Chapter II

Review of Literature

2.1 INTRODUCTION

The human body is surrounded by billions of bacteria that might cause a variety of illnesses; as a result, defensive systems are required. The term "immunity," which derives from the Latin immunitas and means "status of protection," was first used in the 1880s as a result of work by Jenner, Pasteur, and Koch who demonstrated that exposure to certain microorganisms may cause a particular disease and that the illness can be avoided by using vaccines made from the same pathogen (1). In the Eighteen Nineties, natural immunity was described as the resistance to pathogens from the first stumble upon, while artificial immunity was defined as the immunity to withstand illnesses as a result of microorganisms that were hosted via the human body in an advanced time frame (2).

We now recognize that soluble components and cellular immunity make up the immune system. Conventionally, it is further divided into innate immunity and adaptive immunity. Innate immunity, also known as native or natural immunity, is the body's initial line of defense against germs, according to textbooks on immunology. Phagocytes (monocytes, macrophages, and dendritic cells) and natural killer cells are examples of innate immune system cells. Additionally, soluble components of the immune system include cytokines, which are tiny proteins that function as messengers, regulators, and occasionally as killers(3). In contrast, compared to the innate immune system, adaptive immunity reacts to initial infections more slowly. Adaptive immune cells (T cells and B cells) produce a more focused and potent response when they come into contact with infections a second time. Adaptive immunity's soluble components are antibodies, which mature B cells make (3, 4). The

ability of adaptive immunity to form memories and respond considerably more quickly to re-exposure to the same pathogen is a crucial contrast between it and innate immunity (5).

More than 20 years before Edward Jenner, English physician Benjamin Jesty began developing a smallpox vaccine in the 18th and 19th centuries. This was one of the first novel approaches to immunize against various infections.(6, 7)(8). Jesty's plan was to inoculate healthy people, starting with his family, with a sick cow's substance. (9). However, Jenner received recognition for his outstanding work in the creation of vaccinations and the elimination of smallpox.(6, 10). Dairymaids were often believed

to be immune to smallpox at the time. Jenner was using fresh cowpox lesions from a dairymaid to immunize an 8-year-old child. The youngster experienced a little fever about a week later. Jenner continued to inoculate the same kid with new smallpox sores two months later. Jenner determined that the kid was immune since he never got sick(11). This was the first step towards protecting young children from widespread illnesses. In keeping with these discoveries, Louis Pasteur progressed the creation of vaccines in the 19th century by immunizing people with slain harmful organisms to stop the spread of illnesses.(12). A particular antigen can cause an antibody response, according to German Jew Paul Ehrlich, who developed antibodies later in the 19th century. (13).

The immune system is a highly controlled, complicated network. Today's knowledge is the result of earlier discoveries. The immune system's components that are pertinent to this thesis are detailed below:

2.1.1 Monocytes and Dendritic cells:

Large leukocytes called monocytes come from the myeloid lineage. They perform a variety of tasks and take part in several crucial innate immune responses, including as phagocytosis and the generation of cytokines(14, 15). When present in the tissues, circulating monocytes transform into macrophages and dendritic cells(16). Additionally, they are split into two subsets; the classical subset has high levels of CD14, which is a co-receptor for the Toll-like receptor (TLR)-4, which recognizes bacterial lipopolysaccharide (LPS). They demonstrate cell-mediated cytotoxicity that is antibody-dependent (ADCC)(17). However, they can also inhibit activated cells in some circumstances(18, 19). An excellent presenter of peptides from viruses and bacteria, HLA-DR is expressed at high levels by the other subset of cells whereas CD14 is expressed at low levels. These cells also generate large concentrations of interferon-alpha (19-21). Most monocytes lack the FcIII receptor (CD16), however around 10% of blood in circulation does. GM-CSF, M-CSF, and IL-3, as well as inflammatory diseases such coronary artery disease and chronic renal disease, promote these monocytes to proliferate (22-26). When necessary, monocytes may act as both pro- and anti-inflammatory cells due to their flexibility (27, 28). During microbial invasion, pro-inflammatory monocytes can activate memory T cells and NK cells in a cytokine-dependent way (29-31). As an anti-inflammatory component,

monocytes are drawn to the site of inflammation in allergic responses to suppress the reaction (32).

Dendritic cells (DC) can develop from lymphoid or myeloid progenitors (33-35).Langerhans cells, plasmacytoid DC, and classical DC are the three types of DC

seen in mice (LC). Those subsets are further split into several DC groups based on the expression and distribution of their surface antigens. It is possible to find CD8-CD11C+CD11b+ or CD8+CD11C+CD11b- cDC in lymphoid tissues (36, 37). Are they either CD103+CD11b-, CD103-CD11b-, or CD103+CD11b- in gut non-lymphoid tissues? (38, 39). Major Histocompatibility Complex (MHC) class II and CD11c expression are both low in blood and spleen inhabitants known as pDC, which also generate significant quantities of type I IFN (40). The skin is populated by LC, who are CD11b+F4/80+, express a lot of langerin.(41).

As many surface markers are shared by other hematopoietic cell types, such as monocytes and macrophages, it is more difficult to distinguish DC subpopulations in humans(42), DC are typically classified as conventional/classical DC (cDC), plasmacytoid DC (pDC), Langerhans cells, and monocyte-derived DC (mDC) (43). Under both stable and inflammatory situations, cDC are present in the blood circulation and exhibit high levels of CD11c, CD1b/c, and BDCA3. They are highly migratory and often pass through the bloodstream quickly(44, 45). In contrast, as they only differentiate under inflammatory circumstances, mDC were predominantly included in the non-conventional DC (46, 47). However, recent research has indicated that mDC may be present in muscles and intestines in a constant state (48, 49). pDC are long-lived cells that are often found in lymphoid or circulating tissues. Low quantities of MHC-II and CD11c are expressed, but they have a significant capacity to generate IFN- when activated. LC mostly exist in the epidermis and are frequently referred to as "skin DC"(50-52).

2.1.2 Cytokines

Small proteins known as cytokines play a variety of biological roles, such as cell development, differentiation, inflammation, and microbial defense(53-56). Leukocytes, as well as certain epithelial and endothelial cells, are only a few of the numerous cell types that generate cytokines. They work by attaching to their receptors, which are preferentially expressed on particular cell subsets. The inability to create cytokines or the disruption of their activity can result in a variety of illnesses, such as cancer and autoimmune conditions (57-59). The interleukins (IL), interferons and tumor necrosis factors (TNF), are a few of the many cytokine families. IL-2, one of the first ILs to be identified, is crucial for T- and NK-cell proliferation, survival, and heightened killing (60-62). Due to their capacity to cause inflammation, cytokines including IL-2, IL-15, IL-12, IL-6, TNF-, lymphotoxin-alpha (LTA), and IFN- are together referred to as proinflammatory cytokines (63, 64). Contrarily, because they play a role in reducing immune responses, cytokines like IL-10 and TGF- are considered anti-inflammatory cytokines (65-67).

2.1.3 T-cells:

Adaptive immunity must function properly in order to provide the best resistance against various pathogens. T cells, which are produced from the thymus, are capable of mediating effector responses in two phases by employing antigen-specific receptors. Antigen-presenting cells (monocytes, macrophages, DC, and B cells) in the secondary lymph node first excite T cells, which then get activated, divide into various subsets based on the signal received, and multiply. Then, in response to chemokines that are often generated by innate immune cells that are already present at

the infection site, primed T cells travel to the site of infection. Adaptive immune T cells are often divided into CD4 Th1 inflammatory cells that activate macrophages, CD4 Th-2 aid to produce antibody responses, regulatory T cells negatively inhibit effector cells, and CD8 T cells, which are not normally categorized.(62, 64, 67).

