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Review Article

Natural killer cells in patients with hematologic malignancies, solid tumors and in recipients of hematopoietic stem cell transplantation

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Abstract

Natural killer cells represent the first line of defense against infections and tumors and can be derived from various sources including: bone marrow, peripheral blood, specific types of human stem cells, and certain cell lines. The functions of natural killer cells are influenced by: several cytokines, activating and inhibitory receptors, as well as other immune cells such as dendritic cells and mesenchymal stem cells.

Natural killer cells are attractive candidates for adoptive cellular therapy in patients with hematologic malignancies and solid tumors in addition to recipients of various forms of hematopoietic stem cell transplantation as they enhance antitumor effects without causing graft versus host disease. Several clinical trials have shown safety and efficacy of natural killer cell products obtained from autologous as well as allogeneic sources and used in conjunction with cytotoxic chemotherapy, monoclonal antibodies and novel agents.

The following review, which includes extensive literature review on several aspects of natural killer cells, will give particular attention to: the rising role of natural killer cell therapies in patients with malignant hematological disorders, solid tumors and in recipients of stem cell therapies; preparation and manufacture of natural killer cell products; challenges facing the utilization of this form of cellular therapy including evolution of resistance; and maneuvers that can be employed to enhance the efficacy of natural killer cell therapies as well as suggested solutions to resolve the remaining challenges.

More Information

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Introduction

Natural killer (NK) cells are large granular lymphocytes that are: $CD3^-$, $CD56^+$, $CD16^+$, $CD94^+$ and $NKp46^+$ [1-4]. They comprise 5% - 25% of peripheral blood (PB) lymphocytes. Additionally, NK cells are the third population of lymphoid cells and they represent the first line of defense against infections and tumors [3-9]. They develop from common progenitors and differentiate from hematopoietic stem cells (HSCs) in the bone marrow (BM) but diverge into distinct subsets which differ in cytokine production, cytotoxicity, homing and memory traits [10,11]. NK cells can be derived from: BM, PB, cryopreserved umbilical cord blood (UCB), human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), and various cell lines such as NK-92 and KHYG-1 [1,12,13].

NK cells have been traditionally classified as short-lived innate lymphocytes or part of the innate immune system because, unlike T and B cells, NK cells do not express receptors that require gene rearrangements to generate receptor diversity and specificity [6]. Recently, it has been shown that NK cells exhibit many of the features associated with adaptive immunity such as: (1) expansion of pathogen-specific cells, (2) generation of long-lasting memory cells that persist after cognate antigen encounter, (3) ability to mount an enhanced secondary recall response to rechallenge, and (4) having distinct gene regulatory functions by adaptive NK cells [6,14].

Classifications and subsets of NK cells

NK cells can be classified into different subsets according

to: function, immunophenotyping or surface markers, and cytokine production as shown in table 1 [7,15-18]. NK cells are usually classified into: naïve CD56^{bright} CD16^{dim} CD3^{dim} cells; and mature CD56^{dim} CD16^{bright} CD3^{dim} cells. However, a third population (lymphoid tissue-resident NK cells: CD69^{+}, CXCR6^{+}) has been identified recently [15-18]. Also, they are divided into: cytotoxic, tolerant, and regulatory subsets with diverse phenotypes and functions in various body tissues [17].

Invariant NK T (iNKT) cells represent a small population of $\alpha\beta$ T lymphocytes that are derived from HSCs [19-21]. Stimulated iNKT cells rapidly release large amounts of cytokines such as interferon (IFN)-γ and interleukin (IL)-4 that activate NK cells, dendritic cells (DCs), CD4 helper and CD8 cytotoxic T cells [19]. iNKT cells protect against graft versus host disease (GVHD) by inhibition of proliferation of alloreactive T cells, and promotion of expansion of T-regulatory cells [20-23]. Also, iNKT cells can protect against cancer despite that cancer patients have reduced numbers and function of iNKT cells [24]. The histone demethylase UTX regulates the development of iNKT cells through multiple epigenetic mechanisms [25].

Cytokine-induced killer (CIK) cells were first described by Schmidt-Wolf in 1991 [26]. CIK cells are NK-like T-cells that can be: derived from PB mononuclear cells (PBMNCs); costimulated and expanded using cytokines for 14-21 days *in vitro*, and generated from healthy donors or patients with leukemia [27]. CIK cells have a dual functional capacity of both T cells and NK cells ultimately leading to the secretion of perforin and granzymes for the execution of cytotoxicity [9,26]. They have demonstrated cytotoxicity against a variety of malignant or leukemic cells with no or only minor effects on normal hematopoietic progenitor cells [26,27]. Allogeneic CIK cells retain the ability to produce graft versus leukemia (GVL) effect while generating minimal GVHD [27]. CIK cell infusion comprises a safe and a feasible novel immunotherapeutic approach that targets relapse or minimal residual disease (MRD) following hematopoietic stem cell transplantation (HSCT) for hematologic malignancies (HMs) [27,28]. In a recently published study that included 91 patients with various HMs relapsing after allogeneic HSCT, conventional donor lymphocyte infusion (DLI) given to 55 patients was compared to CIK given to 36 patients, the outcome of CIK therapy was superior to that of DLI with higher overall survival (OS), less relapses, and less acute GVHD [26]. However, optimal timing and cell dosage of CIK cells need to be determined [28]. NK cells and CIK cells can be expanded using a variety of clinical-grade approaches before infusion into patients with cancer. Also, CIK cells have the following advantages over other forms of cell therapy: (1) ease of *in vitro* propagation, and (2) obviating the need of exogenous administration of IL-2 for *in vivo* priming [9].

Table 1: Different Systems of Classification of Natural Killer (NK) Cells.

(A) Classification according to immunophenotyping
- Naïve CD56^{bright} CD 16^{dim} CD 3^{dim} NK cells
- Mature CD56^{dim} CD16^{bright} CD 3^{dim} NK cells
- Lymphoid tissue-resident CD69^{+} / CXCR6^{+} NK cells
(B) Classification according to function
- Cytotoxic NK cells
- Tolerant NK cells
- Regulatory NK cells
(C) Classification according to cytokine production
- Class I: innate lymphoid cells (ILCs) secreting interferon γ
- Class II: ILCs secreting interleukin (IL)-13
- Class III: ILCs secreting IL-17 and IL-22

NK cells that express inhibitory killer cell immunoglobulin-like receptors (KIRs), for which respective major histocompatibility complex (MHC) class I ligand is absent on leukemic target cells, can exert alloreactivity *in vitro* and *in vivo* [2]. The inhibitory KIRs permit NK cells to recognize self-human leukocyte antigen (HLA) class I molecules and provide inhibitory signals to preclude killing of the target cells [29].

Development, maturation and function of NK cells

Development and maturation of NK cells: NK cell maturation is a continuous process that is initiated in the BM and is continued in peripheral tissues [30]. Mature NK cells reside in the BM and secondary lymphoid tissues such as lymph nodes [7]. Thus, BM is not only the place for development, maturation, self-renewal and persistence of NK cells, but also it provides a line of defense against infections and tumors through utilizing the presence of NK cells [30]. The stages of development of NK cells include: NK progenitor cells, immature NK cells, and mature NK cells. Also, NK cell development requires the presence of the family of 6 γ chain containing receptors: IL-2R, IL-4R, IL-7R, Il-9R, IL-15R, and IL-21R [7]. Activation of NK cells is regulated by several receptors including: (1) KIRs, (2) CD94-NKG2 family, (3) leukocyte immunoglobulin-like receptors, (4) natural cytotoxicity receptors, and (5) FcγRIIIa (CD16) [12]. After activation, NK cells have the following 3 main functions to participate in immune defense: (1) ability to mediate contact-dependent killing of target cells through mobilization of highly specialized organelles or lytic granules in NK cells; (2) production of soluble factors such as cytokines, chemokines and other regulators to promote direct antidisease effects and to further induce and regulate immunity; and (3) promotion and regulation of immunity through contact-dependent costimulatory and regulatory mechanisms [31].

The molecular mechanisms that regulate NK cell cytotoxicity can be divided into 3 main processes: target cell recognition, target cell contact and immunological synapse, and NK cell-induced target cell death [7]. NK cells contain cytoplasmic granules that include perforin which is a membrane-disrupting protein and granzyme family of serine proteases and they express death ligands which are members of the tumor necrosis factor (TNF) superfamily including: (1) TNF-related apoptosis-inducing ligand, (2) Fas ligand (FasL) which is expressed on activated NK cells and cytotoxic

T lymphocytes, and (3) TNF-like weak inducer of apoptosis [12]. The following factors may potentially influence immune response: expression genes, genetic mutations, alteration of resistance to immunotherapies in leukemic cells, tumor microenvironment consisting of T regulatory cells (T-regs), tumor-associated macrophages, myeloid-derived suppressor cells, and production of cytokines [32]. NK cells selectively kill target cells that downregulate MHC molecules and/or upregulate other activating ligands such as MHC class I chain (MIC)-related antigens: MICA, MICB, and UL-16 binding protein. The use of perforin and granzyme in cytolytic killing is a major mechanism in the elimination of infected cells and tumor cells by NK cells [12].

NK cell function and dysfunction: The development and functions of NK cells are controlled by various cytokines which operate at different stages by regulating distinct signaling pathways. However, IL-15 and IL-21 are instrumental in driving NK cell differentiation and maturation [9,17]. NK cells are heterogeneous with respect to functional activity and cell-surface antigen presentation [15]. Functions of NK cells are greatly influenced by the cellular microenvironment mainly due to cytokines, chemokines and cell-to-cell interaction [17,33]. The main functions of NK cells are: elimination of infected cells during the adoptive phase of immune responses, recognition and destruction of cancer cells in patients with HMs and solid tumors that have evaded cytotoxic T-lymphocytes, reducing the incidence of GVHD following HSCT, and regulation of the outcome of pregnancy [16,17,33]. NK cell function is finely tuned by receptors that transduce inhibitory or activating signals and that recognize both foreign and self-antigens expressed by NK cell-susceptible targets [9,6]. The activating and inhibitory receptors of NK cells recognize molecular structures on cell surfaces [29]. NK cell dysfunction, which predisposes to infections by herpes viruses, is associated with: genetic or hereditary disorders; chronic disorders such as autoimmune diseases and metastatic cancer; exposure to occupational chemicals; and certain viral infections such as human immunodeficiency virus (HIV) [3,8]. The causes of dysfunctional NK cells can be broadly divided into two main categories: (1) quantitative deficiencies with low numbers or absent NK cells and (2) qualitative deficiencies with abnormal function of NK cells. The etiological causes and the associations of quantitative as well as qualitative NK cell deficiencies are shown in tables 2 and 3 [31,34-52].

Control of NK cell functions: NK cells: kill susceptible targets, functionally interact with different immune cells, sense pathogens using certain Toll-like receptors (TLRs), adapt their responses to the local environment, and mount some degree of immunological memory [53]. Several elements in cell metabolism such as: glucose-driven glycolysis, and oxidative metabolism play critical roles in NK cell development, education, memory generation, and antitumor as well as antiviral effector functions [54].

The Foxo family of genes is critical to many aspects of cellular physiology. Foxo1 acts as a negative checkpoint on NK cell maturation as it represses NK cell specification and proliferation. In a mouse model, hematopoietic-specific deletion of Foxo1 has been found to promote NK cell specification and proliferation [55]. Hypoxic environment may profoundly influence the nature of NK cell infiltrate and its effects on immune-mediated responses within tumor tissues by: influencing the NK cell transcriptome, affecting the immunoregulatory functions of NK cells, and changing the chemotactic responses of different NK cell subsets [56].

The development and functions of NK cells are controlled by various cytokines such as: fms-like tyrosine kinase 3 ligand, kit ligand, IL-3, IL-10, IL-18, transforming growth factor-β (TGF-β), and common-γ chain family cytokine which operate at different stages by regulating distinct signaling pathways [17]. IL-2, IL-12, IL-15, and IL-18 regulate to phenotype, proliferation, and function of human cytokine-induced memory-like (CIML) NK cells, while inhibition of NK cell activation and function is achieved by TGF-β, and IL-10 [57,58]. Exposure of CIML-NK cells to ruxolitinib produces very high levels of cytokines such as: TNF-α and IFN-γ [58]. Members of the emerging NK cell checkpoint family including: IL-1R8, IL-15 signaling, cytokine-induced SHz (CIS) containing protein, and TGF-β RIL act as potential drug targets to boost global NK cell function [59].

The micro-RNA, has-miRNA-146a-5p, may be involved in the regulation of KIR expression. Targeting has-miRNA-146a-5p downregulates KIR and may improve NK-mediated antitumor activity [60]. Vitamins: A, B, C, D, and E as well as natural compounds such as: genistein, curcumin, ginseng extract, garlic extract, resveratrol, ashwagandha extract, ingenol mebutate, kumquat pericarp extract, prostratin, lectins, and polysaccharides affect NK cell function by: increasing cytotoxicity, enhancing proliferation, and stimulating cytokine production [61]. Strategies that can be employed to enhance NK cell function are included in table 4 [1,2,32,62-73].

Table 2: Quantitative Deficiencies of Natural Killer Cells (Absent or Low Numbers).

(A) Classical natural killer cell deficiencies associated with specific gene mutations
- GATA2: autosomal dominant
- MCM4 (minichromosomal maintenance complex member-4): autosomal recessive
- MCM10
- RTEL1: autosomal recessive
- IRF8: autosomal recessive
- GINS1
(3) Other associated conditions
- X-linked severe combined immunodeficiency (SCID)
- Autosomal recessive SCID
- IPEX-like syndrome with growth hormone deficiency
- Fanconi anemia
- Dyskeratosis congenita
- Rett syndrome-like with MeCP2 gene mutations
- CD25 deficiency
- XLP type 2
- Non X-linked lymphoproliferative syndrome

Table 3: Qualitative or Functional Natural Killer (NK) Cell Deficiencies.	
Causes of abnormal function of NK cells include	
1- The main causes are: impairment of mechanisms of cytotoxicity or signaling of cytotoxicity and impairment of cytokine production.	
2- Defective degranulation of NK cells occasionally	
3- Abnormal phenotype of NK cells on rare occasions	
Etiology and associations of abnormal function of NK cells include	
(A) Hereditary and genetic abnormalities	
- Mutations in FCG R3A gene: autosomal recessive	- PHL2/3/4/5: familial hemophagocytic lymphohistiocytosis
- Chediak-Higashi syndrome.	- Griscelli syndrome type-2
- Hermansky-Pudliak syndrome	- Papilon-Lefevre syndrome
- Wiscott-Aldrich syndrome	- Hyper-IgE syndrome: autosomal recessive
- May-Hegglin anomaly	- Leukocyte adhesion deficiency type III
- Bloom syndrome	- XLP type I
- PKC-δ deficiency	- NEMO syndrome
- PLC-γ associated immunodeficiency	- ALPS (caspase 8 deficiency)
- STAT1 deficiency	- CRAC channel deficiency
- Bare lymphocyte syndrome	- Severe congenital neutropenia
- X-linked hyper-IgM -1	- Ataxia telangiectasia
- Interleukin (IL)-21 receptor deficiency	- Netherton syndrome
- IL-12/IL-12 receptor deficiency	- X-linked immunodeficiency with magnesium defect
- Nieman-Pick disease type C1	
(2) Acquired causes of natural killer cell deficiencies	
- Stress: physical and psychological.	- Gut dysbiosis
- Vitamin-B12 deficiency	- Sepsis
- Chronic fatigue syndrome	- Myelodysplastic syndromes
- Multiple sclerosis	- Malignancy such as hepatocellular carcinoma
- Surgery in cancer patients: post-operative stress	- Rheumatoid arthritis
- Viral infections such as: chronic hepatitis C infection, and human immunodeficiency virus infection	- Systemic lupus erythromatosus

Table 4: Approaches to Enhance Function and Antitumor Activity of Natural Killer (NK) Cells.
1- Enhancement of NK cell function by: reduction of stress, glutathione, and supplements of: curcumin, magnesium, vitamin-B12, probiotics, ginseng, echinacea, chlorrela, and COQ10
2- Use of extracellular vesicles derived from NK cells
3- Optimal donor selection based on genotypic and phenotypic properties
4- Priming of NK cells: memory-like NK, and CND-109
5- Adoptive transfer of NK cells with *ex vivo* or in vivo cytokine stimulation using: interleukin (IL)-2, IL-12, and IL-15 with its superagonist ALT-803
6- Use of drugs that:
(a) Enhance NK cell antitumor activity such as: thalidomide and lenalidomide
(b) Sensitize tumors to NK cells such as: bortezomib; and histone deacetylase inhibitors including: valproic acid, suberoylanilide hydroxamic acid, and trichostatin
(c) Sensitize leukemic targets and use of antibodies to induce antibody-dependent cellular cytotoxicity or to block inhibitory killer cell immunoglobulin-like receptors
7- Use of immune checkpoint inhibitors such as the novel anti-programmed cell death protein 1 antibody [CT-011], monalizumab, and lirilumab
8- Use of bispecific [BiKE] and trispecific [TriKE] killer engagers:
a- Bispecific antibodies: AFM 13; AFM 22
b- Optimized NK-antibody-dependent cell-mediated cytotoxicity (ADCC) monoclonal antibodies: obintuzumab and mogamulizumab
Examples of monoclonal antibodies include:
(A) Anti-CD20/anti-CD19 for non-Hodgkin lymphoma
(B) Anti-CD30 for Hodgkin lymphoma
(C) Anti-CD19/anti-CD33 for different types of leukemia
9- Use of adoptively infused allogeneic NK cells in haploidentical NK cell transplantation for: myelodysplastic syndromes, multiple myeloma, and acute myeloid leukemia
10- Advancing the field of *ex vivo* manipulation and genetic engineering by:
a. Transduction of chimeric antigen receptors (CARs)
b. Use of CAR-engineered NK cells: Peripheral Blood: Her 2 and NK-92-CD2
c. Genetic modification of NK cells and NK gene editing using: NK-HLA-A and CIS knockout

Education, licencing and memory responses of NK cells

Education and licensing of NK cells refer to the process of acquiring killing or cytokine production after encountering and recognizing self-HLA molecules [9]. The aim of NK cell education is to distinguish self from non-self [7]. Alterations in cellular metabolism or cellular metabolic pathways play a role in NK cell education and immune cell functions. Thus, educated and uneducated NK cell subsets can be distinguished by their metabolic profile regarding glucose metabolism [74]. Approximately 10% - 20% of NK cells remain unlicensed and functionally hyporesponsive due to lack of receptors for self-MHC. However, unlicensed NK cells become alloreactive upon encountering cytokines in a recipient environment after adoptive transfer into recipients of HSCT [9].

