J, Inman CF, et al: Mixed chimerism established by hematopoietic stem cell transplantation is maintained by host and donor T regulatory cells. Blood Adv 3:734-743, 2019

126. de Lalla C, Rinaldi A, Montagna D, et al: Invariant NKT cell reconstitution in pediatric leukemia patients given HLA-haploidentical stem cell transplantation defines distinct CD4+ and CD4- subset dynamics and correlates with remission state. J Immunol 186:4490-4499, 2011

127. Savani BN, Mielke S, Adams S, et al: Rapid natural killer cell recovery determines outcome after T-cell-depleted HLA-identical stem cell transplantation in patients with myeloid leukemias but not with acute lymphoblastic leukemia. Leukemia 21:2145-2152, 2007

128. Ruggeri L, Mancusi A, Capanni M, et al: Donor natural killer cell allorecognition of missing self in haploidentical hematopoietic transplantation for acute myeloid leukemia: Challenging its predictive value. Blood 110:433-440, 2007

129. Jahnke S, Schmid H, Secker KA, et al: Invariant NKT cells from donor lymphocyte infusions (DLI-iNKTs) promote ex vivo lysis of leukemic blasts in a CD1D-dependent manner. Front Immunol 10:1542, 2019

130. Goswami M, Prince G, Biancotto A, et al: Impaired B cell immunity in acute myeloid leukemia patients after chemotherapy. J Transl Med 15:155, 2017

131. Rautenberg C, Germing U, Haas R, et al: Relapse of acute myeloid leukemia after allogeneic stem cell transplantation: Prevention, detection, and treatment. Int J Mol Sci 20:228, 2019

132. Selim AG, Moore AS: Molecular minimal residual disease monitoring in acute myeloid leukemia: Challenges and future directions. J Mol Diagn 20:389-397, 2018

133. Platzbecker U, Wermke M, Radke J, et al: Azacitidine for treatment of imminent relapse in MDS or AML patients after allogeneic HSCT: Results of the RELAZA trial. Leukemia 26:381-389, 2012

134. Schroeder T, Czibere A, Platzbecker U, et al: Azacitidine and donor lymphocyte infusions as first salvage therapy for relapse of AML or MDS after allogeneic stem cell transplantation. Leukemia 27:1229-1235, 2013

135. Gillissen MA, Kedde M, Jong G, et al: AML-specific cytotoxic antibodies in patients with durable graft-versus-leukemia responses. Blood 131:131-143, 2018

136. Knorr DA, Goldberg AD, Stein EM, et al: Immunotherapy for acute myeloid leukemia: From allogeneic stem cell transplant to novel therapeutics. Leuk Lymphoma 60:3350-3362, 2019

137. Sweeney C, Vyas P: The graft-versus-leukemia effect in AML. Front Oncol 9:1217, 2019

138. Bleakley M, Riddell SR: Exploiting T cells specific for human minor histocompatibility antigens for therapy of leukemia. Immunol Cell Biol 89:396-407, 2011

139. Thol F, Schlenk RF, Heuser M, et al: How I treat refractory and early relapsed acute myeloid leukemia. Blood 126:319-327, 2015

140. Wages NA, Chiuzan C, Panageas KS: Design considerations for early-phase clinical trials of immune-oncology agents. J Immunother Cancer 6:81, 2018

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Immune Biology of Acute Myeloid Leukemia: Implications for Immunotherapy

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