2.1.4 Antigen Processing and Presention:

Antigens are traditionally presented on the MHC class I or II molecular complex. Exogenous (extracellular) or endogenous (intracellular) proteins are both shown by MHC molecules (68). Proteolytic breakdown of the targeted protein initiates the antigen presentation pathway. To get rid of accumulated and damaged proteins, the cell uses the biological process of protein degradation (69, 70). For this, the proteasome system is employed. The proteasome is a multi-subunit complex made up of the 20S core unit and many regulatory subunits, including as the 26S and 19S, which bind to the 20S to alter and choose breakdown(71). The immunoproteasome has the 20S core unit plus one regulatory unit, such as the 19S or 11S, despite the fact that all proteasomes have a similar structure made up of three subunits(72). The MHC class I restricted antigen presentation process makes use of the immunoproteasome.(73, 74).

2.1.4.1 Endogenous antigen presenting:

MHC class I molecule activates cytotoxic T lymphocytes (CD8+). All nucleated cells express this molecule, making all cells capable of presenting antigens to CD8+ T lymphocytes. Cytosolic antigens, which can be made by tumor cells, viruses, or other

intracellular microorganisms, are presented by the MHC I molecule. Phagosomes (vesicles) are another source of antigens. Phagosomes transport microorganisms or pathogen products that internalize to the cell cytosol and are processed like the other cytosolic antigens. Antigens are transferred to the endoplasmic reticulum (ER) after processing by the transporter associated with antigen processing (TAP), then via the Golgi are delivered to the cell surface with exocytic vesicles. (8).

2.1.4.2 Exogenous antigen presenting:

Antigen-presenting cells are among the few cell types that express MHC class II molecules. Exogenous antigens are delivered to CD4+ T lymphocytes on MHC II molecules. On the other hand, exogenous antigens can be displayed on the MHC I through a mechanism known as cross-presentation. Unlike endogenous presentation, which takes place within the ER, loading of MHC II takes place outside of it. Only

MHC II is processed after a loading step inside the merged endocytic and exocytic vesicles in the cytosol and is then shown on the cell surface (8).

2.1.5 NK cells

2.1.5.1 Identification of NK cells:

The word "natural" was first used in the middle of the 1970s in reference to the way that NK cells behave, which allows them to detect and attack specific tumor cells without the need for prior immunization(75, 76).

Due to their inability to rearrange their receptors from their germline structure, NK cells—which make about 5–15% of the blood circulating lymphocytes—are referred to be big granular lymphocytes of the innate system (77, 78). The expression of CD56

and absence of CD3 help to identify them. Human NK cells include CD56 (NCAM), whereas those of murine origin do not(79). However, research has indicated that NKp46, a naturally occurring cytotoxic receptor, may be utilized to identify NK cells in several species(80, 81). When there is conflict, a portion of human NK cells express very little or no NKp46, making it challenging to identify NK cells. As a result, their identity must be verified by the absence of other lineage markers (82).

2.1.5.2 Development of NK cells:

There has been debate over the location in humans where NK cell development takes place. Although they originate from CD34+ hematopoietic progenitor cells in the bone marrow, this is not where their development into mature cells is expected to occur (83). As a result of the absence of immature and intermediately developed NK cells in the bone marrow, it is thought that NK cells develop in lymphoid organs instead. Contrarily, in vitro research has demonstrated that immune cells found in the bone marrow may develop CD34+ cells into NK cells by producing cytokines (84, 85).

NK cells from humans may be divided into two distinct groups based on how much of the surface protein CD56 are expressed. The lymphoid tissues are home to CD56bright immune-regulatory cells with outstanding cytokine production potential, whereas CD56dim NK cells, which make up 90% of the population, circulate in the

blood. CD56dim, as opposed to 19 CD56bright, express large amounts of CD16 and have powerful cytotoxic properties(86, 87). Target cells can be killed by CD16-expressing cells using an antibody-dependent cell-mediated cytotoxicity mechanism (ADCC)(88).

2.1.5.3 NK cell Inhibitory receptors:

Through a fine balance between inhibitory and activating receptors, NK-cell activity is controlled. The intensity of the inhibitory receptors' binding, or lack thereof, predicts the outcome. The killer immunoglobulin-like receptors (KIRs), which bind to the MHC class I complex, make up the biggest category of inhibitory receptors (89). Beginning in the 1980s, Kärre and colleagues noticed that the mouse tumour cell line YAC-1, which expressed few MHC class I molecules, was vulnerable to NK cell death(90). Later, as a result of these results, the "missing-self" hypothesis was developed(91). The first inhibitory receptor Ly49 expressed on mouse NK cells was discovered in Yokoyama's lab in 1992(92). Later, in the beginning of the 90s, Moretta and colleagues were the first to find the human KIRs of the NK cells later, at the start of the 1990s(93-95).

2.1.5.4 NK cell Activating receptors:

NK cells also carry activation receptors in addition to inhibitory receptors. FCRIII (CD16), which is found on the majority of NK cells and binds the constant region (Fc) of IgG, is one of the most researched receptors (96, 97). The only receptor that may independently activate NK cells is CD16(98, 99). NKG2D, which ligates the stress-induced molecules MICA/B or ULBP-proteins, and naturally occurring cytotoxic receptors (NCRs, NKp30, NKp46, and NKp44) are among other significant activation receptors (100-105). The ligands for the NCRs have not been extensively researched. Hemagglutinin (HA), a viral protein that ligates NKp44 and NKp46, and the two identified NKp30 ligands BAT3 and B7-H6, are what are now known(106-110). The activation co-receptors DNAM-1 and NKp80, which are important in the control of

NK cell responses to the target, must also be added to the list(111, 112). In many pathogenic and cell-transformation circumstances, these activating receptors are crucial for boosting NK cells. As a result, ADCC has gained widespread acceptance as a method to target both tumor and virus-infected cells (113, 114). Clinical outcomes are predicted by the expression of several NKp30 activation or inhibitory isoforms in patients with gastrointestinal sarcoma (115). The ligation of NKG2D by MICA/B or ULBP proteins has been demonstrated to generate cytotoxic action against hepatoma cells, continuing the line of the variety of NK cell responses(116). The NK cells' co-receptors have been shown to be crucial for battling cytomegalovirus-infected cells and may be involved in malignancies when NK cells have an altered phenotype(117, 118).

The receptors indicated above, with the exception of CD16, must work together to activate NK cell activity. For instance, co-activating DNAM-1, NKG2D, or 2B4 was necessary for NK cells to degranulate, while activating NKp46 alone is insufficient to stimulate NK cell degranulation (119).

2.1.5.5 Regulation of NK cell receptors:

In order to prevent autoimmunity or hypo-activation, NK cell receptor expression is tightly controlled during development. In-depth analyses of the mechanisms governing the KIR family's expression have revealed that healthy people' NK cells typically express at least one KIR. However, different cell types display different heterogenic repertoires (120). There are few theories as to how NK cell receptor expression is controlled. One of them is the licensing or schooling of NK cells; this concept is similar to the theory behind the TCR repertoire, with the exception that NK

cell receptors cannot be rearranged. By attaching various MHC I molecules to their KIRs, NK cells go through an educational process. Studies using mouse models have demonstrated that the expression of an inhibitory receptor for a self-MHC class I on NK cells correlates with NK cell licensing(121). Such engagement is necessary for self-tolerance and fully responsive NK cells(122).

Receiving proinflammatory or anti - inflammatory cytokines, such as IL-12, IL-15, TGF-, and IL-10, is a highly powerful regulator of the activation receptors in the line

of regulating receptors(123-126). Even though there are more and more research looking at how NK cell receptor expression is regulated in many human illnesses, particularly in cancer patients, we still don't fully understand these mechanisms.