Immunological memory is the ability of the immune system to respond rapidly and provide protection against

a previously encountered pathogen. After initial infection, long-lived memory cells are generated and they display heightened responses upon secondary challenge with the same pathogen [75]. The process of memory formation in T cells is generally divided into 3 main phases: expansion, contraction, and memory phases [75,76]. Also, there are 3 major types of NK cell memory or memory-like responses: (1) antigen-specific memory responses, (2) cytomegalovirus (CMV)-adaptive memory responses, and (3) cytokine-induced antigen-independent memory-like responses. However, NK cells might adapt their inhibitory responses for memory [77].

Interactions between NK cells and other immune cells

NK cells interact with other immune cells including: DCs, mesenchymal stem cells (MSCs), macrophages, T cells, and endothelial cells [78]. Activated NK cells regulate the following actions of DCs: cytokine-producing capacity; Th-cell polarizing ability; chemokine expression; migration, editing and maturation; and stimulatory functions. On the other hand, activated DCs are required for the execution of innate and effector functions of NK cells including NK cell differentiation [79-84]. NK cells and DCs mutually influence each other and the bidirectional crosstalk between the 2 components of the innate immune system, that may be well coordinated, plays a pivotal role in the regulation of immune defense against viruses such as CMV, parasites such as Leishmania amazoneasis, and tumors [80,82,85-90]. Activated NK cells are capable of killing MSCs while MSCs can: alter the phenotype of NK cells and modulate NK cell function; increase release of IFN-γ from NK cells in order to enhance defense against infections at the sites of injury; and inhibit IL-2 induced NK cell proliferation [91-97]. The crosstalk or interaction between BM-MSCs and NK cells is complicated and can impact the immunobiology of both cell types [98,99].

GVT effects and GVHD in HSCT

GVT effects and GVHD in allogeneic HSCT: Allogeneic HSCT is an established and a potentially curative therapeutic modality not only for high-risk (HR) HMs such as relapsed/refractory (R/R) acute leukemia but also for several benign conditions [100-102]. GVHD, disease relapse, and infectious complications represent the main causes of morbidity and mortality associated with the use of HSCT [100,103]. Allogeneic HSCT benefits HMs by providing graft versus tumor (GVT) or GVL effects which are mediated by donor-derived T cells as well as NK cells [100,101,104,105]. Thus, the success of allogeneic HSCT depends upon: (1) the infusion of benign stem cells and lymphocytes that are capable of inducing GVT/GVL effect, and (2) the ability of the engrafted immune system to remove residual leukemia or tumor cells through the GVT/GVL effect [104,105].

T lymphocytes are responsible for the development of both acute and chronic GVHD post-HSCT. However, removal or depletion of these cells from allografts results in higher rates of graft failure and relapse of HMs [102]. T cells and NK cells are important in providing GVL effect and both cell types are amenable to *ex vivo* manipulation and clinical manufacture in order to make them more versatile immunotherapeutics [106]. The immunopathophysiology of chronic GVHD is more complicated than that of acute GVHD as it involves complex interactions between several alloreactive and dysregulated cells including: T lymphocytes, B cells, macrophages, neutrophils, DCs, and NK cells [107,108]. Although donor T lymphocytes mainly contribute to the pathophysiology of chronic GVHD, donor B cells contribute to the development of this complication but to a lesser extent [103]. However, specific immune effector cells within the BM allograft have been recognized to correlate with: GVHD, relapse of HM, and OS [103,104].

Prevention of GVHD can be provided by**:** calcineurin inhibitors, various T-cell depletion strategies, and immunomodulatory agents [106]. Strategies to balance immune responses favoring the development of GVT/GVL effects without inducing harmful GVHD are required to: protect against relapse of HMs, treat persistent disease, and improve disease-free survival (DFS) [104]. A thorough flow cytometric analysis of donor cells for phenotypic and allogeneic activity may be valuable in evaluating the pretransplant risk of development of severe acute GVHD [109]. DLI is an effective therapy for patients with acute leukemia relapsing post-allogeneic HSCT, but the development of severe acute GVHD after DLI infusions remains an obstacle to the success of this therapeutic procedure [100]. The use of oncolytic viruses such as myxoma virus is associated with control of GVHD while preserving or even augmenting GVT/GVL effects [101]. In a murine system, adenoviral vectors have been found to stimulate NK cells and ultimately cause enhanced antitumor activity in the absence of transgene expression [110]. Although GVT/GVL effects occur spontaneously following allogeneic HSCT, such effects can be induced by the following maneuvers: (1) optimal donor selection and optimal conditioning therapy; (2) administration of GVHD prophylaxis; (3) DLI infusion; (4) use of allogeneic mismatched NK cells; (5) activated DCs of leukemic origin; (6) generation of multi-leukemia antigen specific T cells or chimeric antigen receptor (CAR)-modified T cells; (7) use of pharmacological agents such as: tyrosine kinase inhibitors (TKIs), fms-like tyrosine kinase 3 (FLT3) inhibitors, and immune check point inhibitors (ICPIs); and (8) allograft engineering by using: negative CD3/CD19 depletion, as well as CD34 positive selection [102,105,106,111,112].

Autologous GVT effects and autologous GVHD: In the setting of autologous HSCT, not only GVT effect but also biopsy proven GVHD can be encountered [113-118]. Hence, GHVD is an increasingly recognized complication of autologous HSCT [113,118]. The risk factors for the development of autologous GVHD include: (1) primary disease as multiple myeloma (MM), non-Hodgkin lymphoma (NHL), and breast cancer; (2) second autologous HSCT; (3) heavily pretreated patients;

(4) female gender; (5) high $CD34^+$ stem cell dose infused; (6) achievement of high levels of absolute lymphocyte count (ALC) after autologous HSCT; and (7) use of certain novel agents such as bortezomib, lenalidomide, pomalidomide and alemtuzumab [113-115,117-119]. Autologous GHVD may occur spontaneously, but can be induced by a number of immunosuppressive drugs [113]. It resembles GVHD occurring after allogeneic HSCT not only clinically but also histologically and can be treated with the same immunosuppressive therapies [113,116,117,119].

The role of NK cells in GVT/GVL and GVHD: Immune reconstitution is a critical process following HSCT [120]. NK cells, regulatory T cells (T regs), MSCs, regulatory B cells (B regs), and myeloid cells play significant roles in posttransplant immune regulation, but NK cells are the first donor-derived lymphocyte population to recover following allogeneic HSCT [120,121]. However, spontaneous and full recovery of the numbers of NK cells as well as their cytotoxic function generally occurs within the first month after allogeneic HSCT [121,122]. Interestingly, patients having acute and chronic GVHD have delayed constitution of NK cells [123]. Acute GVHD has been shown to impair the constitution of total and $CD56^{dim}$ NK cells at 3 months after allogeneic HSCT [124].

NK cells mediate a strong GVT/GVL effect and play an important role in GVHD as adoptively transferred NK cells can potentially reduce acute GVHD by killing host antigen-presenting cells [121]. Various subsets of NK cells play specific functions in the development and manipulation of GVHD. Examples include: (1) $NKG2A^+$ NK cells play a crucial role during early stages of GVHD following HSCT; (2) NKG2C-expressing NK cells have a direct role in the early control of CMV reactivation after allogeneic HSCT; (3) c-Kit^- CD 27^- $CD11b^+$ NK cell population is capable of significantly dimishing GVHD in the setting of fully mismatched allogeneic HSCT by supporting GVL effects whilst providing protection against the development of GVHD; (4) $CD56^{bright}$ NK regulatory cells have been shown to have a much stronger impact on filgrastim-stimulated PB apheresis products than on filgrastim-stimulated BM products as lower proportions of $CD56^{bright}$ NK regulatory cells result in higher rate of chronic GVHD seen in filgrastim-stimulated PB apheresis; (5) iNK cell dose in allogeneic grafts is associated with significant improvement in GVHD and GVHD-free progression-free survival; (6) failure to reconstitute iNK cells following allogeneic HSCT is associated with higher risk of primary disease relapse; (7) low doses of adoptively transferred donor $CD4^+$ iNK cells protect from GVHD while preserving GVT effects as these cells inhibit proliferation of alloreactive T cells and promote robust expansion of donor T regs; and (8) higher doses of $CD4^-$ iNKT cells in PB stem cell allografts are associated with protection from acute GVHD [21,22,121,124-127].

The administration of *ex vivo* expanded NK cells in the early post-transplant period has been shown to be safe, feasible, and encouraging in lowering the rate of relapse of HMs following HSCT [128]. The number of reinfused autologous graft NK cells in the apheresis product affects the ALC recovery following autologous HSCT [129]. Also, the counts of early lymphocyte subsets following allogeneic HSCT have an association with not only acute GVHD but also with post-HSCT outcome [130]. In recipients of HLA-identical allogeneic HSCT, a well-defined donor-activating NK cell receptor genotype protects against relapse of leukemia after HSCT [131]. Mismatch of NK cell receptors and ligands during allogeneic HSCT may be utilized to prevent relapse of leukemia post-HSCT [132]. The following factors have been found to be important in enhancing NK cell alloreactivity: (1) high stem cell dose, (2) extensive T cell depletion, (3) no GVHD prophylaxis, (4) myeloid malignancy as primary disease, (5) donor source: related versus unrelated and haploidentical, (6) ethnicity, (7) disease status at transplantation, and (8) differences in the definition of alloreactivity: phenotypic, genotypic, and mismatching algorithm [133].

Antitumor effects of NK cells

IFN-γ, a product of activated T lymphocytes and NK cells, is a major immunoregulatory cytokine as it produces: TNF-α, IL-1 and IL-2 [134]. In animal models, bortezomib has been shown to enhance the antitumor effects of adoptively infused NK cells, ultimately resulting in delayed tumor growth and prolongation of survival [135]. The antitumor effects of NK cells are mediated by the synergistic actions of IFN-γ and IL-2 [134]. However, the antitumor effects of bortezomib can be potentiated by the administration of IL-2 [135]. Allogeneic NK cells have been found to mediate more potent antitumor effects than H2-matched syngeneic NK cells without causing adverse hematologic effects thus allogeneic NK cells can be used to purge tumor cells contaminating the BM [136].

Antibody-dependent cell-mediated cytotoxicity (ADCC) is a cell-mediated immune defense mechanism in which effector immune cells actively lyse antibody-coated target cells [137]. The ADCC of tumor cells is utilized in the treatment of various malignancies that overexpress unique antigens such as: neuroblastoma, breast carcinoma, and B-cell NHL [137,138]. Among immune cells, only NK cells are known to be major effectors of antibody-mediated ADCC [137]. Thus, ADCC mediated by NK cells is presumed to be a key effector function [139]. However, NK cell education does not influence ADCC levels, but does contribute to antibody-dependent NK cell activation [140]. NK cells harbor the activating differentiation molecule FcγRIIIa, which is also known as CD16a or CD32c, on their cell surfaces. Hence, NK cells are considered the most important effectors of ADCC in humans [141]. Monoclonal antibodies such as rituximab and the humanized anti-CD123 monoclonal antibody utilize different mechanisms including ADCC to destroy cancer cells [138,142-144]. ADCC may be improved by drugs that are able to enhance activity of NK cells as monoclonal antibodies have a significant role in the

induction of ADCC against tumor cells. However, it is difficult to distinguish between the target effect that many monoclonal antibodies exert against specific cell membrane receptors and the ADCC effect that can be induced by monoclonal antibodies [141]. Despite the success of the approved second generation monoclonal antibodies for the treatment several malignant diseases, efforts are made to further augment ADCC *in vivo* by antibody engineering [139].

Epigenetics and NK cells

Cancer arises as a result of an accumulation of genetic mutations and epigenetic abnormalities that are regulated by histone deacetylases (HDACs) which control chromatin condensation and gene expression [145]. HDACs are enzymes that regulate diverse cellular processes such as: (1) expression of genes that are implicated in tumor initiation, progression, and antitumor responses; and (2) cell proliferation, survival, and immune pathways through deacetylation of their protein targets and modulation of gene expression and protein activity [146,147]. However, HDAC activities are frequently dysregulated in patients with cancer [146].

Treatment with epigenetic agents is a novel therapeutic approach that modulates gene expression by targeting the: DNA methylation machinery, histone covalent modification, and micro-RNAs. However, major limitations of epigenetic therapy are the lack of specificity and the consequent global induction of epigenetic changes [148,149]. Treatment with epigenetic drugs can reduce chemotherapy resistance in patients with HMs and solid tumors. Hence, epigenetic agents can be added to cytotoxic chemotherapy or targeted therapies in order to derive chemosensitization benefit [148,150,151]. HDAC inhibitors have been developed as novel anticancer agents in the treatment of myelodysplastic syndromes (MDSs), acute myeloid leukemia (AML), lymphomas, as well as solid tumors and they can be used alone as monotherapies or in combination with other anticancer therapies [145,148,152]. However, HDAC inhibitors can exert deleterious effects on NK cell function, which may weaken immune surveillance and facilitate relapse of the primary malignant disease in patients treated with HDAC inhibitors [145]. Valproic acid, a HDAC inhibitor, has been found to impede the lytic activity of NK cells against leukemic cells in a dose-dependent manner [152].

NKG2D is a major receptor of NK cells and plays a critical role in tumor immunosurveillance. Expression of NKG2D by NK cells is inhibited by valproic acid and enhanced by entinostat which is a narrow-spectrum HDAC inhibitor [153]. NK cells express the activating receptor NKG2D which provides one mechanism by which NK cells recognize their targets [154]. Cancer cells which survive the direct induction of cell death by HDAC inhibitors become targets for NKG2D-expressing cells such as NK cells, $\gamma\delta$ cells and CD8 T cells [155]. Treatment of NK cells with HDAC inhibitors can recover histone acetylation, and restore NK cell activity as well as interferon-γ production [156]. The H3K27me3 histone demethylase UTX regulates development of iNKT cells through multiple epigenetic mechanisms [25]. Combination immunotherapy using HDAC inhibitors and NK cells activated by IL-15 could improve the immune recognition of both therapy-sensitive and therapy-resistant cells of Ewing's sarcoma and sensitize tumor cells for NK cell cytotoxicity [157].

Preparation of NK cells and Improvement of their potency

Preparation of NK cells for clinical use is a complicated process that involves multiple steps and depends on the following factors: (1) the desired primary source of NK cells such as PB, BM, UCB, hESCs, and iPSCs; (2) the specific cell line to be used; and (3) whether to use autologous or allogeneic NK cells. However, details of the steps involved in preparation, manufacture, delivery and tracing of NK cells are shown in table 5 [12,158-162]. The types of available NK cell-based immunotherapies are shown in table 6 [12].

Strategies that can be used to improve NK cell immunotherapies include: (1) optimal donor selection; (2) combination with cytokine stimulation or ICPIs; (3) use of drugs that enhance NK cell antitumor activity or sensitize malignant cells to NK cells; (4) use of bispecific or trispecific killer engagers; (5) use of adoptively infused allogeneic NK cells in haploidentical transplantation; (6) advancing the field of *ex vivo* manipulation and genetic engineering; (7) and priming NK cells and using extracellular vesicles (ECVs) derived from NK cells. The details are included in table 4 [1,2,32,70-73].

Current and future therapeutic uses of NK cells

The potential indications for NK cell therapies: The main potential therapeutic uses for NK cell therapies include: (1) autologous and allogeneic HSCT by providing GVT effect and enhancing engraftment; (2) various HMs including: MM, acute and chronic leukemia, as well as lymphomas; (3) various solid tumors by providing antitumor effects; (4) solid organ transplantation; (5) autoimmune and inflammatory disorders; (6) pregnancy and reproduction; (7) various types of infections; and (8) bronchial asthma [9,12,71,78,163-168].

Examples of non-specific adoptive immunotherapies include: CD3/CD28-activated DLIs; lymphokine-activated killer cells; anti-CD3-activated killer cells; tumor-infiltrating lymphocytes; *in vitro*-generated or selected tumor cytotoxic T lymphocytes; γ/δ-T cells; and NK cells [26]. However, NK cells are attractive candidates for adoptive cellular therapy in patients with HMs and solid tumors, as well as in recipients of allogeneic HSCT as they enhance GVT/GVL effects without causing GVHD [1,26,97,169-174].

NK cells in MM: MM is characterized by gradual immune dysregulation which impairs function of: T and B cells, NK cells, as well as antigen presenting or DCs thus allowing malignant plasma cells to escape immunosurveillance [175].

Table 5: Preparation, Manufacture, Delivery, and Tracing of Natural Killer (NK) Cells.
1. Collection of NK cells:
- NK cells can be collected from peripheral blood (PB) using apheresis or Ficoll separation (specific gravity centrifugal method)
- Alternatively, $CD34^+$ cells can be mobilized from bone marrow (BM) to PB using growth factors (granulocyte-colony stimulating factor or plerixafor) in order to obtain hematopoietic progenitor cells that are $CD34^+/CD45^+$ then to use NK cell differentiation media to generate $CD45^+/CD56^+$ NK cells
2. Cell selection and purification:
- NK cell sorting through positive or negative selection
- Removal of T cells and B cells with magnet beads to increase purity of NK cells
- Flow cytometry can be used to determine the cellular composition of the product (the ratio of NK cells to T cells) with the aim of harvesting highly activated and purified NK cells into blood transfusion bags
3. Culture and *ex vivo* expansion of NK cells:
- NK cells can be cultured using various culture media such as KBM 502 medium
- NK cells that are obtained from PB-mononuclear cells, umbilical cord blood, or human embryonic stem cells can be expanded using various stimuli including:
a. Cytokines such as interleukin (IL)-2, IL-12, and IL-18
b. Monoclonal agonistic antibodies such as: CD16, CD56, and NKp46
c. Allogeneic feeder cells
4. The following additional procedures may occasionally be needed:
a. Treatment with viruses or viral transduction using retroviruses or lentiviruses
b. Irradiation
c. Gene transfer, modification, or manipulation
5. Cryopreservation:
- Cryopreservation may be needed so that the product is kept for future use
- Once needed, it can be thawed
6. Before use, the following procedures are usually performed:
- Evaluation of NK cell viability
- Cytotoxicity assays to determine the phenotype and antitumor activity
- Quality control tests or assays
7. Infusion of NK cell product intravenously.
8. Tracing infused NK cells:
After delivery of NK cells, immunohistochemistry methods can be used to identify NK cells in tumor mass and evaluate the efficacy of the procedure

Table 6: Types of Available Natural Killer (NK) Cell-Based Immunotherapies.
(A) Autologous NK cells:
- They have no risk of graft versus host disease (GVHD)
- Can be employed for: colorectal, non-small cell lung, kidney, and esophageal cancers in addition to melanoma
(B) Allogeneic NK cells:
- Can be used for leukemia, lymphoma, renal cell and colorectal cancers
- To use either HLA-matching donor or haploidentical donor
- In case a haploidentical donor is selected, T cell depletion should be performed to prevent evolution of GVHD
- Selection of allogeneic donor should be based on: haplotype, activating receptors and inhibitory receptors
(C) Combination of NK cells and novel therapies:
Synergistic effect can be obtained by using the following monoclonal antibodies:
- Rituximab
- Alemtuzumab
- Daratumumab
- Obintuzumab
- Elotuzumab

MM cells exhibit specific immunoevasive strategies in order to circumvent and attenuate NK cell function [176]. Transformed plasma cells in MM are susceptible to NK cell-mediated killing by engagement of tumor ligands for activating receptors or missing self-recognition [174-176]. Despite the advancements in novel therapies and autologous HSCT, MM remains an incurable and difficult-to-treat HM due to drug resistance predisposed to by the immunosuppressive microenvironment and clonal evolution which favor disease progression [175]. However, allogeneic HSCT which is associated with significant morbidity and mortality is the only potentially curative therapeutic modality due to its potent graft versus myeloma effect [172].

In MM, NK cell function has been shown to be diminished by specific factors that are active in the tumor microenvironment (TME) [177]. Also, relatively high levels of HLA molecules are expressed in MM [178]. The recognition of plasma cells in patients with MM by NK cells is regulated by: HLA class I/HLA-E, NKG2D receptor and possibly NKG2A receptors, and natural cytotoxicity [178-180]. HLA class I may be involved in the resistance of myeloma cells to NK cell lysis thus contributing to the immune escape and consequently drug resistance in R/R-MM [181]. Tumor progression in patients with MM is associated with decreased expression of activating receptors [182]. However, infusion of large numbers of expanded NK cells which has been shown to be feasible and

safe may be critical to boost their activity *in vivo* [183]. In patients with MM, NK cells have been used in several trials in the setting of autologous as well as allogeneic HSCT as NK cells elicit cytotoxic effects against MM cells and as KIR-ligand mismatch m tables 2 and ay improve the outcome of allogeneic HSCT [172,176,184-186]. NK cell killing of tumor cells in MM can be augmented by: ICPIs, therapeutic antibodies such as daratumomab, immunomodulatory agents such as lenalidomide, indoleamine 2,3 dioxygenase inhibitors, and adoptive transfer of unmanipulated or CAR-engineered NK cells [171,175].

Daratumumab is a CD38-specific monoclonal antibody that induces death of MM cells via various mechanisms including: ADCC, and complement-dependent cytotoxicity [187]. On one hand, it has been shown that daratumumab augments NK cell cytotoxicity against target cells having high expression of CD38 surface markers [177]. On the other hand, it has been shown that daratumumab treatment may induce NK cell depletion thus making daratumumab-treated myeloma patients susceptible to infectious complications such as bacterial infections and reactivation of viruses belonging to the herpes group [188]. Additionally, daratumumab-medicated ADCC can be significantly improved by lenalidomide mainly due to the potent capacity of the latter to activate NK cells [187].

In a one-year follow-up study on patients with MM, it has been shown that lenalidomide therapy neither activated NK cells nor it improved their capacity to degranulate or secrete cytokines and that discontinuation of the drug did not reduce the effector function of NK cells [189]. Immunomodulatory agents and proteasome inhibitor have been shown to upregulate the expression of the activating receptors NKG2D and DNAM-1 on NK cells [182]. Studies have shown that: (1) bortezomib, the first generation proteasome inhibitor, can significantly enhance the sensitivity of MM cells to allogeneic as well as autologous NK cell-mediated lysis, and (2) carfilzomib, the second generation proteasome inhibitor, can also enhance NK cell degranulation and significantly enhance the sensitivity of myeloma cells to NK cell-mediated lysis through downregulation of the expression of newly formed HLA class I on MM cells [186,190].

The excellent safety and feasibility profiles of NK cells make them interesting candidates in combination therapy with novel agents in order to enhance their clinical efficacy in the treatment of MM patients [178]. Blockade or inhibition of KIR2D in patients with smoldering myeloma by IPH2101 monoclonal antibody has been shown to enhance NK cell killing of myeloma cell lines [191]. In a meta-analysis that included 12 clinical trials and 592 patients, adjuvant immunotherapy with DCs and CIK cells has been shown to be safe and efficacious in enhancing the efficacy of chemotherapy administered to patients with MM [192]. Studies have shown that early recovery of donor derived lymphocytes and NK cells after autologous HSCT is associated with improved long-term outcome in patients with MM [193,194]. In a phase I clinical trial that included 10 patients with MM, the administration of allogeneic NK cells derived from UCB has been shown to be safe and feasible [184]. CAR-transduced NK cells and bispecific antibodies utilizing NK cells hold great promise and potential against MM [182].

NK cells in AML: In patients with AML, NK cells are frequently defective thus leading to tumor escape where the continuous cross-talk between AML and NK cells predisposes to immune escape of leukemia and eventually disease relapse [195,196]. Various mechanisms are potentially involved in the inhibition of NK cell function in AML patients and these include: (1) defects in the normal lymphopoiesis, (2) reduction in the expression of activating receptors through cell-to-cell contacts, and (3) production of immunosuppressive soluble agents by AML blast cells [195]. Therefore, it is of vital importance to restore NK cell activity in AML patients by: (1) stimulating immunosurveillance mediated by NK cells, (2) combining conventional chemotherapy with immune mediators that include NK cells, and (3) genetic modification of CIK cells with chimeric receptors specific for the CD33 myeloid antigen [195,197]. A novel sβ3-integrin protein has been identified in patients with AML and this protein has been shown to enhance the cytotoxic activity of NK cells against AML blasts after stimulation with IL-2 and IL-15 [198]. Cytokine-induced memory-like NK cells have been shown to exhibit enhanced antitumor effects against AML blasts [199].

So far, allogeneic HSCT is the only curative therapeutic intervention in patients with AML. However, the most common cause of death in AML patients subjected to allogeneic HSCT is disease relapse [32]. NK cell immunotherapies using: adoptive NK cells, cytokines-based immunotherapies, ICPIs, and bispecific as well as trispecific engagers have the potential to significantly enhance the ability of conventional therapies to eliminate AML after HSCT [32,199]. Initial reports of haploidentical HSCT in AML patients showed favorable effects of alloreactive NK cells on disease relapse and survival by promoting engraftment, enhancing GVL effect and reducing the incidence of GVHD. Subsequently, studies have shown either no difference in the incidence of GVHD or adverse outcomes related to GVHD, infections and disease relapse. Therefore, selecting the most appropriate alloreactive NK cell model and selective expansion of a particular NK cell subset may become vital in restoring NK cell function in the post-HSCT period [133].

Donor KIR-group B profiles and the homozygous of centromeric motif B are the most preferable KIR gene content motifs for HSCT [200]. The benefits of unidirectional graft versus host (GVH)-KIR ligand incompatibility in T-cell replete haploidentical HSCT may be masked by the relatively favorable transplantation outcomes of bidirectionally KIR-ligand matched recipients. So, AML patients with unidirectional host versus graft KIR ligand incompatibility have experienced

significantly higher relapse rates and decreased DFS compared to patients with bidirectionally KIR ligand matched group of patients [201].

In AML patients receiving allogeneic HSCT, alloreactive T cells and NK cells mediate GVL effect thus improving disease outcome by enhancing eradication of leukemia and preventing AML relapse [202]. The use of the combination of cytosine arabinoside cytotoxic chemotherapy and *ex vivo* activation of NK cells has the potential to be a feasible approach to treat AML relapsing after HSCT [203]. A study that included 112 patients with HR-AML, subjected to haploidentical HSCT: 51 patients received allografts from donors with alloreactive NK cells and 61 patients received allografts from donors with no alloreactive NK cells. The study showed that transplantation of NK-alloreactive donors was associated with significantly: lower relapse rate in patients transplanted in complete remission (CR), better event free survival (EFS) in patients transplanted in relapse or in CR, and lower risk of mortality [204].

Studies have shown that IL-2-activated haploidentical NK cell treatment can induce CR in 30% - 50% of patients with R/R-AML and thus can be used as effective bridging therapy to the potentially curative allogeneic HSCT [205-207]. In the first-in-human phase I and phase II trials using either (IV) intravenous (26 patients) or (SC) subcutaneous (16 patients) recombinant human (rh) IL-15 administered with haplo-NK cell therapy after lymphodepletion with cyclophosphamide and fludarabine (CY-Flu) to treat R/R-AML, the following results were obtained: (1) CR was achieved in 35% of patients with CR rates of 32% in recipients of IV IL-15 and 40% in recipients of SC IL-15, (2) cytokine release syndrome (CRS) was reported in 56% of recipients of SC Il-15, (3) SC dosing of rh IL-15 after lymphodepletion prolonged drug exposure thus leading to CRC and neurotoxicity, and (4) strategies to augment *in vivo* expansion of NK cells included: lymphodepletion with CY-Flu before NK cell infusion, depletion of T regs with an IL-2 Diphtheria toxin, and *in vivo* use of recombinant cytokines [207].

NK cells in Acute Lymphoblastic Leukemia (ALL): In patients with malignant diseases, NK cell immunosurveillance may be impaired resulting in tumor escape and disease progression [208]. Precursor B-lineage ALL is associated with immune deficiencies that can be further exacerbated by cytotoxic chemotherapy [209]. The classical prognostic factors in patients with ALL include: (1) age of patient; (2) white blood cell count at presentation; (3) cytogenetic profile; (4) early treatment response; and (5) MRD evaluated by flow cytometry on day 15 of induction chemotherapy [210]. However, presence of NK cells in the BM can serve as an additional prognostic factor in patients with ALL [210]. In these patients, post-induction MRD is a very important prognostic marker. Hence, therapies targeting MRD have been shown to improve the outcome of ALL patients [211]. The following NK-related factors have been found to strongly correlate with post-induction MRD: Fas ligand, granzyme B, NKp46, and KIR2DL5A in NK cells; as well as PI-9 in blast cells [211]. Compared to AML, only a minority of ALL blasts are susceptible to NK cell-mediated killing [212]. Hence, ALL has been considered resistant to NK cell-mediated lysis [208,213]. Not all NK cells are equally cytotoxic against leukemic cells because of differences in receptor gene content and surface expression [211]. Additionally, adult and pediatric ALL blasts show a difference in the expression of the known ligands for NK cell activating receptors. Also, specific phenotypic patterns of expression are associated with molecularly defined subgroups of ALL patients such as Philadelphia chromosome positive ALL patients [212].

$CD56^+$ NK cells obtained from PB or BM of patients with ALL at various stages of disease, including diagnosis, remission, and relapse, can be expanded *ex vivo*. The expanded NK cells have been shown to kill autologous ALL blasts obtained from the same patient spontaneously or through antibody-dependent cytotoxicity [209]. Strategies that have been employed to sensitize ALL blasts to NK cell killing include: (1) stimulation of NK cells by TLR-9 activated plasmacytoid DCs which have the capacity to reinforce the GVL effect of HSCT; (2) drugs such as bortezomib, valproate, and troglitzaone; and (3) genetic modification of NK cells to overcome ALL tumor cell antigens [208,213,214].

Adaptive NK cells have the following distinguishing features: (1) they are highly differentiated NK cells, (2) they expand naturally *in vivo* in response to human CMV infection, (3) they carry unique repertoires of inhibitory KIRs, and (4) they display strong cytotoxicity against tumor cells. Hence, adaptive NK cells hold promise for treatment of refractory ALL either as a bridge to HSCT or as a form of treatment for patients who lack stem cell donors as these cells are capable of eradicating residual blast cells [215]. Several models of adoptive transfer of mature allogeneic NK cells have been used in transplant and non-transplant settings in patients with ALL and AML. Safety and feasibility of such models have been determined but their effectiveness has not been found to be uniform [2].

NK cells in chronic leukemias: Currently, TKIs are the standard therapeutic modality in patients with chronic myeloid leukemia (CML). However, the use of these novel agents is associated with numerous adverse effects [216]. The majority of patients with CML have quantitative as well as qualitative defects in the NK cell compartment of their immune system. Therefore, developing strategies to exploit NK cells for immunotherapy in patients with CML is of vital importance [216,217]. Successful discontinuation of imatinib in patients with CML is associated with high proportion of mature cytokine-producing NK cells [218].

Chronic lymphocytic leukemia (CLL) patients have severe

immune defects that predispose them to a variety of infectious complications [219]. Also, chronic exposure of NK cells to a significant tumor burden has its own consequences on the phenotype and function of these cells, thus rendering NK cells unable to counteract not only infections but also the chronic leukemia itself [220]. Strategies to augment NK cell function, which are being evaluated in clinical trials, will have positive effects on both CLL and the associated infectious complications [219,220]. Blocking NKG2A on NK cells of CLL by monalizumab can enhance NK cell activity by restoring the direct cytotoxicity function [221].

NK cells in lymphomas: In patients with B-cell NHL: the number of NK cells in PB may affect the outcome of patients receiving anti-CD 20-based immunotherapy, functional NK cells infiltrate tissue biopsies and their presence is tissues correlates with survival of these patients [222,223]. The combined genetic and microfluidic assays can evaluate the sensitivity of cells of B-cell NHL to NK cell-based cytotoxicity [224]. T-regs, iNK cells, and B-regs are involved in the pathogenesis of NHL [225]. Additionally, iNK cells and Th17 (T cells that produce IL-17) inhibit tumor growth of B-cell NHL while T regs support tumor growth in this category of lymphoma [226].

The combination of rituximab and lirilumab, which is a NK cell agonist that causes KIR blockade, has potent antilymphoma activity [227]. Also, a recent study showed that prior to the administration of combined chemotherapy and rituximab, an anti-CD 20 monoclonal antibody, patients with NHL had lower levels of B-regs, and to a lesseer extent T-regs but not iNK cells in the PB compared to controls, while following complete remission of NHL, the levels of circulating T-regs, iNK cells, and B-regs were elevated [225].

Expansion of PD-1$^+$ NK cells and PD-L1$^+$ monocytes/macrophages is more prominent in classical Hodgkin lymphoma (cHL) than in diffuse large B-cell lymphoma (DLBCL). Also, programmed cell death protein 1 (PD-1) blockade reverses the immune evasion mediated by the interaction between PD-1$^+$ NK cells and programmed death-ligand 1 (PD-L1)$^+$ monocytes/macrophages [228,229]. NK cells are inhibited directly by malignant B-cells and indirectly by PD-L1/PD-L2 expressing tumor-associated macrophages. Thus, cells of cHL are more sensitive to PD-1 blockade than DLBCL cells [228,229]. In patients with HL, studies have shown that: (1) the immunosuppressive nature of the TME specifically inhibits proliferation and activity of NK cells, (2) malignant Reed-Sternberg cells and other components of the TME express ligands to inhibit NK cells, and (3) although NK cell deficiency begins at the tumor site, ultimately it progresses systematically in patients with advanced disease as the secretion of cytokines and chemokines mediates the systemic immunosuppression. Thus, strategies to reactivate NK cell function or those aimed at blocking the evasive mechanisms displayed by the TME may ultimately identify new immunotherapeutic targets [230,231]. In patients with HL, CD 123 (IL-3Rα) is frequently expressed by malignant cells and the combination of NK cells and the fully humanized anti-CD 123 monoclonal antibody (CSL362) represents a promising future therapeutic strategy [144].

NK cells in HSCT: Allogeneic HSCT has revolutionized the treatment of HMs, but the use of this potentially curative therapy is limited by: GVHD, infections and relapse of the primary disease [27,106,170,232]. Relapse of HM remains the leading cause of treatment failure of allogeneic HSCT [26,32]. Calcineurin inhibitors, T-cell depletion and immunomodulators prevent GVHD but have negative impact on GVL effects [106].

Separating GVL effects from GVHD is of special interest in non-specific cell-based immunotherapy which may eradicate molecular disease and prevent relapse following allogeneic HSCT particularly when leukemia burden is low [26,32]. The recognition of missing-self on target cells is crucial for promoting NK cell-mediated GVL effects [2]. NK cells have a central role in tumor-cell surveillance but leukemic cells have great capacity to escape NK cell recognition and killing thus limiting the use of NK cells in cellular immunotherapy [72].