2.1.5.6 NK cell cytotoxicity:

IFN- and TNF- are examples of the pro-inflammatory cytokines that NK cells generate after activation or in the absence of inhibition (127-130). Target cells cause NK cells to integrate via their adhering molecules, such as LFA-1, which causes Ca+ release and subsequent polarization of the cells. This process also results in the degranulation of perforin-containing lytic granules(131, 132). In another direct killing process, death receptors are ligated. The cognate receptors present on target cells are bound by death ligands produced on the surface of NK cells, such as TNF-related apoptosis-inducing ligand (TRAIL) and Fas-ligand (FasL). While TRAIL binds to one soluble receptor and four known membrane-bound receptors, the FasL exclusively binds to its single receptor, Fas. When TRAIL binds to the extracellular domain of TRAIL-receptors DR4 and DR5, the signal is transformed to the intracellular domain, where it recruits and activates caspase, which then starts the apoptotic signal-

transduction pathway(133). By expressing the other two membrane-bound TRAIL receptors, known as decoy receptors DcR1 and DcR2, which are either missing or do not act as intracellular death-domains, normal cells can often be distinguished from altered cells(134-137).

2.1.5.7Memory NK cells:

NK cells are often regarded as short-lived innate lymphocytes without antigen specificity and a low proliferation potential. Recent research has refuted this paradigm, revealing surprise findings that NK cells have adaptive immunological characteristics. Regarding a second challenge, O'Leary et al. showed that a subset of liver-resident NK cells is capable of triggering particular hapten-induced responses in mice missing T and B cells (138). In mouse models, CMV infection may lead to the development of memory NK cells(139). The idea of NK cell memory is still relatively new, and it has mostly been tested in virus-infection models (140). Additional research using other disease models is necessary. In healthy and disease-ridden

situations, NK cells react differently. The NK cell responses in the tumor microenvironment are covered in the next segment.

2.2 TUMOR IMMUNOLOGY:

Six biological traits that human cancers acquire during the course of their multi-step evolution constitute the characteristics of cancer. Maintaining proliferative signaling, dodging growth inhibitors, preventing cell death, permitting replicative immortality, initiating angiogenesis, and turning on invasion and metastasis are a few of these (141). Reprogramming of energy metabolism and escaping immune destruction are

two novel hallmarks that have emerged as a result of advancements in tumor biology research (142).

2.2.1 Immune surveillance:

When Ehrlich initially proposed the theory in 1909, the immune system's involvement in regulating transformation cells was highly debatable(143). Burnet updated the idea of "natural" tumor prevention later in the 1950s. Burnet thought that antigens unique to tumor cells may end immunological tolerance and trigger an efficient immune response that would end carcinogenesis(144, 145). When transgenic mouse models were used to validate tumor immune surveillance in chemically produced as well as spontaneous tumors in the 1990s, the concept was finally accepted. At that time, it was shown that effector cells such as T, B, and NK cells as well as interferons play a crucial role (146-148). Transgenic mice missing the gene RAG, which is required for the rearrangement of immunoglobulin and T cell receptors, provided additional proof of immune surveillance when they were subcutaneously injected with the chemical carcinogen 3′-methylcholanthrene (MCA). Sarcomas were produced in 60% of the mice as opposed to just 19% of WT animals(148). Immunosuppressed transplant patients who have a higher risk of getting cancer provide more proof in favor of immune monitoring(149, 150). Finally, during the past ten years, several research involving cancer patients have demonstrated that a favorable prognosis is correlated with large levels of infiltrating lymphocytes, particularly T cells (151-154).

2.2.2 Immune escape:

Numerous variables either promote or prevent the growth of cancer. These variables may be influenced by the surrounding environment or the altered cells (intrinsic to the tumor) (tumor-cell-extrinsic). Three crucial cancer immune-editing processes, known as the "3 Es" paradigm (elimination, equilibrium, and escape), are involved in the genesis of cancer.

Elimination is a safeguard against unchecked proliferation that involves the immune system's removal of the damaged cells, or immune surveillance(155-157). Moving on to the following stage, "equilibrium," when more resistant tumor cells emerge due to immune selection as they become less immunogenic as a result of long-term immune effector cell resistance(158). The tumor immune "escape" has been attained when the immune system has no or very little control on the tumor mass (159).

Three kinds of immune escape by tumors—loss of recognition, absence of susceptibility, and induction of immune suppression—have been identified (160). The inability to present tumor-specific antigens when T cells are no longer able to detect them is one of the most well-known examples of loss of recognitions (161). Moreover, in order to prevent effector cells from killing them, tumor cells typically block signals, down-regulate, or shed receptors or ligands, which makes the tumor less susceptible(162-164).

2.2.3 Tumor microenvironment:

It is well recognized that the tumor microenvironment is made up of a diverse population of cells and secreted substances, including not just tumor cells but also immune cells and cytokines. Selected cell types and tumor microenvironment components are discussed in this session.

2.2.3.1 Membrane bound proteins:

Tumor cells that have undergone immune editing may lose or overexpress certain proteins that are crucial for immune detection or suppression. For the activation and priming of T cells, HLA molecules are crucial. Cancer patients and mouse tumor models both exhibit failure to present antigen. Such deletion of antigens is caused by HLA total loss, alterations in the antigen-presenting apparatus, or even loss of antigen production(165, 166). Cancer cells that no longer express MHC class I are resistant to T cell destruction. Instead, these tumor cells are susceptible to NK cell destruction. The death receptor Fas, stress ligands for NKG2D, and down-modulating TRAIL-receptor-mediated apoptosis by upregulating FLIP are all ways that tumor cells might evade NK cell destruction(167-169).The programmed death ligands 1 and 2 (PD-L1/PD-L2), which are expressed on a variety of cancers, have received a lot of attention recently. To avoid hyperactivity, they interact with the PD-1 receptor present on activated immune cells(170-174). Both NK cell and T cell antitumor activity are decreased upon contact with tumor cells, and this is clinically associated with a poor prognosis(175-177). CTLA-4, HLA-G, and HLA-E are other comparable molecules that are overexpressed and interfere with T cell and NK cell activities by integrating with malignancies. Note that these compounds influence immune-suppression early on (178-181).

2.2.3.2 Tumor-induced transcriptions factors:

The increased activity of some transcriptional factors, specifically signal transducer and activator of transcription (STAT)3, which is constitutively phosphorylated in many cancers, is another way that tumor cells inhibit the immune system (182, 183).

Inhibited CD8+ T cell and Th1 cell immune surveillance has been linked to STAT3 activation in malignancies(184-186). Tumor STAT3 activation triggers the production of inhibitory cytokines such as IL-10 and TGF-β (187).

2.2.3.3 Secreted factors in the tumor microenvironment:

Although the kind and quantity of the components released in various tumors may vary, "master" regulators appear to be often generated. TGF-, IL-10, IL-6, GM-CSF,

and inflammatory mediators including COX-2 and prostaglandin E2 (PGE2) are some of these inhibitory factors (188-192). The microenvironment's suppressive cytokines, such as TGF-, prevent dendritic cells from differentiating and maturing, which inhibits the cross-presentation of tumor antigens to T cells(193). IL-10 is another effective inhibitor, directly affecting the generation of TNF- and IFN- by NK cells and T cells. Additionally, it prevents macrophages from having a cytotoxic impact and from being able to create IL-12(194, 195). By suppressing DC, skewing cytokine production, promoting angiogenesis, and blocking apoptosis, the immune-modulators indicated above contribute to a cascade of inflammatory responses that advance cancer(196-199). Collectively, host innate and adaptive immune systems are typically severely compromised by tumor growth.

Tumors have an immune-suppressive environment that is comprised of intricate processes and the participation of numerous immune cells and elements. It is therefore difficult to cover every one of them in this thesis. The function of NK cells and their interactions with tumor cells and certain immune-suppressive cells are highlighted in the next session.

2.2.4Immune suppression of NK cells:

Understanding how NK cells interact with tumor cells as well as how they function in the tumor microenvironment may help us better understand NK cell responses against cancer.

2.2.4.1 Regulatory T cells:

Regulatory T cells are one of the immune-suppressive cell types most closely linked to the development of tumors (Treg). They may be identified by the expression of the transcription factors CD4, CD25, and CD127 (CD4+CD25+CD127low/negative) as well as FoxP3(200). Different malignancies increase the growth of Treg, and their buildup is associated with reduced immune cell activity and a bad prognosis(201-206). Treg suppresses NK cells in a cell-contact-dependent manner, attenuating their cytotoxicity with membrane-bound TGF- β(207). The high affinity IL-2 receptor-alpha (IL-2R) is expressed by Treg, and they require IL-2 to operate properly. They

consume IL-2 that is generated by other cells, which raises the possibility that T cells and NK cells are suppressed by IL-2 deprivation(208, 209).

2.2.4.2 Myeloid-derived suppressor cells:

Myeloid-derived suppressor cells (MDSCs) are a diverse population of immature DC, macrophage, and granulocyte precursors that have suppressive function(210). Recently, it has been suggested that critical immune-regulators in a variety of solid and hematologic malignancies are called myeloid-derived suppressor cells (MDSCs)(211, 212). The monocytic MDSCs (moMDSCs) and the granulocytic MDSCs (grMDSCs) are the two categories of MDSC (213). In mice, grMDSCs

exhibit CD11b, Gr-1, Ly6G, and low Ly6C, whereas moMDSCs exhibit CD11b, Gr-1, high Ly6C, and no Ly6C. Different phenotypes of MDSCs in humans are linked to various malignancies(214-218). Their inhibitory action is accomplished by a variety of methods, but mainly through the generation of reactive oxygen species (ROS), arginine depletion, and suppressive cytokines such IL-10 and TGF- β(219-222). Recent research sought to determine how MDSCs are produced and how they inhibit T cells in vitro (223-225). The relationship between T cells and MDSCs has been well studied, but little is known about how these cells affect NK cell responses.

2.2.4.3 Tumor-associated macrophages:

The main myeloid-derived population in the tumor microenvironment is composed of macrophages. It has been hypothesized that tumor-associated macrophages (TAMs) actively encourage the development and spread of tumors (226, 227). TAMs are defined as a population of several unique pro- (M2)- and anti- (M1)-tumoral subpopulations. TAMs can employ direct and indirect T cell inhibition, Treg recruitment, and IL-10 production as immune suppressive strategies in the tumor microenvironment(228-230).

2.2.4.4 Immune-regulatory Dendritic cells:

Recent investigations of a less understood cell type reveal that immune-regulatory Dendritic cells, a subset of myeloid-derived immune regulatory cells, are pro-tumorigenic (regDC). They arise from cDC, and their presence in malignancies is

associated with a bad clinical prognosis(231, 232). An accumulation of regDC in a lung cancer pre-clinical investigation supports tumor development and inhibits anti-tumor action(233).

2.2.5 Immunotherapy:

Immunotherapy seeks to boost immunity to get rid of cancer. Immunotherapy can be classified as passive (antibody therapy, cell therapy), active (vaccines, active non-specific therapy, cytokines), or both, depending on how the patient's immune system is activated (listed below).

Active immunotherapy

1. The purpose of tumor vaccines is to either stimulate the body's natural anti-tumor immune response or to cause immunological identification of the tumor cells. However, a significant issue with this sort of therapy is the tumor's poor immunogenicity and the already diminished number of functional immune compartments. These vaccines can be cell-based (whole-tumor cell vaccination, DC-vaccine), or they can be based on tumor components (DNA vaccine, antigen peptide vaccine, and exosome-based vaccine)(234-237).

2. Immunotherapy frequently employs cytokines to promote immune responses such effector cell differentiation, proliferation, and activation, as well as APC recruitment. Such cytokines include IL-2, IFN- α, and GM-CSF; nevertheless, the systematic administration of these therapy results in high rates of toxicity (238).

Passive immunotherapy

1. One of the first methods of cancer immunotherapy was antibody-based treatment. Monoclonal antibodies (mAB) have the ability to directly destroy the targeted tumour cells, activate an immune system component (ADCC), or obstruct the routes used by the tumour cells to signal in an inhibiting manner. Anti-CD20 (Rituximab), anti-

HER2 (Trastuzumab), anti-VEGF (Bevacizumab), anti-EGFR (Cetuximab), and anti-CTLA-4 (Ipilimumab) are some of the mABs mentioned here(239). Resistance building is a key issue with long-term antibody-based treatment(240).

2. The notion of adoptive cell therapy using ex-vivo activated immune cells was first sparked by the significant immunological hypo-responsiveness in the tumor microenvironment. It has been demonstrated that tumor infiltrating lymphocytes (TILs) are receptive to host tumor-specific antigens but are suppressed in the tumor mass. Numerous research has looked into the possibility of growing these cells ex-vivo and reintroducing them into patients. Patients with melanoma have seen incredible results from this therapy(241). Genetic alterations, T cells with a particular TCR transduced, and T cells that express the chimeric antigen receptor (CAR) are examples of other T cell treatments (242, 243). As was already noted, the tumor microenvironment significantly inhibits the immune response to cancer. As a result, medicines that target immunosuppressive cell populations are becoming more common. The following lists other immunotherapy targets.

2.2.5.1 Targeting Treg:

Treg targeting for therapeutic purposes has made some progress, but not much. In order to decrease the quantity of Treg, a variety of therapeutic treatments have been proposed; however, these drugs also target effector cell activity, not just Treg. These treatments aim to increase Treg proliferation(244, 245), and reduce their functionality by using TLR agonists(108, 246). Recently, it was proposed to employ mAB CTLA-4 as a target for controlling Treg in cancer patients. Though improved anti-tumor

activity by effector T cells is seen in preclinical and clinical trials, an expansion of Treg suggests a secondary benefit of CTLA-4 therapy(247, 248).

2.2.5.2 Targeting MDSC:

MDSCs are challenging to selectively deplete because they lack unique identifying markers. Instead, researchers have looked for ways to reduce the immunosuppressive substances MDSCs produce. It is advised to prevent MDSC differentiation, expansion, and their suppressive activity in preclinical studies for therapeutic

purposes(249). Amiloride is used to treat hypertension, however when given to tumor-bearing mice, it reduced the STAT3-dependent MDSC suppressive function by preventing the generation of tumour exosomes(250). A tyrosine kinase inhibitor called sunitinib targets a variety of growth factors, including M-CSF and VGEF receptors. Sunitinib treatment inhibited the growth of MDSC and increased the expression of Th1 IFN- in tumor-bearing rats(251). PGE2 induces MDSCs while preventing APC from differentiating from bone marrow(252). Celecoxib and acetylsalicylic acid (Aspirin), COX-2 inhibitors, lower the systematic level of PGE2 and, as a result, the generation of ROS, arginase, and the MDSC chemoattractant CCL2 by MDSCs(253-255).

2.2.5.3 Immunological checkpoint Blocking:

To increase the beneficial effects of effector cells and decrease the suppressive effects of suppressor cells like Treg and MDSCs in malignancies, immunological checkpoints have to be targeted. Boosting immune effector functions was the main goal of immunotherapeutic approaches like CTLA-4 blocking by mAB (Ipilimumab). Currently, a number of clinical trials have employed ipilimumab in cancer patients

with positive objective responses and stable illness(256-259). The PD-1: PD-L1 axis is another inhibitory checkpoint protein with the potential to recover worn-out CD8+ T cells in mouse models and prolong life in cancer patients (260). It's interesting to note that blocking PD-1 increases the cytotoxic capacity of effector cells while decreasing the suppressive impact of Treg(261).