NK cells are the first subset of donor-derived lymphocytes to reconstitute after HSCT thus they may protect against relapse in the early months following HSCT by providing GVL effect without causing GVHD [1,29,169,232]. In recipients of HSCT, NK cells provide protection against bacterial infections at mucosal barriers and viral infections particularly those caused by CMV both of which are associated with significant morbidity and mortality in this group of patients [233]. CMV infection stimulates and expands a distinctive population of NK cells that expresses the NKG2C receptors and exhibits enhanced effector functions [234]. However, the initial wave of NK cells that reconstitutes in the early post-transplantation period is rather dysfunctional [234,235]. Nevertheless, rapid immune recovery after allogeneic HSCT predicts clinical outcome [236]. Although immune recovery post-HSCT has been evaluated in the PB, it can also be evaluated by BM examination. Also, evaluation of absolute lymphocyte subsets, particularly the status of NK cell recovery in the BM on day 21 after HSCT predicts clinical outcome [236]. Presence of a KIR B haplotype in donors and lack of recipient HLA-C epitope in recipients provide protection against relapse of AML following allogeneic HSCT. Additionally, strategies combining NK cell infusions with CD16-binding antibodies or immune engagers could make NK cell antigen specific [234].

Although the initial studies on the use of autologous NK cells were disappointing, the use of allogeneic NK cells has resulted in favorable outcomes in both transplant and non-transplant settings and this led to the advancement of NK immunotherapy over the last decade [1,169]. Donor NK cells play significant roles in: promotion of hematopoietic

engraftment following HSCT, preventing relapse of HM post-allogeneic HSCT by mediating GVL effects, and regulation of GVHD by suppression of alloreactive T-cell responses [169,232]. Enhancement of GVL without increasing the incidence of GVHD can be achieved by adopting the following maneuvers: optimal donor selection, optimal conditioning therapy, administration of GVHD prophylaxis, and administration of T-cells and donor-derived NK cells which are amenable to *ex vivo* manipulation and clinical manufacture [106]. Studies have shown that: augmentation of T-cell alloreactivity may be influenced by NK cells in recipients of T-cell deleted allografts, and while immunosuppression with sirolimus and expansion of T-regulatory cells may decrease the incidence of acute GVHD by suppressing the development of T-cell mediated alloreactivity [170,237,238].

NK cell infusions derived from PB and UCB contain contaminating T-cells whose stimulation by cytokines produced by NK cells may trigger GVHD *in vivo* thus limiting the safety and efficacy of NK cell infusions in allogeneic HSCT. However, NK cells obtained from iPSCs, hESCs, and NK cell lines are free of contamination with T and B cells thus offering alternative sources of NK cells that can be used in adoptive immunotherapy [164]. Owing to the short-lived and limited *in vivo* activity of the effectors involved, non-specific immunotherapy is dependent on repeat administrations [26].

NK cells are negatively regulated by MHC class I-specific inhibitory receptors [239]. NK cells lacking inhibitory receptors for self MHC class I ligands are hyporesponsive. However, responsive NK cells in the donors of allogeneic HSCT may become aberrantly activated and functionally competent in the recipients of HLA-identical allografts [240]. Because NK cell education after HSCT is driven by donor ligands, NK cell specific to a ligand present in the donor but absent in the recipient could remain responsive even long after transplantation and may exert a long-term GVL effect [241]. Donor selection for the KIR B haplotype of the centromeric motifs can improve survival in recipients of HLA-identical sibling allografts [242]. KIRs recognize groups of HLA class I alleles and missing expression of the KIR ligand on mismatched allogeneic cells can trigger NK cell alloreactivity [239]. Most NK cells express the inhibitory KIRs [243]. Allowing a greater T-cell content in the allograft could reduce the infection-related morbidity and mortality that are associated with extensive T cell depletion in mismatched transplants thus facilitating the use of mismatched allogeneic HSCT in elderly individuals and in heavily pretreated patients [239]. In a study the included 2062 patients with AML, CML, and MDSs subjected to unrelated allogeneic HSCT, missing KIR ligands were found to be associated with lower rates of relapse and higher incidences of GVHD [243].

Although, the use of post-transplant cyclophosphamide (PTC) as GVHD prophylaxis has revolutionized haploidentical HSCT, PTC eliminates most mature donor NK cells infused in the graft including alloreactive NK cells [244,245]. However, recovery of NK cells after haploidentical HSCT is greatly influenced by other subsets of immune cells and by drugs used in the post-transplant period [244]. Although NK cell infusion given to 10 patients with AML in CR1 led to a 2 year EFS of 100%, a prospective phase II study that was performed in 2 centers and that included 16 patients with HR leukemia and multiply relapsed tumors subjected to haploidentical HSCT showed that preemptive NK cell infusions had no apparent effect on the rates of graft failure or disease relapse [246,247]. NK cells generated after haploidentical HSCT are blocked at an immature state that has specific phenotype and impaired functioning and this has negative impact on immune responsiveness and clinical outcome following HSCT [248]. Haploidentical HSCT offers the benefits of rapid and nearly universal donor availability and has been accepted worldwide as an alternative therapeutic modality for patients with HR-HMs who do not have HLA-identical sibling donors [249]. A phase I clinical trial using membrane bound IL-21 *ex vivo*-expanded donor derived NK cells given to patients with HR-HMs receiving haploidentical HSCT showed that NK cell infusions were associated with: improved NK cell function, lower relapse rate, and low incidence of viral infections in the post-transplant period [250]. In patients with acute leukemia subjected to haploidentical allogeneic grafts: early CMV reactivation and expression of $CD56^{bright}$ $CD16^{dim}$ $DNAM1^{+}$ NK cells were associated with GVL effect reflected by lower relapse rates [251]. Also, in a retrospective study that included 246 patients with HMs subjected to allogeneic HSCT, NK cell reconstitution was associated with lower rate of disease relapse after HSCT particularly in patients with CMV reactivation [252].

Unidirectional KIR ligand incompatibility in the host versus graft effect has a detrimental effect on the outcome of T-cell-replete haploidentical HSCT in adults with AML [201]. Studies have shown that: (1) NK cells mediate GVL effect which is crucial to cure patients with HR-acute leukemia subjected to haploidentical HSCT; (2) graft manipulation based on depletion of $\alpha\beta$ T cells and B cells allows infusion of fully mature and alloreactive NK cells; and (3) reconstitution of iNK cells in PB following haploidentical HSCT in children with HMs is associated with disease control [253,254].

In a study that included 45 recipients of HLA matched HSCT grafts from related and unrelated donors subjected to reduced intensity conditioning (RIC) including antithymocyte globulin, the following results were obtained: NK cells recovered quickly after HSCT regardless the donor type; rapid quantitative reconstitution of the NK cell compartment despite the administration of potent immunosuppression in the conditioning therapy and in the post-HSCT period; the rapidly reemerging NK cells remained immature for > 6 months; and the rapid reconstitution of cytokine production correlated with lower relapse rates and prolongation of OS [235]. Manipulation of type of lymphocytes may be instrumental in

reducing the relatively high relapse rate following allogeneic HSCT with RIC [234]. In a study that included 909 patients with AML and MDSs subjected to RIC-allogeneic HSCT from unrelated donors, it was shown that KIR-HLA combinations recapitulated some but not all KIR-HLA effects observed in myeloablative allografts [255]. Also, in a study that included 282 patients with HMs subjected to allogeneic HSCT with non-myeloablative conditioning therapy: engraftment of donor NK cells correlated with lower risk of relapse and no GVHD, while engraftment of donor T cells correlated with higher risk of GVHD [256].

NK cells in solid tumors: Cancer cells frequently produce platelet derived growth factor receptor (PDGFR)-β which, through autocrine and paracrine PDGFR-β signaling, promotes tumor growth, cell proliferation, metastasis, stromal recruitment, angiogenesis, and epithelial-mesenchymal transition [257]. NK cells play a major role in the immune response to certain malignancies by several mechanisms that include: (1) directly by secretion of potent immune mediators such as targeted secretion of cytokines or cytotoxic granules to cause cytolysis of transformed cells, (2) indirectly by orchestrating anti-tumor immune responses to prevent metastatic spread by engagement of the activating receptor NKp46 on NK cells, (3) the human immunoreceptor NKp44 expressed on NK cells and the innate lymphoid cells recognize PDGF-DD produced by tumor cells and this plays a major part in the control of tumor growth by NK cells, and (4) NK cells recruit conventional type I DCs into the TME to promote immune control of tumors [6,7,72,257-259]. Thus, NK cells play key roles in innate and adaptive responses through unique NK cell activation mechanisms during early host defense against viruses and tumors by performing 2 major roles: contact dependent cytotoxicity and cytokine production for immune modulation [6,258,260].

Target cell apoptosis is primarily mediated by perforin and genzyme B. Also, the regulation of the immune responses is mediated by secretion of cytokines such as: IFN-γ, TNF-α, IL-1, IL-3, and granulocyte-macrophage colony-stimulating factor [3,260]. NK cells are attractive candidates for adoptive cellular therapy in: (1) cancer: HMs such as acute leukemia, and solid tumors, with either CAR-engineered NK cells or combining NK cells with CD16 binding antibodies or immune engagers; and (2) allogeneic HSCT including haploidentical allografts to protect against disease relapse by enhancing GVL effect without causing GVHD [1,2,10,72,106,234,242,261]. NK cells have crucial role in protection against cancer relapse [13,232]. The antitumor activity of NK cells is regulated by a sophisticated network of activating and inhibitory receptors [13]. Viral and non-viral methods have been adopted to genetically engineer NK cells in order to improve their antitumor activity [13].

The metastatic spread of malignant cells to distant sites, which is regulated by TME and systemic processes that include immunosurveillance, is a principal cause of cancer-related death [262]. NK cells are crucial for immunosurveillance and are essential for controlling metastatic dissemination of cancer cells [59,262]. However, NK cells are highly dysfunctional and reduced in number in patients with solid tumors [71]. Also, antitumor response of NK cells faces plenty of limitations [73]. Adoptive transfer of large numbers of cytolytic NK cells to induce antitumor responses is widely explored in cancer immunotherapy [71]. In preclinical studies: (1) ECVs derived from NK cells have shown promising antitumor effects, and (2) genetic engineering of NK cells to express CARs to redirect their antitumor specificity has shown significant promise [73,263]. Monoclonal antibodies and bispecific killer engagers may enhance specificity by inhibition of CD16 shedding and enhance NK cytotoxicity [264]. PDGF-DD-induced NK cytokines such as TNF-α and IFN-γ can trigger tumor cell-cycle arrest in mouse models [257].

Several studies have shown the following effects of NK cells in different cancers: NK cells have been shown to be effective in patients with advanced lung cancer; Herceptin-treated NK cells have been found to have therapeutic potential in the treatment of patients with human epidermal growth factor receptor 2 ($Her2^+$) and Herceptin-intolerant breast cancer; expanded and cryopreserved NK cells are promising candidates for cellular immunotherapy in patients with pancreatic carcinoma; NK cells inhibit metastesis of ovarian carcinoma cells in murine models; CIK cells may become a novel therapeutic modality for rhabdomyosarcoma after allogeneic HSCT; CAR-engineered CIK cells may become valuable in the treatment of HR soft tissue sarcoma in children; and expanded and CIK cells are safe and well tolerated and they enhance cytotoxicity against gastric carcinoma [162,265-271]. A meta-analysis, that included 29 clinical trials involving 2610 patients, has been shown that the combination of CIK/DC-CIK immunotherapy and cytotoxic chemotherapy: enhances the immune function of patients, alleviates the adverse effects of chemotherapy, and improves the overall response, disease control, and quality of life [272].

Glioblastoma (GB) is the most aggressive primary brain malignancy in adults and it carries poor prognosis as it is still incurable [273,274]. Studies have shown that CAR-engineered and PD-1 inhibited NK cells exhibit antitumor effects and can induce apoptosis of GB cells [273-276]. GB stem-like cells are more susceptible to lysis by NK cells than differentiated GB cells [277]. In animal models, pretreatment of GB with bortezomib has been shown to promote NK cell cytotoxicity and to inhibit tumor growth ultimately leading to prolonged survival [278]. Varicella zoster virus (VZV) is the only virus with negative correlation with GB [169,279]. NK cells represent a significant barrier to oncolytic herpes simplex virus therapy of GB [280]. Oncolytic virotherapy provokes the antitumor activity of NK cells by triggering antiviral immune responses [281]. NK cell immunotherapy has shown promising effects in the treatment of childhood solid tumors such as: rhabdomyosarcoma,

Ewing's sarcoma, and neuroblastoma due to prominent GVT effects both in transplant setting and in combination with antibodies [282].

NK cells and infections: NK cells are involved in the host immune response against infections caused by viral, bacterial, and fungal pathogens which are significant causes of morbidity and mortality in immunocompromised hosts. Hence, there is interest in strengthening the immune response in immunocompromised individuals by: (1) use of cytokines or growth factors, or (2) adoptive cellular therapies including: donor granulocytes, pathogen-specific T cells, and adoptively transferred or transfused NK cells [163]. In polymicrobial sepsis, there is immunoparalysis that includes impairment of both the number as well as the function of NK cells [283].

NK cells can act as rheostats, regulating T cell-mediated support for the antiviral CD8 T cells that control viral pathogenesis and persistence [284]. NK cells play a vital role in host defense against HIV, herpes viruses, hepatitis B virus (HBV), and hepatitis C virus (HCV) [3]. The hepatic NK cell populations that are involved in controlling HCV infection may also be involved in the control of HCV-associated liver damage [285]. NKG2C-expressing NK cells are involved in the early control of CMV reactivation following allogeneic HSCT [124]. Two NK cell subsets might play a critical role in the immune response against Dengue virus infection [286]. NK cells are important in herpes virus infections as patients with deficiencies of NK cells experience systemic and life-threatening infections that are caused by herpes viruses [287]. VZV productively infects human NK cells and actively manipulates their phenotype thus NK cells play a potential role in the pathogenesis of VZV infections [288].

In immunocompromised hosts including recipients of HSCT and cancer patients, recovery of the immune system has a major impact on the outcome of infectious complications that represent a significant cause of morbidity and mortality in this group of patients [163,287]. Strategies that can be employed to strengthen the host immune response to counteract infections include the use of: growth factors; specific cytokines and adoptive cellular therapies such as granulocyte transfusions, pathogen-specific T-cells and adoptive transfer of NK cells [163]. NK cells have a major role to play in controlling various infectious complications including: (1) viral infections such as: HIV, and HBV; (2) parasitic infections such as: toxoplasmosis, malaria, leishmaniasis, and trypanosomiasis; and (3) bacterial sepsis due to: Streptococcus pneumoniae, and Escherichia coli [3,78,283].

NK cells play a major role in the immune response to certain viral infections by: (1) direct cytolysis or killing of virus-infected cells in order to rapidly control viral infection, and (2) secretion of potent immune mediators such as IFN-γ and other cytokines [3,8,289,290]. NK cells share features with long-lived adaptive immune cells and this can impact disease pathogenesis through inhibition of adaptive immune responses by virus-specific T and B cells as NK cells are potent regulators of antiviral T and B cell responses [290]. NK cells can produce persistent memory in response to certain viral infections particularly those caused by CMV [14]. NK cells have multiple mechanisms to kill virus-infected cells through the engagement of extracellular death receptors, and through exocytosis of cytotoxic granules. However, mediation of cytolysis occurs through: engagement of death receptors expressed on target cells, and expression by NK cells of multiple extracellular ligands including fas ligand and TNF-related apoptosis-induced ligand ultimately resulting in apoptosis of the target cells [8].

VZV actively manipulates the NK cell phenotype through productive infection. NK cells have a potential role in VZV pathogenesis and they are implicated in controlling infections caused by VZV [288]. Decreased NK cell function is associated with: (1) several genetic or hereditary disorders, (2) several chronic disorders such as: chronic fatigue syndrome, depression, autoimmune diseases, metastatic cancer, and exposure to occupational chemicals, and (3) certain viral infections such as HIV [3]. Although NK cell deficiencies are rare, they predispose to infections by herpes viruses [8]. VZV-infects NK cells using multiple entry mechanisms and causes: (1) cell to cell interaction with VZV-infected epithelial cells during early encounter or entry, and (2) subsequent modulation of NK cell function and phenotype resulting in stimulation of chemokine receptors and CD57 expression and inhibition of the expression of CD56, CD 16 and FcVRIII [8,288].

Challenges facing the clinical utilization of NK cells

Acquisition of large numbers of mature and functional NK cells that can be derived and differentiated from UCB-CD3$^+$HSCs is easily accessible, but optimal clinical protocols for NK cell therapies in leukemia and other cancers are still lacking [291]. Although the use of viral vectors has achieved the highest level of efficiency of gene transfer of NK cells, the utilization of nonviral vectors and other gene transfer approaches such as: electroporation, lipofection, nanoparticles, and trogocytosis are emerging [13,261]. Despite the extensive number of preclinical studies only a handful of NK cell-based therapies have progressed to the clinic. As of mid-2018, there were only 8 registered clinical trials utilizing genetically engineered NK cells [13]. For successful translation of genetically modified NK cells, issues related to: viral vector safety, efficacy, and compliance with regulatory guidelines become vitally important [13,73]. Despite the numerous challenges associated with the preclinical and clinical development of NK cell-based therapies for cancer, NK cells have several unique immunological properties that enable them to be potentially effective means for cancer immunotherapy [292].

Maturation of NK cells starts in the BM then continues in peripheral tissues. Upon differentiation, mature NK cells migrate outside the BM and peculiar subsets of NK cells home back to or localize in the BM compartment to perform specific functions [30]. Human BM-resident NK cells have a unique transcriptional profile and resemble resident memory $CD8^+$ T cells [18]. Persistence of NK cells *in vivo* can be improved by: IL-2 and IL-15 [12]. Homing of NK cells to target tissues can be improved by: (1) transfection with CCR7mRNA electroporation, (2) transfer of CCR7 protein from feeder cells using trogocytosis, and (3) genetic modification that targets homing receptors [12]. The major contributing factors for resistance to NK cell therapies are shown in table 7 [164,293].