2.2.5.4 DC vaccines:

The importance of preclinical research to produce DC-vaccines in vitro has been emphasized since DC are the most effective APC. Dendritic cells originating from monocytes (mDC) produced in vitro have proved an excellent method for producing DC vaccines. Independent studies' observations demonstrate that naturally existing human mDC need IL-4 or GM-CSF to develop into mDC in vivo (262-264). So, these cytokines have been utilized in vitro to distinguish blood monocytes(265).

The development of therapeutic vaccines for cancer patients has spurred the in vitro maturation of blood monocytes to fully developed mDC over the past 20 years(266-270). Briefly, after maturation when various cytokines or TLR-agonists are used and loaded with tumor-specific antigens, blood monocytes are differentiated to immature DC by IL-4 and GM-CSF(271, 272). The goal of creating therapeutic DC vaccines has been to stimulate T cells to produce potent anti-tumor immune responses. Despite the fact that DC can induce anti-tumor T cell responses(272-275), the therapeutic effect for cancer patients has only been marginal(276, 277).

NK CELLS IN THE CLINIC:

2.3.1 KIRs as targets:

Numerous research has been done to improve NK cell anti-tumor efficacy against cancer. Initial attempts to infuse LAK (lymphokine activated killer cells)/NK cells in cancer patients with or without IL-2 injection were made in the 1980s, but these individuals showed little clinical responses and were believed to be paralyzed by the tumor immune-suppression(278-280). After NK cell injection in patients with solid tumors, no total tumor rejection has been seen so far(281-283). However, individuals with hematological malignancies have shown improved response to adoptive immunotherapy using NK cells(284, 285). Avoiding the interaction of inhibitory receptors KIRs with homologous HLA and choosing "mismatched" clones for adoptive transfer of NK cells is one of the key methods employed in these effective treatments (286-288). Therefore, it is crucial to evaluate the tumor phenotype before NK cell infusion, forecast the tumors' vulnerability to NK cell lysing in order to choose NK cell clones that will be more advantageous, or choose patients who will respond well to a certain therapy.

The notion of creating monoclonal antibodies to inhibit KIRs arose from such research demonstrating the therapeutic advantage of utilizing mismatched NK cell clones. Anti-inhibitory KIR mAb IPH2101 has successfully completed phase I trials in acute myeloid leukemia and multiple myeloma, indicating a safe profile in patients and the ability to block KIR for extended periods of time with little adverse

effects(289, 290). When NK cell activity in these individuals was assessed, response markers such as raised blood levels of TNF-, the NK cell and monocyte

chemoattractant MIP-1, and enhanced expression levels of CD69 and partly CD25 were found(290).

2.3.2 Sensitization of tumor cells to NK cell-mediated killing:

There have been suggested additional treatments to make tumor cells vulnerable to NK cell targeting. Targeting B-cell lymphomas, Rituximab or Mabthera are specific chimeric antibodies targeting CD20(291). Studies using mAB and IL-2 in combination demonstrated that this type of therapy can facilitate NK cell ADCC targeting of the tumor cells (292, 293). Recent therapies have focused on enhancing NK cell-driven tumor cell death mediated by death receptors. The relationship between NK- or T-cell TRAIL and tumor cell death has been demonstrated in several in vitro and in vivo investigations. Through increased TRAIL-R expression, pharmaceutical treatments like as proteasome inhibitors, anthracycline antibiotics, and histone deacetylase inhibitors improve tumor sensitivity to NK cells(294-298).

2.3.3Improve NK cell anti-tumor activity:

Death ligands are not expressed at all or very little on dormant NK cells (TRAIL and FasL). To increase the cytotoxic activity of NK cells, efforts should be made to up-regulate the expression of death ligands on NK cells. In addition to increasing the expression of death ligands on NK cells, cytokines like IL-2 also boost NK cell proliferation and cytotoxicity in vivo(299-301). It has been demonstrated in vitro that drugs like lenalidomide and zoledronic acid boost TRAIL expression on NK cells, which correlates with an increase in cytotoxicity(302, 303).

Both mouse models and human patients have demonstrated improved NK cell function after pre-conditioning. Radiation therapy and/or chemotherapy are two possible forms of treatment. By increasing, for example, stress ligands, NK cell proliferation, and inducing NK cell responses to the usual treatment, such treatment promotes NK cell identification of the tumor cells (304, 305).

Effective NK cell-based immunotherapy requires the fusion of many approaches to boost activity and decrease repression in the tumor microenvironment.

Reference:

1. Hilleman MRJV. Vaccines in historic evolution and perspective: a narrative of vaccine discoveries. 2000;18(15):1436-47.
2. Zinkernagel RMJAroi. On natural and artificial vaccinations. 2003;21:515.
3. Delves PJ, Roitt IMJNEjom. The immune system. 2000;343(1):37-49.
4. Parkin J, Cohen BJTL. An overview of the immune system. 2001;357(9270):1777-89.
5. Murphy K, Weaver C. Janeway's immunobiology: Garland science; 2016.
6. Riedel S, editor Edward Jenner and the history of smallpox and vaccination. Baylor University Medical Center Proceedings; 2005: Taylor & Francis.
7. Pead PJJTL. Benjamin Jesty: new light in the dawn of vaccination. 2003;362(9401):2104-9.
8. Abbas AK, Lichtman AH, Pillai S. Cellular and molecular immunology E-book: Elsevier Health Sciences; 2014.
9. Hammarsten JF, Tattersall W, Hammarsten JJTotAC, Association C. Who discovered smallpox vaccination? Edward Jenner or Benjamin Jesty? 1979;90:44.
10. Bloch HJAjodoc. Edward Jenner (1749-1823): The history and effects of smallpox, inoculation, and vaccination. 1993;147(7):772-4.
11. Willis NJSmj. Edward Jenner and the eradication of smallpox. 1997;42(4):118-21.
12. Pasteur LJTYjob, medicine. Summary report of the experiments conducted at Pouilly-le-Fort, near Melun, on the anthrax vaccination, 1881. 2002;75(1):59.
13. Strebhardt K, Ullrich AJNRC. Paul Ehrlich's magic bullet concept: 100 years of progress. 2008;8(6):473-80.
14. Auffray C, Sieweke MH, Geissmann FJAroi. Blood monocytes: development, heterogeneity, and relationship with dendritic cells. 2009;27(1):669-92.
15. Gordon S, Taylor PRJNri. Monocyte and macrophage heterogeneity. 2005;5(12):953-64.
16. Robbins CS, Swirski FKJC, sciences ml. The multiple roles of monocyte subsets in steady state and inflammation. 2010;67(16):2685-93.
17. Figdor CG, Bont WS, Touw I, de Roos J, Roosnek EE, de Vries JE. Isolation of functionally different human monocytes by counterflow centrifugation elutriation. 1982.

18. Jondal M, Merrill J, Ullberg MJSjoi. Monocyte-induced human natural killer cell suppression followed by increased cytotoxic activity during short-term in vitro culture in autologous serum. 1981;14(5):555-63.

19. Fernandez L, MacSween JJI. The suppressive effects of monocytes in the autologous mixed lymphocyte reaction. 1981;44(4):653.

20. Grage-Griebenow E, Flad HD, Ernst MJJolb. Heterogeneity of human peripheral blood monocyte subsets. 2001;69(1):11-20.

21. Grage-Griebenow E, Flad HD, Ernst MJJolb. Fcγ receptor I (CD64)-negative human monocytes are potent accessory cells in viral antigen-induced T cell activation and exhibit high IFN-α-producing capacity. 1996;60(3):389-96.

22. Klimchenko O, Di Stefano A, Geoerger B, Hamidi S, Opolon P, Robert T, et al. Monocytic cells derived from human embryonic stem cells and fetal liver share common differentiation pathways and homeostatic functions. 2011;117(11):3065-75.

23. Ziegler-Heitbrock L, Ancuta P, Crowe S, Dalod M, Grau V, Hart DN, et al. Nomenclature of monocytes and dendritic cells in blood. 2010;116(16):e74-e80.

24. Ancuta P, Rao R, Moses A, Mehle A, Shaw SK, Luscinskas FW, et al. Fractalkine preferentially mediates arrest and migration of CD16+ monocytes. 2003;197(12):1701-7.

25. Schlitt A, Heine GH, Blankenberg S, Espinola-Klein C, Dopheide JF, Bickel C, et al. CD14+ CD16+ monocytes in coronary artery disease and their relationship to serum TNF-α levels. 2004;92(08):419-24.

26. Ramírez R, Carracedo J, Merino A, Soriano S, Ojeda R, Alvarez-Lara MA, et al. CD14+ CD16+ monocytes from chronic kidney disease patients exhibit increased adhesion ability to endothelial cells. 2011;171:57-61.

27. Arnold L, Henry A, Poron F, Baba-Amer Y, Van Rooijen N, Plonquet A, et al. Inflammatory monocytes recruited after skeletal muscle injury switch into antiinflammatory macrophages to support myogenesis. 2007;204(5):1057-69.

28. Hanai H, Iida T, Takeuchi K, Watanabe F, Yamada M, Kikuyama M, et al. Adsorptive depletion of elevated proinflammatory CD14+ CD16+ DR++ monocytes in patients with inflammatory bowel disease. 2008;103(5):1210-6.

29. Soudja SMH, Ruiz AL, Marie JC, Lauvau GJI. Inflammatory monocytes activate memory CD8+ T and innate NK lymphocytes independent of cognate antigen during microbial pathogen invasion. 2012;37(3):549-62.

30. Huffnagle GB, Strieter RM, Standiford TJ, McDonald RA, Burdick MD, Kunkel SL, et al. The role of monocyte chemotactic protein-1 (MCP-1) in the recruitment of monocytes and CD4+ T cells during a pulmonary Cryptococcus neoformans infection. 1995;155(10):4790-7.

31. Hart OM, Athie-Morales V, O'Connor GM, Gardiner CMJTJoI. TLR7/8-mediated activation of human NK cells results in accessory cell-dependent IFN-γ production. 2005;175(3):1636-42.

32. Egawa M, Mukai K, Yoshikawa S, Iki M, Mukaida N, Kawano Y, et al. Inflammatory monocytes recruited to allergic skin acquire an anti-inflammatory M2 phenotype via basophil-derived interleukin-4. 2013;38(3):570-80.

33. Doulatov S, Notta F, Eppert K, Nguyen LT, Ohashi PS, Dick JEJNi. Revised map of the human progenitor hierarchy shows the origin of macrophages and dendritic cells in early lymphoid development. 2010;11(7):585-93.

34. Ardavín C, del Hoyo GMn, Martín P, Anjuère F, Arias CF, Marín AR, et al. Origin and differentiation of dendritic cells. 2001;22(12):691-700.

35. Schmid MA, Kingston D, Boddupalli S, Manz MGJIr. Instructive cytokine signals in dendritic cell lineage commitment. 2010;234(1):32-44.

36. Shortman K, Heath WRJIr. The CD8+ dendritic cell subset. 2010;234(1):18-31.

37. Proietto AI, van Dommelen S, Zhou P, Rizzitelli A, D'Amico A, Steptoe RJ, et al. Dendritic cells in the thymus contribute to T-regulatory cell induction. 2008;105(50):19869-74.

38. Del Rio ML, Bernhardt G, Rodriguez-Barbosa JI, Förster RJIr. Development and functional specialization of CD103+ dendritic cells. 2010;234(1):268-81.

39. Varol C, Vallon-Eberhard A, Elinav E, Aychek T, Shapira Y, Luche H, et al. Intestinal lamina propria dendritic cell subsets have different origin and functions. 2009;31(3):502-12.

40. Reizis B, Bunin A, Ghosh HS, Lewis KL, Sisirak VJAroi. Plasmacytoid dendritic cells: recent progress and open questions. 2011;29:163.

41. Merad M, Ginhoux F, Collin MJNRI. Origin, homeostasis and function of Langerhans cells and other langerin-expressing dendritic cells. 2008;8(12):935-47.

42. Merad M, Sathe P, Helft J, Miller J, Mortha AJAroi. The dendritic cell lineage: ontogeny and function of dendritic cells and their subsets in the steady state and the inflamed setting. 2013;31.

43. Liu K, Victora GD, Schwickert TA, Guermonprez P, Meredith MM, Yao K, et al. In vivo analysis of dendritic cell development and homeostasis. 2009;324(5925):392-7.

44. Shortman K, Liu Y-JJNRI. Mouse and human dendritic cell subtypes. 2002;2(3):151-61.

45. Waskow C, Liu K, Darrasse-Jèze G, Guermonprez P, Ginhoux F, Merad M, et al. The receptor tyrosine kinase Flt3 is required for dendritic cell development in peripheral lymphoid tissues. 2008;9(6):676-83.

46. Huang Q, Liu D, Majewski P, Schulte LC, Korn JM, Young RA, et al. The plasticity of dendritic cell responses to pathogens and their components. 2001;294(5543):870-5.

47. Yrlid U, Jenkins CD, MacPherson GGJTJoI. Relationships between distinct blood monocyte subsets and migrating intestinal lymph dendritic cells in vivo under steady-state conditions. 2006;176(7):4155-62.

48. Varol C, Landsman L, Fogg DK, Greenshtein L, Gildor B, Margalit R, et al. Monocytes give rise to mucosal, but not splenic, conventional dendritic cells. 2007;204(1):171-80.

49. Langlet C, Tamoutounour S, Henri S, Luche H, Ardouin L, Grégoire C, et al. CD64 expression distinguishes monocyte-derived and conventional dendritic cells and reveals their distinct role during intramuscular immunization. 2012;188(4):1751-60.

50. Geissmann F, Manz MG, Jung S, Sieweke MH, Merad M, Ley KJS. Development of monocytes, macrophages, and dendritic cells. 2010;327(5966):656-61.

51. MacDonald KP, Munster DJ, Clark GJ, Dzionek A, Schmitz J, Hart DNJB, The Journal of the American Society of Hematology. Characterization of human blood dendritic cell subsets. 2002;100(13):4512-20.

52. Kapsenberg MLJNRI. Dendritic-cell control of pathogen-driven T-cell polarization. 2003;3(12):984-93.

53. Griffiths S, Cawley JJL. The effect of cytokines, including IL-1, IL-4, and IL-6, in hairy cell proliferation/differentiation. 1990;4(5):337-40.

54. Katz J, Weiss H, Goldman B, Kanety H, Stannard B, Leroith D, et al. Cytokines and growth factors modulate cell growth and insulin-like growth factor binding protein secretion by the human salivary cell line (HSG). 1995;165(2):223-7.

55. Bradding P, Feather I, Wilson S, Bardin P, Heusser C, Holgate S, et al. Immunolocalization of cytokines in the nasal mucosa of normal and perennial rhinitic subjects. The mast cell as a source of IL-4, IL-5, and IL-6 in human allergic mucosal inflammation. 1993;151(7):3853-65.

56. Morrison PJ, Ballantyne SJ, Kullberg MCJI. Interleukin-23 and T helper 17-type responses in intestinal inflammation: from cytokines to T-cell plasticity. 2011;133(4):397-408.