Table 7: Causes of Resistance to Natural Killer (NK) Cell Therapies.
1. Ability of solid tumors to escape immunosurveillance
2. Decreased expression of activating receptors of NK cells
3. Overexpression of inhibitory receptors of NK cells
4. Decreased activation and persistence of NK cells
5. Defective cytokine production
6. Abnormal intracellular signaling molecules
7. Inefficient trafficking of NK cells to tumor sites
8. Senescence resulting in defective cytolytic response
9. Contamination of blood-derived NK cell products by T lymphocytes

Conclusions and Future Directions

The role of NK cell therapy in patients with HMs, solid tumors and in recipients of various forms of HSCT is evolving rapidly. The utilization of NK cells in conjunction with cytotoxic chemotherapy, and novel therapies including monoclonal antibodies has increased the response rates of patients with HMs and solid tumors to the standard therapeutic modalities. In general, cancer patients have qualitative and quantitative NK cell deficiencies, but there are several maneuvers to enhance NK cell function in these immunocompromised individuals. There are several limitations facing the clinical utilization of NK cell-base immunotherapies that need to be resolved. These challenges include: evolution of resistance to therapy; having control quality and safety measures; design of specific protocols for preparation and manufacture; banking and cryopreservation of harvested NK cell products; administration and therapeutic use of each type and source of NK cells; and finally tracing of the infused NK cells.

References

1. Mehta RS, Randolph B, Daher M, Rezvani K. NK cell therapy for hematologic malignancies. Int J Hematol. 2018; 107: 262-270. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/29383623

2. Handgretinger R, Lang P, André MC. Exploitation of natural killer cells for the treatment of acute leukemia. Blood. 2016; 127: 3341-3349. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/27207791

3. See DM, Khemka P, Sahl L, Bui T, Tilles JG. The role of natural killer cells in viral infections. Scand J Immunol. 1997; 46: 217-224. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/9315107

4. Freud AG, Mundy-Bosse BL, Yu J, Caligiuri MA. The broad spectrum of human natural killer cell diversity. Immunity. 2017; 47: 820-833. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/29166586

5. Crinier A, Milpied P, Escalière B, Piperoglou C, Galluso J, et al. High-dimensional single-cell analysis identifies organ-specific signatures and conserved NK cell subsets in humans and mice. Immunity. 2018; 49: 971-986. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30413361

6. Orr MT, Lanier LL. Natural killer cell education and tolerance. Cell. 2010; 142: 847-856. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/20850008

7. Abel AM, Yang C, Thakar MS, Malarkannan S. Natural killer cells: development, maturation, and clinical utilization. Front Immunol. 2018; 9: 1869. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30150991

8. van Erp EA, van Kampen MR, van Kasteren PB, de Wit J. Viral infection of human natural killer cells. Viruses. 2019; 11: 243. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30870969

9. Pittari G, Filippini P, Gentilcore G, Grivel JC, Rutella S. Revving up natural killer cells and cytokine-induced killer cells against hematological malignancies. Front Immunol. 2015; 6: 230. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/26029215

10. Collins PL, Cella M, Porter SI, Li S, Gurewitz GL, Hong HS, et al. Gene regulatory programs conferring phenotypic identities to human NK cells. Cell. 2019; 176: 348-360. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30595449

11. Yoon SR, Kim TD, Choi I. Understanding of molecular mechanisms in natural killer cell therapy. Exp Mol Med. 2015; 47: 141. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/25676064

12. Harada Y, Teraishi K, Ishii M, Ban H, Yonemitsu Y. Clinical applications of natural killer cells. In: Natural killer cells. Edited by Aribi M. Intech Open. 2017.

13. Matosevic S. Viral and nonviral engineering of natural killer cells as emerging adoptive cancer immunotherapies. J Immunol Res. 2018; 2018: 4054815. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30306093

14. Tesi B, Schlums H, Cichocki F, Bryceson YT. Epigenetic regulation of adaptive NK cell diversification. Trends Immunol. 2016; 37: 451-461. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/27160662

15. Robertson MJ. Role of chemokines in the biology of natural killer cells. J Leukoc Biol. 2002; 71: 173-183. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/11818437

16. Maghazachi AA. Role of chemokines in the biology of natural killer cells. Curr Top Microbiol Immunol. 2010; 341: 37-58. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/20369317

17. Wu Y, Tian Z, Wei H. Developmental and functional control of natural killer cells by cytokines. Front Immunol. 2017; 8: 930. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/28824650

18. Melsen JE, Lugthart G, Vervat C, Kielbasa SM, van der Zeeuw SAJ, et al. Human bone marrow-resident natural killer cells have a unique transcriptional profile and resemble resident memory $CD8^+$ T cells. Front Immunol. 2018; 9: 1829. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30186282

19. Smith DJ, Liu S, Ji S, Li B, McLaughlin J, Cheng D, et al. Genetic engineering of hematopoietic stem cells to generate invariant natural killer T cells. Proc Natl Acad Sci USA. 2015; 112: 1523-1528. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/25605948

20. Chaidos A, Patterson S, Szydlo R, Chaudhry MS, Dazzi F, et al. Graft invariant natural killer T-cell dose predicts risk of acute graft-versus-host disease in allogeneic hematopoietic stem cell transplantation. Blood. 2012; 119: 5030-5036. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/22371885

21. Mavers M, Maas-Bauer K, Negrin RS. Invariant natural killer T cells as suppressors of graft-versus-host disease in allogeneic hematopoietic stem cell transplantation. Front Immunol. 2017; 8: 900. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/28824628

22. Du J, Paz K, Thangavelu G, Schneidawind D, Baker J, Flynn R, et al. Invariant natural killer T cells ameliorate murine chronic GVHD by expanding donor regulatory T cells. Blood. 2017; 129: 3121-3125. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/28416503

23. Schneidawind D, Pierini A, Alvarez M, Pan Y, Baker J, et al. $CD4^+$ invariant natural killer T cells protect from murine GVHD lethality through expansion of donor $CD4^+CD25^+FoxP3^+$ regulatory T cells. Blood. 2014; 124: 3320-3328. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/25293774

24. Sun W, Wang Y, East JE, Kimball AS, Tkaczuk K, et al. Invariant natural killer T cells generated from human adult hematopoietic stem-progenitor cells are poly-functional. Cytokine. 2015; 72: 48-57. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/25569376

25. Beyaz S, Kim JH, Pinello L, Xifaras ME, Hu Y, et al. The histone demethylase UTX regulates the lineage-specific epigenetic program of invariant natural killer T cells. Nat Immunol. 2017; 18: 184-195. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/27992400

26. Merker M, Salzmann-Manrique E, Katzki V, Huenecke S, Bremm M, et al. Clearance of hematologic malignancies by allogeneic cytokine-induced killer cell or donor lymphocyte infusions. Biol Blood Marrow Transplant. 2019; 25: 1281-1292. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30878607

27. Yang XY, Zeng H, Chen FP. Cytokine-induced killer cells: a novel immunotherapy strategy for leukemia. Oncol Lett. 2015; 9: 535-541. https://www.ncbi.nlm.nih.gov/pubmed/25621022

28. Rettinger E, Huenecke S, Bonig H, Merker M, Jarisch A, et al. Interleukin-15-activated cytokine-induced killer cells may sustain remission in leukemia patients after allogeneic stem cell transplantation: feasibility, safety and first insights on efficacy. Haematologica. 2016; 101: 153-156. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/26768688

29. Mavers M, Bertaina A. High-risk leukemia: past, present, and future role of NK cells. J Immunol Res. 2018; 2018: 1586905. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/29850617

30. Bonanni V, Sciumè G, Santoni A, Bernardini G. Bone marrow NK cells: origin, distinctive features, and requirements for tissue localization. Front Immunol. 2019; 10: 1569. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31354722

31. Mace EM, Orange JS. Emerging insights into human health and NK cell biology from the study of NK cell deficiencies. Immunol Rev. 2019; 287: 202-225. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30565241

32. Hattori N, Nakamaki T. Natural killer immunotherapy for minimal residual disease eradication following allogeneic hematopoietic stem cell transplantation in acute myeloid leukemia. Int J Mol Sci. 2019; 20: 2057. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31027331

33. Chiossone L, Vacca P, Orecchia P, Croxatto D, Damonte P, Astigiano S, et al. In vivo generation of decidual natural killer cells from resident hematopoietic progenitors. Haematologica. 2014; 99: 448-457. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/24179150

34. Orange JS. Understanding natural killer cell deficiency. IG Living. 2018; 32-34.

35. Mace EM, Orange JS. Genetic causes of human NK cell deficiency and their effect on NK cell subsets. Front Immunol. 2016; 7: 545. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/27994588

36. Vargas-Hernández A, Forbes LR. The impact of immunodeficiency on NK cell maturation and function. Curr Allergy Asthma Rep. 2019; 19: 2. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30847722

37. Mace EM. Phosphoinositide-3-kinase signaling in human natural killer cells: new insights from primary immunodeficiency. Front Immunol. 2018; 9: 445. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/29563913

38. Orange JS. Natural killer cell deficiency. J Allergy Clin Immunol. 2013; 132: 515-525. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/23993353

39. Shabrish S, Kelkar M, Chavan N, Desai M, Bargir U, et al. Natural killer cell degranulation defect: a cause for impaired NK-cell cytotoxicity and hyperinflammation in Fanconi anemia patients. Front Immunol. 2019; 10: 490. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30949167

40. Ham H, Billadeau DD. Human immunodeficiency syndromes affecting human natural killer cell cytolytic activity. Front Immunol. 2014; 5: 2. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/24478771

41. Angka L, Khan ST, Kilgour MK, Xu R, Kennedy MA, et al. Dysfunctional natural killer cells in the aftermath of cancer surgery. Int J Mol Sci. 2017; 18: E1787. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/28817109

42. Guo Y, Patil NK, Luan L, Bohannon JK, Sherwood ER. The biology of natural killer cells during sepsis. Immunology. 2018; 153: 190-202. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/29064085

43. Hejazi M, Manser AR, Fröbel J, Kündgen A, Zhao X, et al. Impaired cytotoxicity associated with defective natural killer cell differentiation in myelodysplastic syndromes. Haematologica. 2015; 100: 643-652. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/25682594

44. Tamura J, Kubota K, Murakami H, Sawamura M, Matsushima T, et al. Immunomodulation by vitamin B12: augmentation of $CD8^+$ T lymphocytes and natural killer (NK) cell activity in vitamin B12-deficient patients by methyl-B12 treatment. Clin Exp Immunol. 1999; 116: 28-32. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/10209501

45. Gill HS, Rutherfurd KJ, Cross ML. Dietary probiotic supplementation enhances natural killer cell activity in the elderly: an investigation of age-related immunological changes. J Clin Immunol. 2001; 21: 264-271. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/11506196

46. Chiang BL, Sheih YH, Wang LH, Liao CK, Gill HS. Enhancing immunity by dietary consumption of a probiotic lactic acid bacterium (Bifidobacterium lactis HN019): optimization and definition of cellular immune responses. Eur J Clin Nutr. 2000; 54: 849-855. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/11114680

47. Takeda K, Okumura K. CAM and NK cells. Evid Based Complement Alternat Med. 2004; 1: 17-27.

48. Witek-Janusek L, Albuquerque K, Chroniak KR, Chroniak C, Durazo-Arvizu R, et al. Effect of mindfulness based stress reduction on immune function, quality of life and coping in women newly diagnosed with early stage breast cancer. Brain Behav Immun. 2008; 22: 969-981. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/18359186

49. Speak AO, Te Vruchte D, Davis LC, Morgan AJ, Smith DA, et al. Altered distribution and function of natural killer cells in murine and human Niemann-Pick disease type C1. Blood. 2014; 123: 51-60. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/24235134

50. Sung PS, Jang JW. Natural killer cell dysfunction in hepatocellular carcinoma: pathogenesis and clinical implications. Int J Mol Sci. 2018; 19: 3648. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30463262

51. Holder KA, Russell RS, Grant MD. Natural killer cell function and dysfunction in hepatitis C virus infection. Biomed Res Int. 2014; 2014: 903764. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/25057504

52. Caligiuri M, Murray C, Buchwald D, Levine H, Cheney P, et al. Phenotypic and functional deficiency of natural killer cells in patients with chronic fatigue syndrome. J Immunol. 1987; 139: 3306-3313. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/2824604

53. Vitale M, Cantoni C, Della Chiesa M, Ferlazzo G, Carlomagno S, et al. An historical overview: the discovery of how NK cells can kill enemies, recruit defense troops, and more. Front Immunol. 2019; 10: 1415. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31316503

54. Poznanski SM, Ashkar AA. What defines NK cell functional fate: phenotype or metabolism? Front Immunol. 2019; 10: 1414. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31275330

55. Huang P, Wang F, Yang Y, Lai W, Meng M, et al. Hematopoietic-specific deletion of Foxo1 promotes NK cell specification and proliferation. Front Immunol. 2019; 10: 1016. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31139183

56. Parodi M, Raggi F, Cangelosi D, Manzini C, Balsamo M, Blengio F, et al. Hypoxia modifies the transcriptome of human NK cells, modulates their immunoregulatory profile, and influences NK cell subset migration. Front Immunol. 2018; 9: 2358. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30459756

57. Darji A, Kaushal A, Desai N, Rajkumar S. Natural killer cells: from defense to immunotherapy in cancer. J Stem Cell Res Ther. 2018; 8: 419.

58. Terrén I, Mikelez I, Odriozola I, Gredilla A, González J, Orrantia A, et al. Implication of interleukin-12/15/18 and ruxolitinib in the phenotype, proliferation, and polyfunctionality of human cytokine-preactivated natural killer cells. Front Immunol. 2018; 9: 737. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/29713323

59. Souza-Fonseca-Guimaraes F, Cursons J, Huntington ND. The emergence of natural killer cells as a major target in cancer immunotherapy. Trends Immunol. 2019; 40: 142-158. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30639050

60. Pesce S, Squillario M, Greppi M, Loiacono F, Moretta L, et al. New miRNA signature heralds human NK cell subsets at different maturation steps: involvement of miR-146a-5p in the regulation of KIR expression. Front Immunol. 2018; 9: 2360. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30374356

61. Grudzien M, Rapak A. Effect of natural compounds on NK cell activation. J Immunol Res. 2018; 2018: 4868417. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30671486

62. Ravaglia G, Forti P, Maioli F, Bastagli L, Facchini A, et al. Effect of micronutrient status on natural killer cell immune function in healthy free-living subjects aged >/=90 y. Am J Clin Nutr. 2000; 71: 590-598. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/10648276

63. Kwak JH, Baek SH, Woo Y, Han JK, Kim BG, et al. Beneficial immunostimulatory effect of short-term Chlorella supplementation: enhancement of natural killer cell activity and early inflammatory response (randomized, double-blinded, placebo-controlled trial). Nutr J. 2012; 11: 53. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/22849818

64. Currier NL, Miller SC. The effect of immunization with killed tumor cells, with/without feeding of Echinacea purpurea in an erythroleukemic mouse model. J Altern Complement Med. 2002; 8: 49-58. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/11890433

65. Partearroyo T, Úbeda N, Montero A, Achón M, Varela-Moreiras G. Vitamin B (12) and folic acid imbalance modifies NK cytotoxicity, lymphocytes B and lymphoprolipheration in aged rats. Nutrients. 2013; 5: 4836-4848. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/24288024

66. Chaigne-Delalande B, Li FY, O'Connor GM, Lukacs MJ, Jiang P, et al. $Mg2^+$ regulates cytotoxic functions of NK and CD8 T cells in chronic EBV infection through NKG2D. Science. 2013; 341: 186-191. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/23846901

67. Fiala M. Curcumin and omega-3 fatty acids enhance NK cell-induced apoptosis of pancreatic cancer cells but curcumin inhibits interferon-γ production: benefits of omega-3 with curcumin against cancer. Molecules. 2015; 20: 3020-3026. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/25685909

68. Millman AC, Salman M, Dayaram YK, Connell ND, Venketaraman V. Natural killer cells, glutathione, cytokines, and innate immunity against Mycobacterium tuberculosis. J Interferon Cytokine Res. 2008; 28: 153-165. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/18338948

69. Dahlberg CI, Sarhan D, Chrobok M, Duru AD, Alici E. Natural killer cell-based therapies targeting cancer: possible strategies to gain and sustain anti-tumor activity. Front Immunol. 2015; 6: 605. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/26648934

70. Bassani B, Baci D, Gallazzi M, Poggi A, Bruno A, et al. Natural killer cells as key players of tumor progression and angiogenesis: old and novel tools to divert their pro-tumor activities into potent anti-tumor effects. Cancers (Basel). 2019; 11: 461. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30939820

71. Veluchamy JP, Kok N, van der Vliet HJ, Verheul HMW, de Gruijl TD, et al. The rise of allogeneic natural killer cells as a platform for cancer immunotherapy: recent innovations and future developments. Front Immunol. 2017; 8: 631. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/28620386

72. Chouaib S, Pittari G, Nanbakhsh A, El Ayoubi H, Amsellem S, et al. Improving the outcome of leukemia by natural killer cell-based immunotherapeutic strategies. Front Immunol. 2014; 5: 95. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/24672522

73. Hu W, Wang G, Huang D, Sui M, Xu Y. Cancer immunotherapy based on natural killer cells: current progress and new opportunities. Front Immunol. 2019; 10: 1205. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31214177

74. Pfeifer C, Highton AJ, Peine S, Sauter J, Schmidt AH, et al. Natural killer cell education is associated with a distinct glycolytic profile. Front Immunol. 2018; 9: 3020. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30619362

75. O'Sullivan TE, Sun JC, Lanier LL. Natural killer cell memory. Immunity. 2015; 43: 634-645.

76. Min-Oo G, Kamimura Y, Hendricks DW, Nabekura T, Lanier LL. Natural killer cells: walking three paths down memory lane. Trends Immunol. 2013; 34: 251-258. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/23499559

77. Cooper MA. Natural killer cells might adapt their inhibitory receptors for memory. Proc Natl Acad Sci USA. 2018; 115: 11357-11359. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30337482

78. Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S. Functions of natural killer cells. Nat Immunol. 2008; 9: 503-510.