57. Dinarello CAJEjoi. Historical insights into cytokines. 2007;37(S1):S34-S45.

58. Hartwell D, Levine J, Fenton M, Francis C, Leslie C, Beller DJIl. Cytokine dysregulation and the initiation of systemic autoimmunity. 1994;43(1-2):15-21.

59. Saxena V, Lienesch DW, Zhou M, Bommireddy R, Azhar M, Doetschman T, et al. Dual roles of immunoregulatory cytokine TGF-β in the pathogenesis of autoimmunity-mediated organ damage. 2008;180(3):1903-12.

60. Smith KAJS. Interleukin-2: inception, impact, and implications. 1988;240(4856):1169-76.

61. Yang RK, Kalogriopoulos NA, Rakhmilevich AL, Ranheim EA, Seo S, Kim K, et al. Intratumoral treatment of smaller mouse neuroblastoma tumors with a recombinant protein consisting of IL-2 linked to the hu14. 18 antibody increases intratumoral CD8+ T and NK cells and improves survival. 2013;62(8):1303-13.

62. Ebina N, Gallardo D, Shau H, Golub SJBjoc. IL-1 and IL-4 as reciprocal regulators of IL-2 induced lymphocyte cytotoxicity. 1990;62(4):619-23.

63. Šenolt L, Vencovský J, Pavelka K, Ospelt C, Gay SJAr. Prospective new biological therapies for rheumatoid arthritis. 2009;9(2):102-7.

64. KORNER H, Sedgwick JDJI, biology c. Tumour necrosis factor and lymphotoxin: molecular aspects and role in tissue-specific autoimmunity. 1996;74(5):465-72.

65. O'Garra A, Barrat FJ, Castro AG, Vicari A, Hawrylowicz CJIr. Strategies for use of IL-10 or its antagonists in human disease. 2008;223(1):114-31.

66. Yoshimura A, Muto GJNc-r, ligands. TGF-β function in immune suppression. 2010:127-47.

67. Marietta EV, Chen Y, Weis JHJEjoi. Modulation of expression of the anti-inflammatory cytokines interleukin-13 and interleukin-10 by interleukin-3. 1996;26(1):49-56.

68. Villadangos JA, Schnorrer PJNRI. Intrinsic and cooperative antigen-presenting functions of dendritic-cell subsets in vivo. 2007;7(7):543-55.

69. Dahlmann B, Kuehn LJMbr. The 20S/26S proteasomal pathway of protein degradation in muscle tissue. 1995;21(1):57-62.

70. Voss P, Grune TJAa. The nuclear proteasome and the degradation of oxidatively damaged proteins. 2007;32(4):527-34.

71. Volker C, Lupas AJTPUPDP. Molecular evolution of proteasomes. 2002:1-22.

72. Bardag-Gorce FJWjogW. Effects of ethanol on the proteasome interacting proteins. 2010;16(11):1349.

73. Groettrup M, Ruppert T, Kuehn L, Seeger M, Standera S, Koszinowski U, et al. The Interferon-γ-inducible 11 S Regulator (PA28) and the LMP2/LMP7 Subunits Govern the Peptide Production by the 20 S Proteasome in Vitro (∗). 1995;270(40):23808-15.

74. Sijts AJ, Standera S, Toes RE, Ruppert T, Beekman NJ, van Veelen PA, et al. MHC class I antigen processing of an adenovirus CTL epitope is linked to the levels of immunoproteasomes in infected cells. 2000;164(9):4500-6.

75. Kiessling R, Klein E, Wigzell HJEjoi. „Natural” □ killer cells in the mouse. I. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Specificity and distribution according to genotype. 1975;5(2):112-7.

76. Herberman RB, Nunn ME, Lavrin DHJIjoc. Natural cytotoxic reactivity of mouse lymphoid cells against syngeneic and allogeneic tumors. I. Distribution of reactivity and specificity. 1975;16(2):216-29.

77. Grossman Z, Herberman RBJCr. Natural killer cells and their relationship to T-cells: hypothesis on the role of T-cell receptor gene rearrangement on the course of adaptive differentiation. 1986;46(6):2651-8.

78. Moretta L, Ciccone E, Mingari MC, Biassoni R, Moretta AJAii. Human natural killer cells: origin, clonality, specificity, and receptors. 1993;55:341-80.

79. Lanier LL, Testi R, Bindl J, Phillips JHJTJoem. Identity of Leu-19 (CD56) leukocyte differentiation antigen and neural cell adhesion molecule. 1989;169(6):2233-8.

80. Walzer T, Bléry M, Chaix J, Fuseri N, Chasson L, Robbins SH, et al. Identification, activation, and selective in vivo ablation of mouse NK cells via NKp46. 2007;104(9):3384-9.

81. Biassoni R, Pessino A, Bottino C, Pende D, Moretta L, Moretta AJEjoi. The murine homologue of the human NKp46, a triggering receptor involved in the induction of natural cytotoxicity. 1999;29(3):1014-20.

82. Caligiuri MAJB, The Journal of the American Society of Hematology. Human natural killer cells. 2008;112(3):461-9.

83. Galy A, Travis M, Cen D, Chen BJI. Human T, B, natural killer, and dendritic cells arise from a common bone marrow progenitor cell subset. 1995;3(4):459-73.

84. Chinen H, Matsuoka K, Sato T, Kamada N, Okamoto S, Hisamatsu T, et al. Lamina propria c-kit+ immune precursors reside in human adult intestine and differentiate into natural killer cells. 2007;133(2):559-73.

85. Vacca P, Vitale C, Montaldo E, Conte R, Cantoni C, Fulcheri E, et al. CD34+ hematopoietic precursors are present in human decidua and differentiate into natural killer cells upon interaction with stromal cells. 2011;108(6):2402-7.

86. Farag SS, Caligiuri MAJBr. Human natural killer cell development and biology. 2006;20(3):123-37.

87. De Maria A, Bozzano F, Cantoni C, Moretta LJPotNAoS. Revisiting human natural killer cell subset function revealed cytolytic CD56dimCD16+ NK cells as rapid producers of abundant IFN-γ on activation. 2011;108(2):728-32.

88. Fast L, Hansen J, Newman WJTJoI. Evidence for T cell nature and heterogeneity within natural killer (NK) and antibody-dependent cellular cytotoxicity (ADCC) effectors: a comparison with cytolytic T lymphocytes (CTL). 1981;127(2):448-52.

89. Moretta L, Moretta AJCoii. Killer immunoglobulin-like receptors. 2004;16(5):626-33.

90. Piontek GE, Taniguchi K, Ljunggren H, Grönberg A, Kiessling R, Klein G, et al. YAC-1 MHC class I variants reveal an association between decreased NK

sensitivity and increased H-2 expression after interferon treatment or in vivo passage. 1985;135(6):4281-8.

91. Ljunggren H-G, Kärre KJIt. In search of the 'missing self': MHC molecules and NK cell recognition. 1990;11:237-44.

92. Karlhofer FM, Ribaudo RK, Yokoyama WMJN. MHC class I alloantigen specificity of Ly-49+ IL-2-activated natural killer cells. 1992;358(6381):66-70.

93. Moretta A, Sivori S, Vitale M, Pende D, Morelli L, Augugliaro R, et al. Existence of both inhibitory (p58) and activatory (p50) receptors for HLA-C molecules in human natural killer cells. 1995;182(3):875-84.

94. Moretta A, Vitale M, Bottino C, Orengo A, Morelli L, Augugliaro R, et al. P58 molecules as putative receptors for major histocompatibility complex (MHC) class I molecules in human natural killer (NK) cells. Anti-p58 antibodies reconstitute lysis of MHC class I-protected cells in NK clones displaying different specificities. 1993;178(2):597-604.

95. Wagtmann N, Rajagopalan S, Winter CC, Peruui M, Long EOJI. Killer cell inhibitory receptors specific for HLA-C and HLA-B identified by direct binding and by functional transfer. 1995;3(6):801-9.