79. Piccioli D, Sbrana S, Melandri E, Valiante NM. Contact-dependent stimulation and inhibition of dendritic cells by natural killer cells. J Exp Med. 2002; 195: 335-341. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/11828008

80. Harizi H. Reciprocal crosstalk between dendritic cells and natural killer cells under the effects of PGE2 in immunity and immunopathology. Cell Mol Immunol. 2013; 10: 213-221. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/23524652

81. Gerosa F, Baldani-Guerra B, Nisii C, Marchesini V, Carra G, Trinchieri G. Reciprocal activating interaction between natural killer cells and dendritic cells. J Exp Med. 2002; 195: 327-333.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11828007

82. Ferlazzo G, Morandi B. Cross-talks between natural killer cells and distinct subsets of dendritic cells. Front Immunol. 2014; 5: 159.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24782864

83. Leno-Durán E, Muñoz-Fernández R, Olivares EG, Tirado-González I. Liaison between natural killer cells and dendritic cells in human gestation. Cell Mol Immunol. 2014; 11: 449-455.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24954224

84. Walzer T, Dalod M, Robbins SH, Zitvogel L, Vivier E. Natural-killer cells and dendritic cells: "l'union fait la force". Blood. 2005; 106: 2252-2258.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15933055

85. Calmeiro J, Carrascal M, Gomes C, Falcão A, Cruz MT, Neves BM. Heighlighting the role of DC-NK cell interplay in immunobiology and immunotherapy. 2018.

86. Van Elssen CH, Oth T, Germeraad WT, Bos GM, Vanderlocht J. Natural killer cells: the secret weapon in dendritic cell vaccination strategies. Clin Cancer Res. 2014; 20: 1095-1103.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24590885

87. Sanabria MX, Vargas-Inchaustegui DA, Xin L, Soong L. Role of natural killer cells in modulating dendritic cell responses to Leishmania amazonensis infection. Infect Immun. 2008; 76: 5100-5109.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18794295

88. Moretta A. Natural killer cells and dendritic cells: rendezvous in abused tissues. Nat Rev Immunol. 2002; 2: 957-964.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12461568

89. Andoniou CE, Van Dommelen SL, Voigt V, Andrews DM, Brizard G, et al. Interaction between conventional dendritic cells and natural killer cells is integral to the activation of effective antiviral immunity. Nat Immunol. 2005; 6: 1011-1019.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16142239

90. Mavilio D, Lombardo G, Kinter A, Fogli M, La Sala A, et al. Characterization of the defective interaction between a subset of natural killer cells and dendritic cells in HIV-1 infection. J Exp Med. 2006; 203: 2339-2350.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17000867

91. Spaggiari GM, Capobianco A, Becchetti S, Mingari MC, Moretta L. Mesenchymal stem cell-natural killer cell interactions: evidence that activated NK cells are capable of killing MSCs, whereas MSCs can inhibit IL-2-induced NK-cell proliferation. Blood. 2006; 107: 1484-1490.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16239427

92. Casado JG, Tarazona R, Sanchez-Margallo FM. NK and MSCs crosstalk: the sense of immunomodulation and their sensitivity. Stem Cell Rev Rep. 2013; 9: 184-189.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23397451

93. Spaggiari GM, Capobianco A, Abdelrazik H, Becchetti F, Mingari MC, et al. Mesenchymal stem cells inhibit natural killer-cell proliferation, cytotoxicity, and cytokine production: role of indoleamine 2,3-dioxygenase and prostaglandin E2. Blood. 2008; 111: 1327-1333.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17951526

94. Thomas H, Jäger M, Mauel K, Brandau S, Lask S, et al. Interaction with mesenchymal stem cells provokes natural killer cells for enhanced IL-12/IL-18-induced interferon-gamma secretion. Mediators Inflamm. 2014; 2014: 143463.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24876666

95. Sotiropoulou PA, Perez SA, Gritzapis AD, Baxevanis CN, Papamichail M. Interactions between human mesenchymal stem cells and natural killer cells. Stem Cells 2006; 24: 74-85.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16099998

96. Galland S, Vuille J, Martin P, Letovanec I, Caignard A, Fregni G, et al. Tumor-derived mesenchymal stem cells use distinct mechanisms to block the activity of natural killer cell subsets. Cell Rep. 2017; 20: 2891-2905.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28930684

97. Petri RM, Hackel A, Hahnel K, Dumitru CA, Bruderek K, et al. Activated tissue-resident mesenchymal stromal cells regulate natural killer cell immune and tissue-regenerative function. Stem Cell Rep. 2017; 9: 985-998.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28781075

98. Najar M, Fayyad-Kazan M, Merimi M, Burny A, Bron D, et al. Mesenchymal stromal cells and natural killer cells: a complex story of love and hate. Curr Stem Cell Res Ther. 2019; 14: 14-21.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30207245

99. Najar M, Fayyad-Kazan M, Meuleman N, Bron D, Fayyad-Kazan H, Lagneaux L, et al. Mesenchymal stromal cells of the bone marrow and natural killer cells: cell interactions and cross modulation. J Cell Commun Signal. 2018; 12: 673-688.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29350342

100. Yan CH, Liu QF, Wu DP, Zhang X, Xu LP, et al. Prophylactic donor lymphocyte infusion (DLI) followed by minimal residual disease and graft-versus-host disease-guided multiple DLIs could improve outcomes after allogeneic hematopoietic stem cell transplantation in patients with refractory/relapsed acute leukemia. Biol Blood Marrow Transplant. 2017; 23: 1311-1319.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28483716

101. Villa NY, Rahman MM, McFadden G, Cogle CR. Therapeutics for graft versus-host disease: from conventional therapies to novel virotherapeutic strategies. Viruses. 2016; 8: 85.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27011200

102. Chang YJ, Zhao XY, Huang XJ. Strategies for enhancing and preserving anti-leukemia effects without aggravating graft-versus-host disease. Front Immunol. 2018; 9: 3041.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30619371

103. Vasu S, Geyer S, Bingman A, Auletta JJ, Jaglowski S, et al. Granulocyte colony-stimulating factor-mobilized allografts contain activated immune cell subsets associated with risk of acute and chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2016; 22: 658-668.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26743340

104. Miller JS, Warren EH, van den Brink MR, Ritz J, Shlomchik WD, et al. NCI first international workshop on the biology, prevention, and treatment of relapse after allogeneic hematopoietic stem cell transplantation: report from the Committee on the Biology Underlying Recurrence of Malignant Disease following Allogeneic HSCT: graft-versus-tumor/leukemia reaction. Biol Blood Marrow Transplant. 2010; 16: 565-586.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20152921

105. Dickinson AM, Norden J, Li S, Hromadnikova I, Schmid C, et al. Graft-versus-leukemia effect following hematopoietic stem cell transplantation for leukemia. Front Immunol. 2017; 8: 496.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28638379

106. Cruz CR, Bollard CM. T-cell and natural killer cell therapies for hematologic malignancies after hematopoietic stem cell transplantation: enhancing the graft-versus-leukemia effect. Haematologica. 2015; 100: 709-719.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26034113

107. Cooke KR, Luznik L, Sarantopoulos S, Hakim FT, Jagasia M, et al. The biology of chronic graft-versus-host Disease: a task force report from the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease. Biol Blood Marrow Transplant. 2017; 23: 211-234.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27713092

108. Yu H, Tian Y, Wang Y, Mineishi S, Zhang Y. Dendritic cell regulation of graft-vs.-host disease: immunostimulation and tolerance. Front Immunol. 2019; 10: 93.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30774630

109. Sairafi D, Stikvoort A, Gertow J, Mattsson J, Uhlin M. Donor cell composition and reactivity predict risk of acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. J Immunol Res. 2016; 2016: 5601204.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27965986

110. Ruzek MC, Kavanagh BF, Scaria A, Richards SM, Garman RD. Adenoviral vectors stimulate murine natural killer cell responses and demonstrate antitumor activities in the absence of transgene expression. Mol Ther. 2002; 5: 115-124.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11829518

111. Weber G, Gerdemann U, Caruana I, Savoldo B, Hensel NF, et al. Generation of multi-leukemia antigen-specific T cells to enhance the graft-versus-leukemia effect after allogeneic stem cell transplant. Leukemia. 2013; 27: 1538-1547.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23528871

112. Bertaina A, Roncarolo MG. Graft engineering and adoptive immunotherapy: new approaches to promote immune tolerance after hematopoietic stem cell transplantation. Front Immunol. 2019; 10: 1342.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31354695

113. Kanfar S, Al-Anazi KA. Autologous graft versus host disease: an updated review. Ann Stem Cell Regenerat Med. 2018; 1: 1002.

114. Porrata LF. Clinical evidence of autologous graft versus tumor effect. Am J Immunol. 2009; 5: 1-7.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27635143

115. Porrata LF. Autologous graft-versus-tumor effect: reality or fiction? Adv Hematol. 2016; 2016: 5385972.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27635143

116. Kline J, Subbiah S, Lazarus HM, Van Besien K. Autologous graft-versus-host disease: harnessing anti-tumor immunity through impaired self-tolerance. Bone Marrow Transplant. 2008; 41: 505-513.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18026144

117. Holmberg L, Kikuchi K, Gooley TA, Adams KM, Hockenbery DM, et al. Gastrointestinal graft-versus-host disease in recipients of autologous hematopoietic stem cells: incidence, risk factors, and outcome. Biol Blood Marrow Transplant. 2006; 12: 226-234.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16443520

118. Batra A, Cottler-Fox M, Harville T, Rhodes-Clark BS, Makhoul I, et al. Autologous graft versus host disease: an emerging complication in patients with multiple myeloma. Bone Marrow Res. 2014; 2014: 891427.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24876970

119. Hammami MB, Talkin R, Al-Taee AM, Schoen MW, Goyal SD, et al. Autologous graft-versus-host disease of the gastrointestinal tract in patients with multiple myeloma and hematopoietic stem cell transplantation. Gastroenterology Res. 2018; 11: 52-57.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29511407

120. Schneidawind D, Pierini A, Negrin RS. Regulatory T cells and natural killer T cells for modulation of GVHD following allogeneic hematopoietic cell transplantation. Blood 2013; 122: 3116-21.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24068494

121. Hu LJ, Zhao XY, Yu XX, Lv M, Han TT, et al. Quantity and quality reconstitution of NKG2A^{+} natural killer cells are associated with graft-versus-host disease after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2019; 25: 1-11.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30142416

122. Jiang YZ, Barrett AJ, Goldman JM, Mavroudis DA. Association of natural killer cell immune recovery with a graft-versus-leukemia effect independent of graft-versus-host disease following allogeneic bone marrow transplantation. Ann Hematol. 1997; 74: 1-6.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/9031607

123. Huenecke S, Cappel C, Esser R, Pfirrmann V, Salzmann-Manrique E, et al. Development of three different NK cell subpopulations during immune reconstitution after pediatric allogeneic hematopoietic stem cell transplantation: prognostic markers in GvHD and viral infections. Front Immunol. 2017; 8: 109.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28239380

124. Kheav VD, Busson M, Scieux C, Peffault de Latour R, Maki G, et al. Favorable impact of natural killer cell reconstitution on chronic graft-versus-host disease and cytomegalovirus reactivation after allogeneic hematopoietic stem cell transplantation. Haematologica. 2014; 99: 1860-1867.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25085354

125. Meinhardt K, Kroeger I, Bauer R, Ganss F, Ovsiy I, et al. Identification and characterization of the specific murine NK cell subset supporting graft-versus-leukemia- and reducing graft-versus-host-effects. Oncoimmunology. 2015; 4: e981483.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25949862

126. Kariminia A, Ivison S, Ng B, Rozmus J, Sung S, et al. CD56 ^{bright} natural killer regulatory cells in filgrastim primed donor blood or marrow products regulate chronic graft-versus-host disease: the Canadian Blood and Marrow Transplant Group randomized 0601 study results. Haematologica. 2017; 102: 1936-1946.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28935847

127. Schneidawind D, Pierini A, Alvarez M, Pan Y, Baker J, et al. CD4^{+} invariant natural killer T cells protect from murine GVHD lethality through expansion of donor CD4^{+}CD25^{+}FoxP3^{+} regulatory T cells. Blood. 2014; 124: 3320-3328.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25293774

128. Van Elssen CHMJ, Ciurea SO. NK cell therapy after hematopoietic stem cell transplantation: can we improve anti-tumor effect? Int J Hematol. 2018; 107: 151-156.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29196968

129. Porrata LF, Gastineau DA, Padley D, Bundy K, Markovic SN. Re-infused autologous graft natural killer cells correlates with absolute lymphocyte count recovery after autologous stem cell transplantation. Leuk Lymphoma. 2003; 44: 997-1000.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12854901

130. Huttunen P, Taskinen M, Siitonen S, Saarinen-Pihkala UM. Impact of very early CD4(+) / CD8(+) T cell counts on the occurrence of acute graft-versus-host disease and NK cell counts on outcome after pediatric allogeneic hematopoietic stem cell transplantation. Pediatr Blood Cancer. 2015; 62: 522-528.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25417898

131. Verheyden S, Schots R, Duquet W, Demanet C. A defined donor activating natural killer cell receptor genotype protects against leukemic relapse after related HLA-identical hematopoietic stem cell transplantation. Leukemia. 2005; 19: 1446-1451.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15973456

132. Farag SS, Fehniger TA, Ruggeri L, Velardi A, Caligiuri MA. Natural killer cell receptors: new biology and insights into the graft-versus-leukemia effect. Blood. 2002; 100: 1935-1947.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12200350

133. Gill S, Olson JA, Negrin RS. Natural killer cells in allogeneic transplantation: effect on engraftment, graft- versus-tumor, and graft-versus-host responses. Biol Blood Marrow Transplant. 2009; 15: 765-776.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19539207

134. Whiteside TL. The natural killer (NK) cell and synergistic antitumor effects of interferon-gamma and interleukin-2. Cancer Invest. 1990; 8: 565-566.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/2124947

135. Lundqvist A, Yokoyama H, Smith A, Berg M, Childs R. Bortezomib

treatment and regulatory T-cell depletion enhance the antitumor effects of adoptively infused NK cells. Blood. 2009; 113: 6120-6127. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/19202127

136. Koh CY, Ortaldo JR, Blazar BR, Bennett M, Murphy WJ. NK-cell purging of leukemia: superior antitumor effects of NK cells H2 allogeneic to the tumor and augmentation with inhibitory receptor blockade. Blood. 2003; 102: 4067-4075. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/12893752

137. Kim Y, Lee SH, Kim CJ, Lee JJ, Yu D, et al. Canine non-B, non-T NK lymphocytes have a potential antibody-dependent cellular cytotoxicity function against antibody-coated tumor cells. BMC Vet Res. 2019; 15:339. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31610784

138. Wang W, Erbe AK, Hank JA, Morris ZS, Sondel PM. NK cell-mediated antibody-dependent cellular cytotoxicity in cancer immunotherapy. Front Immunol. 2015; 6: 368. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/26284063

139. Seidel UJ, Schlegel P, Lang P. Natural killer cell mediated antibody-dependent cellular cytotoxicity in tumor immunotherapy with therapeutic antibodies. Front Immunol. 2013; 4: 76. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/23543707

140. Lisovsky I, Kant S, Tremblay-McLean A, Isitman G, Kiani Z, et al. Differential contribution of education through KIR2DL1, KIR2DL3, and KIR3DL1 to antibody-dependent (AD) NK cell activation and ADCC. J Leukoc Biol. 2019; 105: 551-563. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30698860

141. Lo Nigro C, Macagno M, Sangiolo D, Bertolaccini L, Aglietta M, et al. NK-mediated antibody-dependent cell-mediated cytotoxicity in solid tumors: biological evidence and clinical perspectives. Ann Transl Med. 2019; 7: 105. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31019955

142. Hassenrück F, Knödgen E, Göckeritz E, Midda SH, Vondey V, et al. Sensitive detection of the natural killer cell-mediated cytotoxicity of anti-CD20 antibodies and its impairment by B-cell receptor pathway inhibitors. Biomed Res Int. 2018; 2018: 1023490. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/29750146

143. Li Y, Huang K, Liu L, Qu Y, Huang Y, et al. Effects of complement and serum IgG on rituximab-dependent natural killer cell-mediated cytotoxicity against Raji cells. Oncol Lett. 2019; 17: 339-347. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30655772

144. Ernst D, Williams BA, Wang XH, Yoon N, Kim KP, et al. Humanized anti-CD123 antibody facilitates NK cell antibody-dependent cell-mediated cytotoxicity (ADCC) of Hodgkin lymphoma targets via ARF6/PLD-1. Blood Cancer J. 2019; 9: 6. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30647406

145. Rossi LE, Avila DE, Spallanzani RG, Ziblat A, Fuertes MB, et al. Histone deacetylase inhibitors impair NK cell viability and effector functions through inhibition of activation and receptor expression. J Leukoc Biol. 2012; 91: 321-331. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/22124136

146. Tiper IV, Webb TJ. Histone deacetylase inhibitors enhance CD1d-dependent NKT cell responses to lymphoma. Cancer Immunol Immunother. 2016; 65: 1411-1421. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/27614429

147. Fiegler N, Textor S, Arnold A, Rölle A, Oehme I, et al. Downregulation of the activating NKp30 ligand B7-H6 by HDAC inhibitors impairs tumor cell recognition by NK cells. Blood. 2013; 122: 684-693. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/23801635

148. Al-Anazi WK, Al-Anazi KA. Epigenetics in myelodysplastic syndromes. J Mol Genet Med. 2019; 3: 1-17.

149. Chahin H, Ekong B, Fandy TE. Epigenetic therapy in malignant and chronic diseases. J Pharmacogenom Pharmacoproteomics. 2013; 4: 118.

150. Strauss J, Figg WD. Using epigenetic therapy to overcome chemotherapy resistance. Anticancer Res. 2016; 36: 1-4. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/26722021

151. Ronnekleiv-Kelly SM, Sharma A, Ahuja N. Epigenetic therapy and chemosensitization in solid malignancy. Cancer Treat Rev. 2017; 55: 200-208. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/28431263

152. Shi X, Li M, Cui M, Niu C, Xu J, et al. Epigenetic suppression of the antitumor cytotoxicity of NK cells by histone deacetylase inhibitor valproic acid. Am J Cancer Res. 2016; 6: 600-614. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/27152238

153. Ni L, Wang L, Yao C, Ni Z, Liu F, et al. The histone deacetylase inhibitor valproic acid inhibits NKG2D expression in natural killer cells through suppression of STAT3 and HDAC3. Sci Rep. 2017; 7: 45266. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/28338101

154. Greene TT, Tokuyama M, Knudsen GM, Kunz M, Lin J, et al. A Herpesviral induction of RAE-1 NKG2D ligand expression occurs through release of HDAC mediated repression. Elife. 2016; 5: e14749. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/27874833

155. Skov S, Pedersen MT, Andresen L, Straten PT, Woetmann A, et al. Cancer cells become susceptible to natural killer cell killing after exposure to histone deacetylase inhibitors due to glycogen synthase kinase-3-dependent expression of MHC class I-related chain A and B. Cancer Res. 2005; 65: 11136-11145. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/16322264

156. Krukowski K, Eddy J, Kosik KL, Konley T, Janusek LW, et al. Glucocorticoid dysregulation of natural killer cell function through epigenetic modification. Brain Behav Immun. 2011; 25: 239-249. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/20656012

157. Berghuis D, Schilham MW, Vos HI, Santos SJ, Kloess S, et al. Histone deacetylase inhibitors enhance expression of NKG2D ligands in Ewing sarcoma and sensitize for natural killer cell-mediated cytolysis. Clin Sarcoma Res. 2012; 2: 8. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/22587892

158. Choi JW, Lee ES, Kim SY, Park SI, Oh S, et al. Cytotoxic effects of *ex vivo*-expanded natural killer cell-enriched lymphocytes (MYJ1633) against liver cancer. BMC Cancer. 2019; 19: 817. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31426763

159. Zhu H, Kaufman DS. An improved method to produce clinical-scale natural killer cells from human pluripotent stem cells. Methods Mol Biol. 2019; 2048: 107-119. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31396935

160. Min B, Choi H, Her JH, Jung MY, Kim HJ, et al. Optimization of large-scale expansion and cryopreservation of human natural killer cells for anti-tumor therapy. Immune Netw. 2018; 18: 31. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30181919

161. Oyer JL, Igarashi RY, Kulikowski AR, Colosimo DA, Solh MM, et al. Generation of highly cytotoxic natural killer cells for treatment of acute myelogenous leukemia using a feeder-free, particle-based approach. Biol Blood Marrow Transplant. 2015; 21: 632-639. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/25576425

162. Xie S, Wu Z, Niu L, Chen J, Ma Y, et al. Preparation of highly activated natural killer cells for advanced lung cancer therapy. Onco Targets Ther. 2019; 12: 5077-5086. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31308687

163. Schmidt S, Tramsen L, Rais B, Ullrich E, Lehrnbecher T. Natural killer cells as a therapeutic tool for infectious diseases - current status and future perspectives. Oncotarget 2018; 9: 20891-20907. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/29755697

164. Lupo KB, Matosevic S. Natural killer cells as allogeneic effectors in adoptive cancer immunotherapy. Cancers (Basel) 2019; 11: 769. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31163679

165. Hu W, Wang G, Huang D, Sui M, Xu Y. Cancer immunotherapy based on natural killer cells: current progress and new opportunities. Front Immunol. 2019; 10: 1205. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31214177

166. Zhang J, Zheng H, Diao Y. Natural killer cells and current applications of chimeric antigen receptor-modified NK-92 cells in tumor immunotherapy. Int J Mol Sci. 2019; 20: 317. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30646574

167. Miller JS. Therapeutic applications: natural killer cells in the clinic. Hematology Am Soc Hematol Educ Program. 2013; 2013: 247-253. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/24319187

168. Bachanova V, Miller JS. NK cells in therapy of cancer. Crit Rev Oncog. 2014; 19: 133-141. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/24941379

169. Al-Anazi KA. The rising role of natural killer cells in patients with malignant hematological disorders and in recipients of hematopoietic stem cell transplantation. J Stem Cell Ther Transplant. 2019; 3: 23-27.

170. Chan YLT, Zuo J, Inman C, Croft W, Begum J, et al. NK cells produce high levels of IL-10 early after allogeneic stem cell transplantation and suppress development of acute GVHD. Eur J Immunol. 2018; 48: 316-329. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/28944953

171. Carlsten M, Korde N, Kotecha R, Reger R, Bor S, et al. Checkpoint inhibition of KIR2D with the monoclonal antibody IPH2101 induces contraction and hyporesponsiveness of NK Cells in patients with myeloma. Clin Cancer Res. 2016; 22: 5211-5222. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/27307594

172. Gabriel IH, Sergeant R, Szydlo R, Apperley JF, DeLavallade H, et al. Interaction between KIR3DS1 and HLA-Bw4 predicts for progression-free survival after autologous stem cell transplantation in patients with multiple myeloma. Blood. 2010; 116: 2033-2039. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/20562327

173. Rezvani K, Rouce R, Liu E, Shpall E. Engineering natural killer cells for cancer immunotherapy. Mol Ther. 2017; 25: 1769-1781. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/28668320

174. Hoteit R, Bazarbachi A, Antar A, Salem Z, Shammaa D, et al. KIR genotype distribution among patients with multiple myeloma: Higher prevalence of KIR 2DS4 and KIR 2DS5 genes. Meta Gene. 2014; 2: 730-736. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/25606456

175. Pittari G, Vago L, Festuccia M, Bonini C, Mudawi D, et al. Restoring natural killer cell immunity against multiple myeloma in the era of new drugs. Front Immunol. 2017; 8: 1444. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/29163516

176. Benson DM Jr, Hofmeister CC, Padmanabhan S, Suvannasankha A, Jagannath S, et al. A phase 1 trial of the anti-KIR antibody IPH2101 in patients with relapsed/refractory multiple myeloma. Blood. 2012; 120: 4324-4333. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/23033266

177. Mahaweni NM, Bos GMJ, Mitsiades CS, Tilanus MGJ, Wieten L. Daratumumab augments alloreactive natural killer cell cytotoxicity towards CD38^{+} multiple myeloma cell lines in a biochemical context mimicking tumour microenvironment conditions. Cancer Immunol Immunother. 2018; 67: 861-872. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/29500635

178. Mahaweni NM, Ehlers FAI, Bos GMJ, Wieten L. Tuning natural killer cell anti-multiple myeloma reactivity by targeting inhibitory signaling via KIR and NKG2A. Front Immunol. 2018; 9: 2848. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30564241

179. Carbone E, Neri P, Mesuraca M, Fulciniti MT, Otsuki T, et al. HLA class I, NKG2D, and natural cytotoxicity receptors regulate multiple myeloma cell recognition by natural killer cells. Blood. 2005; 105: 251-258. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/15328155

180. Sarkar S, van Gelder M, Noort W, Xu Y, Rouschop KM, et al. Optimal selection of natural killer cells to kill myeloma: the role of HLA-E and NKG2A. Cancer Immunol Immunother. 2015; 64: 951-63. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/25920521

181. Gao M, Gao L, Yang G, Tao Y, Hou J, et al. Myeloma cells resistance to NK cell lysis mainly involves an HLA class I-dependent mechanism. Acta Biochim Biophys Sin (Shanghai). 2014; 46: 597-604. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/24850305

182. Mohyuddin GR, Qazilbash MH. The therapeutic role of natural killer cells in multiple myeloma. Adv Cell Gene Ther. 2019; 2: 49.

183. Szmania S, Lapteva N, Garg T, Greenway A, Lingo J, et al. *Ex vivo*-expanded natural killer cells demonstrate robust proliferation in vivo in high-risk relapsed multiple myeloma patients. J Immunother. 2015; 38: 24-36. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/25415285

184. Shah N, Li L, McCarty J, Kaur I, Yvon E, et al. Phase I study of cord blood-derived natural killer cells combined with autologous stem cell transplantation in multiple myeloma. Br J Haematol. 2017; 177: 457-466. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/28295190

185. Kröger N, Shaw B, Iacobelli S, Zabelina T, Peggs K, et al. Clinical Trial Committee of the British Society of Blood and Marrow Transplantation and the German Cooperative Transplant Group. Comparison between antithymocyte globulin and alemtuzumab and the possible impact of KIR-ligand mismatch after dose-reduced conditioning and unrelated stem cell transplantation in patients with multiple myeloma. Br J Haematol. 2005; 129: 631-643. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/15916686

186. Shi J, Tricot G, Szmania S, Rosen N, Garg TK, et al. Infusion of haplo-identical killer immunoglobulin-like receptor ligand mismatched NK cells for relapsed myeloma in the setting of autologous stem cell transplantation. Br J Haematol. 2008; 143: 641-653. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/18950462

187. Nijhof IS, Lammerts van Bueren JJ, van Kessel B, Andre P, Morel Y, et al. Daratumumab-mediated lysis of primary multiple myeloma cells is enhanced in combination with the human anti-KIR antibody IPH2102 and lenalidomide. Haematologica. 2015; 100: 263-268. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/25510242

188. Nahi H, Chrobok M, Gran C, Lund J, Gruber A, et al. Infectious complications and NK cell depletion following daratumumab treatment of multiple myeloma. PLoS One. 2019; 14: e0211927. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30759167

189. Besson L, Charrier E, Karlin L, Allatif O, Marçais A, et al. One-year follow-up of natural killer cell activity in multiple myeloma patients treated with adjuvant lenalidomide therapy. Front Immunol. 2018; 9: 704. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/29706958

190. Yang G, Gao M, Zhang Y, Kong Y, Gao L, et al. Carfilzomib enhances natural killer cell-mediated lysis of myeloma linked with decreasing expression of HLA class I. Oncotarget. 2015; 6: 26982-26994. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/26323098

191. Korde N, Carlsten M, Lee MJ, Minter A, Tan E, et al. A phase II trial of pan-KIR2D blockade with IPH2101 in smoldering multiple myeloma. Haematologica. 2014; 99: 81-83. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/24658821

192. Wang Y, Lv B, Li K, Zhang A, Liu H. Adjuvant immunotherapy of dendritic cells and cytokine-induced killer cells is safe and enhances chemotherapy efficacy for multiple myeloma in China: a meta-analysis of clinical trials. Drug Des Devel Ther. 2017; 11: 3245-3256. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/29180849

193. Rueff J, Medinger M, Heim D, Passweg J, Stern M. Lymphocyte subset recovery and outcome after autologous hematopoietic stem cell transplantation for plasma cell myeloma. Biol Blood Marrow Transplant. 2014; 20: 896-899.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24631739

194. Skerget M, Skopec B, Zver S. Repopulation of lymphocytes and natural killer cells on day 15 following first autologous stem cell transplantation in myeloma patients correlates with the number of reinfused lymphocytes and natural killer T cells in the autologous graft. Blood. 2016; 128: 5820.

195. Dulphy N, Chrétien AS, Khaznadar Z, Fauriat C, Nanbakhsh A, et al. Underground adaptation to a hostile environment: acute myeloid leukemia vs. natural killer cells. Front Immunol. 2016; 7: 94.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27014273

196. Stringaris K, Sekine T, Khoder A, Alsuliman A, Razzaghi B, et al. Leukemia-induced phenotypic and functional defects in natural killer cells predict failure to achieve remission in acute myeloid leukemia. Haematologica. 2014; 99: 836-847.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24488563

197. Marin V, Pizzitola I, Agostoni V, Attianese GM, Finney H, et al. Cytokine-induced killer cells for cell therapy of acute myeloid leukemia: improvement of their immune activity by expression of CD33-specific chimeric receptors. Haematologica. 2010; 95: 2144-2152.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20713459

198. Skaik Y, Vahlsing S, Goudeva L, Eiz-Vesper B, Battermann A, et al. Secreted β3-integrin enhances natural killer cell activity against acute myeloid leukemia cells. PLoS One. 2014; 9: e98936.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24919191

199. Romee R, Rosario M, Berrien-Elliott MM, Wagner JA, Jewell BA, et al. Cytokine-induced memory-like natural killer cells exhibit enhanced responses against myeloid leukemia. Sci Transl Med. 2016; 8: 357.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27655849

200. Bao X, Wang M, Zhou H, Zhang H, Wu X, et al. Donor killer immunoglobulin-like receptor profile Bx1 imparts a negative effect and centromeric B-specific gene motifs render a positive effect on standard-risk acute myeloid leukemia/myelodysplastic syndrome patient survival after unrelated donor hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2016; 22: 232-239.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26371372

201. Yahng SA, Jeon YW, Yoon JH, Shin SH, Lee SE, et al. Negative impact of unidirectional host-versus-graft killer cell immunoglobulin-like receptor ligand mismatch on transplantation outcomes after unmanipulated haploidentical peripheral blood stem cell transplantation for acute myeloid leukemia. Biol Blood Marrow Transplant. 2016; 22: 316-323.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26415557

202. Parisi S, Lecciso M, Ocadlikova D, Salvestrini V, Ciciarello M, et al. The more, the better: "do the right thing" for natural killer immunotherapy in acute myeloid leukemia. Front Immunol. 2017; 8: 1330.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29097997

203. Holubova M, Leba M, Gmucova H, Caputo VS, Jindra P, et al. Improving the clinical application of natural killer cells by modulating signals signal from target cells. Int J Mol Sci. 2019; 20: E3472.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31311121

204. Ruggeri L, Mancusi A, Capanni M, Urbani E, Carotti A, et al. Donor natural killer cell allorecognition of missing self in haploidentical hematopoietic transplantation for acute myeloid leukemia: challenging its predictive value. Blood. 2007; 110: 433-440.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17371948

205. Cooley S, McCullar V, Wangen R, Bergemann TL, Spellman S, et al. KIR reconstitution is altered by T cells in the graft and correlates with clinical outcomes after unrelated donor transplantation. Blood. 2005; 106: 4370-4376.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16131567

206. Bachanova V, Cooley S, Defor TE, Verneris MR, Zhang B, et al. Clearance of acute myeloid leukemia by haploidentical natural killer cells is improved using IL-2 diphtheria toxin fusion protein. Blood. 2014; 123: 3855-3863.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24719405

207. Cooley S, He F, Bachanova V, Vercellotti GM, DeFor TE, et al. First-in-human trial of rhIL-15 and haploidentical natural killer cell therapy for advanced acute myeloid leukemia. Blood Adv. 2019; 3: 1970-1980.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31266741

208. Jardine L, Hambleton S, Bigley V, Pagan S, Wang XN, et al. Sensitizing primary acute lymphoblastic leukemia to natural killer cell recognition by induction of NKG2D ligands. Leuk Lymphoma. 2013; 54: 167-173.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22742576

209. Fei F, Lim M, George AA, Kirzner J, Lee D, et al. Cytotoxicity of CD56-positive lymphocytes against autologous B-cell precursor acute lymphoblastic leukemia cells. Leukemia 2015; 29: 788-797.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25134458

210. Mizia-Malarz A, Sobol-Milejska G. NK cells as possible prognostic factor in childhood acute lymphoblastic leukemia. Dis Markers. 2019; 2019: 3596983.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30719179

211. Sullivan EM, Jeha S, Kang G, Cheng C, Rooney B, et al. NK cell genotype and phenotype at diagnosis of acute lymphoblastic leukemia correlate with postinduction residual disease. Clin Cancer Res. 2014; 20: 5986-5994.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25281696

212. Torelli GF, Peragine N, Raponi S, Pagliara D, De Propris MS, et al. Recognition of adult and pediatric acute lymphoblastic leukemia blasts by natural killer cells. Haematologica. 2014; 99: 1248-1254.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24658822

213. Lelaidier M, Dìaz-Rodriguez Y, Cordeau M, Cordeiro P, Haddad E, et al. TRAIL-mediated killing of acute lymphoblastic leukemia by plasmacytoid dendritic cell-activated natural killer cells. Oncotarget. 2015; 6: 29440-29455.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26320191

214. Brentjens RJ. Cellular therapies in acute lymphoblastic leukemia. Curr Opin Mol Ther. 2009; 11: 375-382.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19649982

215. Liu LL, Béziat V, Oei VYS, Pfefferle A, Schaffer M, et al. *Ex vivo* expanded adaptive NK cells effectively kill primary acute lymphoblastic leukemia cells. Cancer Immunol Res. 2017; 5: 654-665.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28637877

216. Lee HR, Baek KH. Role of natural killer cells for immunotherapy in chronic myeloid leukemia. Oncol Rep. 2019; 41: 2625-2635.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30896812

217. Chen CI, Koschmieder S, Kerstiens L, Schemionek M, Altvater B, et al. NK cells are dysfunctional in human chronic myelogenous leukemia before and on imatinib treatment and in BCR-ABL-positive mice. Leukemia. 2012; 26: 465-474.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21904381

218. Ilander M, Olsson-Strömberg U, Schlums H, Guilhot J, Brück O, et al. Increased proportion of mature NK cells is associated with successful imatinib discontinuation in chronic myeloid leukemia. Leukemia. 2017; 31: 1108-1116.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27890936

219. Reiners KS, Topolar D, Henke A, Simhadri VR, Kessler J, et al. Soluble ligands for NK cell receptors promote evasion of chronic lymphocytic leukemia cells from NK cell anti-tumor activity. Blood 2013; 121: 3658-3665.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23509156

220. MacFarlane AW, Jillab M, Smith MR, Katherine Alpaugh R, et al. Natural killer cell dysfunction in chronic lymphocytic leukemia is associated with loss of the mature KIR3DL1^{+} subset. Blood. 2014; 124: 3318.

221. McWilliams EM, Mele JM, Cheney C, Timmerman EA, Fiazuddin F, et al. Therapeutic CD94/NKG2A blockade improves natural killer cell dysfunction in chronic lymphocytic leukemia. Oncoimmunology. 2016; 5: e1226720.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27853650

222. Klanova M, Oestergaard MZ, Trněný M, Hiddemann W, et al. Prognostic impact of natural killer cell count in follicular lymphoma and diffuse large B-cell lymphoma patients treated with immunochemotherapy. Clin Cancer Res. 2019; 25: 4634-4643.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31053601

223. Decaup E, Rossi C, Gravelle P, Laurent C, Bordenave J, et al. A tridimensional model for NK cell-mediated ADCC of follicular lymphoma. Front Immunol. 2019; 10: 1943.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31475004

224. Sarkar S, Sabhachandani P, Ravi D, Potdar S, Purvey S, et al. Dynamic analysis of human natural killer cell response at single-cell resolution in B-cell non-Hodgkin lymphoma. Front Immunol. 2017; 8: 1736.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29312292

225. Boulassel MR, Al Qarni Z, Burney I, Khan H, Al-Zubaidi A, et al. Levels of regulatory T cells and invariant natural killer cells and their associations with regulatory B cells in patients with non-Hodgkin lymphoma. Mol Clin Oncol. 2018; 9: 677-682.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30546901

226. Hus I, Bojarska-Junak A, Kamińska M, Dobrzyńska-Rutkowska A, et al. Imbalance in circulatory iNKT, Th17 and T regulatory cell frequencies in patients with B-cell non-Hodgkin's lymphoma. Oncol Lett. 2017; 14: 7957-7964.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29250184

227. Kohrt HE, Thielens A, Marabelle A, Sagiv-Barfi I, Sola C, et al. Anti-KIR antibody enhancement of anti-lymphoma activity of natural killer cells as monotherapy and in combination with anti-CD20 antibodies. Blood. 2014; 123: 678-86.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24326534

228. Vari F, Arpon D, Keane C, Hertzberg MS, Talaulikar D, et al. Immune evasion via PD-1/PD-L1 on NK cells and monocyte/macrophages is more prominent in Hodgkin lymphoma than DLBCL. Blood 2018; 131: 1809-1819.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29449276

229. Alinari L. Awakening exhausted NK cells in lymphoma. Blood. 2019; 131: 1768-1769.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29674350

230. Chiu J, Ernst DM, Keating A. Acquired natural killer cell dysfunction in the tumor microenvironment of classic Hodgkin lymphoma. Front Immunol. 2018; 9: 267.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29491867

231. Aldinucci D, Borghese C, Casagrande N. Formation of the immunosuppressive microenvironment of classic Hodgkin lymphoma and therapeutic approaches to counter it. Int J Mol Sci. 2019; 20: 2416.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31096713

232. Simonetta F, Alvarez M, Negrin RS. Natural killer cells in graft-versus-host-disease after allogeneic hematopoietic cell transplantation. Front Immunol. 2017; 8: 465.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28487696

233. Palmer JM, Rajasekaran K, Thakar MS, Malarkannan S. Clinical relevance of natural killer cells following hematopoietic stem cell transplantation. J Cancer. 2013; 4: 25-35.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23386902

234. Cooley S, Parham P, Miller JS. Strategies to activate NK cells to prevent relapse and induce remission following hematopoietic stem cell transplantation. Blood. 2018; 131: 1053-1062.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29358179

235. Pical-Izard C, Crocchiolo R, Granjeaud S, Kochbati E, Just-Landi S, et al. Reconstitution of natural killer cells in HLA-matched HSCT after reduced-intensity conditioning: impact on clinical outcome. Biol Blood Marrow Transplant. 2015; 21: 429-39.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25579888

236. Hattori N, Saito B, Sasaki Y, Shimada S, Murai S, et al. Status of natural killer cell recovery in day 21 bone marrow after allogeneic hematopoietic stem cell transplantation predicts clinical outcome. Biol Blood Marrow Transplant. 2018; 24: 1841-1847.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29753837

237. Shah NN, Baird K, Delbrook CP, Fleisher TA, Kohler ME, et al. Acute GVHD in patients receiving IL-15/4-1BBL activated NK cells following T-cell-depleted stem cell transplantation. Blood. 2015; 125: 784-792.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25452614

238. Chen YB, Efebera YA, Johnston L, Ball ED, Avigan D, et al. Increased $Foxp3^{+}Helios^{+}$regulatory T cells and decreased acute graft-versus-host disease after allogeneic bone marrow transplantation in patients receiving sirolimus and RGI-2001, an activator of invariant natural killer T cells. Biol Blood Marrow Transplant. 2017; 23: 625-634.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28104514

239. Ruggeri L, Capanni M, Urbani E, Perruccio K, Shlomchik WD, et al. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Science. 2002; 295: 2097-2100.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11896281

240. Björklund AT, Schaffer M, Fauriat C, Ringdén O, Remberger M, et al. NK cells expressing inhibitory KIR for non-self-ligands remain tolerant in HLA-matched sibling stem cell transplantation. Blood. 2010; 115: 2686-2694.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20097883

241. Haas P, Loiseau P, Tamouza R, Cayuela JM, Moins-Teisserenc H, et al. NK-cell education is shaped by donor HLA genotype after unrelated allogeneic hematopoietic stem cell transplantation. Blood. 2011 20; 117: 1021-1029.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21045194

242. Zhou H, Bao X, Wu X, Tang X, Wang M, et al. Donor selection for killer immunoglobulin-like receptors B haplotype of the centromeric motifs can improve the outcome after HLA-identical sibling hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2014; 20: 98-105.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24516895

243. Miller JS, Cooley S, Parham P, Farag SS, Verneris MR, et al. Missing KIR ligands are associated with less relapse and increased graft-versus-host disease (GVHD) following unrelated donor allogeneic HCT. Blood. 2007; 109: 5058-5061.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17317850

244. Russo A, Oliveira G, Berglund S, Greco R, Gambacorta V, et al. NK cell recovery after haploidentical HSCT with posttransplant cyclophosphamide: dynamics and clinical implications. Blood. 2018; 131: 247-262.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28986344

245. Wang Y, Wu DP, Liu QF, Xu LP, Liu KY, et al. Low-dose post-transplant cyclophosphamide and anti-thymocyte globulin as an effective strategy for GVHD prevention in haploidentical patients. J Hematol Oncol. 2019; 12: 88.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31481121

246. Rubnitz JE, Inaba H, Ribeiro RC, Pounds S, Rooney B, et al. NKAML: a pilot study to determine the safety and feasibility of haploidentical natural killer cell transplantation in childhood acute myeloid leukemia. J Clin Oncol. 2010; 28: 955-959.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20085940

247. Stern M, Passweg JR, Meyer-Monard S, Esser R, Tonn T, et al. Pre-emptive immunotherapy with purified natural killer cells after

haploidentical SCT: a prospective phase II study in two centers. Bone Marrow Transplant. 2013; 48: 433-438.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22941380

248. Nguyen S, Dhedin N, Vernant JP, Kuentz M, Al Jijakli A, et al. NK-cell reconstitution after haploidentical hematopoietic stem-cell transplantations: immaturity of NK cells and inhibitory effect of NKG2A override GvL effect. Blood. 2005; 105: 4135-4142.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15687235

249. Chang YJ, Zhao XY, Huang XJ. Immune reconstitution after haploidentical hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2014; 20: 440-449.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24315844

250. Ciurea SO, Schafer JR, Bassett R, Denman CJ, Cao K, et al. Phase 1 clinical trial using mbIL21 *ex vivo*-expanded donor-derived NK cells after haploidentical transplantation. Blood. 2017; 130: 1857-1868.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28835441

251. Jang JE, Hwang DY, Chung H, Kim SJ, Eom JI, et al. Early cytomegalovirus reactivation and expansion of $CD56^{bright}$ $CD16^{dim/-}$ $DNAM1^{+}$ natural killer cells are associated with antileukemia effect after haploidentical stem cell transplantation in acute leukemia. Biol Blood Marrow Transplant. 2019; 25: 2070-2078.

252. Ando T, Suzuki T, Ishiyama Y, Koyama S, Tachibana T, et al. Impact of cytomegalovirus reactivation and natural killer reconstitution on outcomes after allogeneic hematopoietic stem cell transplantation: a single-center analysis. Biol Blood Marrow Transplant. 2019; 19: 30639-30641.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31563574

253. Locatelli F, Pende D, Falco M, Della Chiesa M, Moretta A. NK cells mediate a crucial graft-versus-leukemia effect in haploidentical-HSCT to cure high-risk acute leukemia. Trends Immunol. 2018; 39: 577-590.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29793748

254. Casorati G, de Lalla C, Dellabona P. Invariant natural killer T cells reconstitution and the control of leukemia relapse in pediatric haploidentical hematopoietic stem cell transplantation. Oncoimmunology. 2012; 1: 355-357.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22737613

255. Sobecks RM, Wang T, Askar M, Gallagher MM, Haagenson M, et al. Impact of KIR and HLA genotypes on outcomes after reduced-intensity conditioning hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2015; 21: 1589-1596.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25960307

256. Baron F, Petersdorf EW, Gooley T, Sandmaier BM, Malkki M, et al. What is the role for donor natural killer cells after nonmyeloablative conditioning? Biol Blood Marrow Transplant. 2009; 15: 580-588.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19361750

257. Barrow AD, Edeling MA, Trifonov V, Luo J, Goyal P, et al. Natural killer cells control tumor growth by sensing a growth factor. Cell. 2018; 172: 534-548.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29275861

258. Dyck L, Lynch L. New job for NK cells: architects of the tumor microenvironment. Immunity. 2018; 48: 9-11.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29343443

259. Böttcher JP, Bonavita E, Chakravarty P, Blees H, et al. NK cells stimulate recruitment of cDC1 into the tumor microenvironment promoting cancer immune control. Cell. 2018; 172: 1022-1037.e14.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29429633

260. Yoon SR, Kim TD, Choi I. Understanding of molecular mechanisms in natural killer cell therapy. Exp Mol Med. 2015; 47: e141.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25676064

261. Mehta RS, Rezvani K. Chimeric antigen receptor expressing natural killer cells for the immunotherapy of cancer. Front Immunol. 2018; 9: 283.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29497427

262. López-Soto A, Gonzalez S, Smyth MJ, Galluzzi L. Control of metastasis by NK cells. Cancer Cell. 2017; 32: 135-154.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28810142

263. Rezvani K, Rouce RH. The application of natural killer cell immunotherapy for the treatment of cancer. Front Immunol. 2015; 6: 578.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26635792

264. Knorr DA, Bachanova V, Verneris MR, Miller JS. Clinical utility of natural killer cells in cancer therapy and transplantation. Semin Immunol. 2014; 26: 161-172.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24618042

265. Tian X, Wei F, Wang L, Yu W, Zhang N, et al. Herceptin enhances the antitumor effect of natural killer cells on breast cancer cells expressing human epidermal growth factor receptor-2. Front Immunol. 2017; 8: 1426.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29163501

266. Oh E, Min B, Li Y, Lian C, Hong J, et al. Cryopreserved human natural killer cells exhibit potent antitumor efficacy against orthotopic pancreatic cancer through efficient tumor-homing and cytolytic ability (running title: cryopreserved NK cells exhibit antitumor effect). Cancers (Basel). 2019; 11: E966.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31324057

267. Sun Y, Yao Z, Zhao Z, Xiao H, Xia M, et al. Natural killer cells inhibit metastasis of ovarian carcinoma cells and show therapeutic effects in a murine model of ovarian cancer. Exp Ther Med. 2018; 16: 1071-1078.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30116358

268. Kuçi S, Rettinger E, Voss B, Weber G, Stais M, et al. Efficient lysis of rhabdomyosarcoma cells by cytokine-induced killer cells: implications for adoptive immunotherapy after allogeneic stem cell transplantation. Haematologica. 2010; 95: 1579-1586.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20378565

269. Merker M, Pfirrmann V, Oelsner S, Fulda S, Klingebiel T, et al. Generation and characterization of ErbB2-CAR-engineered cytokine-induced killer cells for the treatment of high-risk soft tissue sarcoma in children. Oncotarget. 2017; 8: 66137-66153.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29029499

270. Yu M, Luo H, Fan M, Wu X, Shi B, et al. Development of GPC3-specific chimeric antigen receptor-engineered natural killer cells for the treatment of hepatocellular carcinoma. Mol Ther. 2018; 26: 366-378.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29339014

271. Du Y, Wei Y. Therapeutic potential of natural killer cells in gastric cancer. Front Immunol. 2019; 9: 3095.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30719024

272. Zhang L, Mu Y, Zhang A, Xie J, Chen S, et al. Cytokine-induced killer cells/dendritic cells-cytokine induced killer cells immunotherapy combined with chemotherapy for treatment of colorectal cancer in China: a meta-analysis of 29 trials involving 2,610 patients. Oncotarget. 2017; 8: 45164-45177.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28404886

273. Tanaka Y, Nakazawa T, Nakamura M, Nishimura F, Matsuda R, et al. *Ex vivo*-expanded highly purified natural killer cells in combination with temozolomide induce antitumor effects in human glioblastoma cells in vitro. PLoS One. 2019; 14: e0212455.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30840664

274. Genßler S, Burger MC, Zhang C, Oelsner S, Mildenberger I, et al. Dual targeting of glioblastoma with chimeric antigen receptor-engineered natural killer cells overcomes heterogeneity of target antigen expression and enhances antitumor activity and survival. Oncoimmunology. 2015; 5: e1119354.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27141401

275. Murakami T, Nakazawa T, Natsume A, Nishimura F, Nakamura M, et al. Novel human NK cell line carrying CAR targeting EGFRvIII induces antitumor effects in glioblastoma cells. Anticancer Res. 2018; 38: 5049-5056.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30194149

276. Huang BY, Zhan YP, Zong WJ, Yu CJ, Li JF, et al. The PD-1/B7-H1 pathway modulates the natural killer cells versus mouse glioma stem cells. PLoS One. 2015; 10: e0134715.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26266810

277. Haspels HN, Rahman MA, Joseph JV, Gras Navarro A, Chekenya M. Glioblastoma stem-like cells are more susceptible than differentiated cells to natural killer cell lysis mediated through killer immunoglobulin-like receptors-human leukocyte antigen ligand mismatch and activation receptor-ligand interactions. Front Immunol. 2018; 9: 1345.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29967607

278. Gras Navarro A, Espedal H, Joseph JV, Trachsel-Moncho L, Bahador M, et al. Pretreatment of glioblastoma with bortezomib potentiates natural killer cell cytotoxicity through TRAIL/DR5 mediated apoptosis and prolongs animal survival. Cancers (Basel). 2019; 11: E996.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31319548

279. Lee ST, Bracci P, Zhou M, Rice T, Wiencke J, et al. Interaction of allergy history and antibodies to specific varicella-zoster virus proteins on glioma risk. Int J Cancer. 2014; 134: 2199-2210.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24127236

280. Alvarez-Breckenridge CA, Yu J, Price R, Wojton J, Pradarelli J, et al. NK cells impede glioblastoma virotherapy through NKp30 and NKp46 natural cytotoxicity receptors. Nat Med. 2012; 18: 1827-1834.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23178246

281. Li Y, Sun R. Tumor immunotherapy: New aspects of natural killer cells. Chin J Cancer Res. 2018; 30: 173-196.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29861604

282. Kimpo MS, Oh B, Lee S. The role of natural killer cells as a platform for immunotherapy in pediatric cancers. Curr Oncol Rep. 2019; 21: 93.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31502008

283. Jensen IJ, Winborn CS, Fosdick MG, Shao P, Tremblay MM, Shan Q, et al. Polymicrobial sepsis influences NK-cell-mediated immunity by diminishing NK-cell-intrinsic receptor-mediated effector responses to viral ligands or infections. PLoS Pathog. 2018; 14: e1007405.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30379932

284. Welsh RM, Waggoner SN. NK cells controlling virus-specific T cells: Rheostats for acute vs. persistent infections. Virology. 2013; 435: 37-45.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23217614

285. Golden-Mason L, Rosen HR. Natural killer cells: multifaceted players with key roles in hepatitis C immunity. Immunol Rev. 2013; 255: 68-81.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23947348

286. Keawvichit R, Khowawisetsut L, Lertjuthaporn S, Tangnararatchakit K, Apiwattanakul N, Yoksan S, et al. Differences in activation and tissue homing markers of natural killer cell subsets during acute dengue infection. Immunology. 2018; 153: 455-465.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29105052

287. De Pelsmaeker S, Romero N, Vitale M, Favoreel HW. Herpesvirus evasion of natural killer cells. J Virol. 2018; 92: 105-117.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29540598

288. Campbell TM, McSharry BP, Steain M, Ashhurst TM, Slobedman B, et al. Varicella zoster virus productively infects human natural killer cells and manipulates phenotype. PLoS Pathog. 2018; 14: e1006999.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/29709039

289. Hammer Q, Romagnani C. About training and memory: NK-cell adaptation to viral infections. Adv Immunol. 2017; 133: 171-207.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28215279

290. Waggoner SN, Reighard SD, Gyurova IE, Cranert SA, Mahl SE, et al. Roles of natural killer cells in antiviral immunity. Curr Opin Virol. 2016; 16: 15-23.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26590692

291. Herrera L, Salcedo JM, Santos S, Vesga MÁ, Borrego F, Eguizabal C. OP9 feeder cells are superior to M2-10B4 cells for the generation of mature and functional natural killer cells from umbilical cord hematopoietic progenitors. Front Immunol. 2017; 8: 755.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28713379

292. Grossenbacher SK, Aguilar EG, Murphy WJ. Leveraging natural killer cells for cancer immunotherapy. Immunotherapy. 2017; 9: 487-497.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28472904

293. Nayyar G, Chu Y, Cairo MS. Overcoming resistance to natural killer cell based immunotherapies for solid tumors. Front Oncol. 2019; 9: 51.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30805309