96. Kay HD, Bonnard GD, West WH, Herberman RBJTJoI. A functional comparison of human Fc-receptor-bearing lymphocytes active in natural cytotoxicity and antibody-dependent cellular cytotoxicity. 1977;118(6):2058-66.

97. Iwaszko M, Bogunia-Kubik KJAiete. Clinical significance of the HLA-E and CD94/NKG2 interaction. 2011;59(5):353-67.

98. Bryceson YT, Ljunggren H-G, Long EOJB, The Journal of the American Society of Hematology. Minimal requirement for induction of natural cytotoxicity and intersection of activation signals by inhibitory receptors. 2009;114(13):2657-66.

99. Bryceson YT, March ME, Ljunggren H-G, Long EOJB. Synergy among receptors on resting NK cells for the activation of natural cytotoxicity and cytokine secretion. 2006;107(1):159-66.

100. Moretta L, Moretta AJTEj. Unravelling natural killer cell function: triggering and inhibitory human NK receptors. 2004;23(2):255-9.

101. Lanier LLJAroi. NK cell recognition. 2005;23(1):225-74.

102. Moretta A, Bottino C, Vitale M, Pende D, Cantoni C, Mingari MC, et al. Activating receptors and coreceptors involved in human natural killer cell-mediated cytolysis. 2001;19(1):197-223.

103. Moretta A, Biassoni R, Bottino C, Mingari MC, Moretta LJIt. Natural cytotoxicity receptors that trigger human NK-cell-mediated cytolysis. 2000;21(5):228-34.

104. Diefenbach A, Jamieson AM, Liu SD, Shastri N, Raulet DHJNi. Ligands for the murine NKG2D receptor: expression by tumor cells and activation of NK cells and macrophages. 2000;1(2):119-26.

105. Cao W, Xi X, Wang Z, Dong L, Hao Z, Cui L, et al. Four novel ULBP splice variants are ligands for human NKG2D. 2008;20(8):981-91.

106. Brandt CS, Baratin M, Yi EC, Kennedy J, Gao Z, Fox B, et al. The B7 family member B7-H6 is a tumor cell ligand for the activating natural killer cell receptor NKp30 in humans. 2009;206(7):1495-503.

107. Pogge von Strandmann E, Simhadri VR, von Tresckow B, Sasse S, Reiners K, Hansen HP, et al. Human leukocyte antigen-B-associated transcript 3 is released from tumor cells and engages the NKp30 receptor on natural killer cells. 2007;27(6):965-74.

108. Zhang Y, Luo F, Cai Y, Liu N, Wang L, Xu D, et al. TLR1/TLR2 agonist induces tumor regression by reciprocal modulation of effector and regulatory T cells. 2011;186(4):1963-9.

109. Arnon TI, Lev M, Katz G, Chernobrov Y, Porgador A, Mandelboim OJEjoi. Recognition of viral hemagglutinins by NKp44 but not by NKp30. 2001;31(9):2680-9.

110. Arnon TI, Achdout H, Lieberman N, Gazit R, Gonen-Gross T, Katz G, et al. The mechanisms controlling the recognition of tumor-and virus-infected cells by NKp46. 2004;103(2):664-72.

111. Gilfillan S, Chan CJ, Cella M, Haynes NM, Rapaport AS, Boles KS, et al. DNAM-1 promotes activation of cytotoxic lymphocytes by nonprofessional antigen-presenting cells and tumors. 2008;205(13):2965-73.

112. Welte S, Kuttruff S, Waldhauer I, Steinle AJNi. Mutual activation of natural killer cells and monocytes mediated by NKp80-AICL interaction. 2006;7(12):1334-42.

113. GONIK B, LOO LS, WEST S, KOHL SJAjori, microbiology. Natural killer cell cytotoxicity and antibody-dependent cellular cytotoxicity to herpes simplex virus-infected cells in human pregnancy. 1987;13(1):23-6.

114. Collins SM, Bakan CE, Swartzel GD, Hofmeister CC, Efebera YA, Kwon H, et al. Elotuzumab directly enhances NK cell cytotoxicity against myeloma via CS1 ligation: evidence for augmented NK cell function complementing ADCC. 2013;62(12):1841-9.

115. Delahaye NF, Rusakiewicz S, Martins I, Ménard C, Roux S, Lyonnet L, et al. Alternatively spliced NKp30 isoforms affect the prognosis of gastrointestinal stromal tumors. 2011;17(6):700-7.

116. Armeanu S, Bitzer M, Lauer UM, Venturelli S, Pathil A, Krusch M, et al. Natural killer cell–mediated lysis of hepatoma cells via specific induction of NKG2D ligands by the histone deacetylase inhibitor sodium valproate. 2005;65(14):6321-9.

117. Magri G, Muntasell A, Romo N, Sáez-Borderías A, Pende D, Geraghty DE, et al. NKp46 and DNAM-1 NK-cell receptors drive the response to human cytomegalovirus-infected myeloid dendritic cells overcoming viral immune evasion strategies. 2011;117(3):848-56.

118. Cremer I, Fridman WH, Sautès-Fridman CJO. Tumor microenvironment in NSCLC suppresses NK cells function. 2012;1(2):244-6.

119. Long EO, Sik Kim H, Liu D, Peterson ME, Rajagopalan SJAroi. Controlling natural killer cell responses: integration of signals for activation and inhibition. 2013;31:227-58.

120. Andersson S, Malmberg J-A, Malmberg K-JJEcr. Tolerant and diverse natural killer cell repertoires in the absence of selection. 2010;316(8):1309-15.

121. Kim S, Poursine-Laurent J, Truscott SM, Lybarger L, Song Y-J, Yang L, et al. Licensing of natural killer cells by host major histocompatibility complex class I molecules. 2005;436(7051):709-13.

122. Yokoyama WM, Kim SJIr. Licensing of natural killer cells by self-major histocompatibility complex class I. 2006;214(1):143-54.

123. Zhang C, Zhang J, Niu J, Zhou Z, Zhang J, Tian ZJHi. Interleukin-12 improves cytotoxicity of natural killer cells via upregulated expression of NKG2D. 2008;69(8):490-500.

124. Pahl JH, Ruslan SEN, Kwappenberg K, van Ostaijen-Ten Dam MM, van Tol MJ, Lankester AC, et al. Antibody-dependent cell lysis by NK cells is preserved after sarcoma-induced inhibition of NK cell cytotoxicity. 2013;62(7):1235-47.

125. Watanabe M, Kono K, Kawaguchi Y, Mizukami Y, Mimura K, Maruyama T, et al. NK cell dysfunction with down-regulated CD16 and up-regulated CD56 molecules in patients with esophageal squamous cell carcinoma. 2010;23(8):675-81.

126. Rudnicka K, Matusiak A, Miszczyk E, Rudnicka W, Tenderenda M, Chmiela MJA. Immunophenotype of peripheral blood natural killer cells and IL-10 serum levels in relation to Helicobacter pylori status. 2013;121(9):806-13.

127. Smyth MJ, Cretney E, Kelly JM, Westwood JA, Street SE, Yagita H, et al. Activation of NK cell cytotoxicity. 2005;42(4):501-10.

128. Handa K, Suzuki R, Matsui H, Shimizu Y, Kumagai KJTJoI. Natural killer (NK) cells as a responder to interleukin 2 (IL 2). II. IL 2-induced interferon gamma production. 1983;130(2):988-92.

129. Wang R, Jaw JJ, Stutzman NC, Zou Z, Sun PDJJolb. Natural killer cell-produced IFN-γ and TNF-α induce target cell cytolysis through up-regulation of ICAM-1. 2012;91(2):299-309.

130. Bryceson YT, March ME, Barber DF, Ljunggren H-G, Long EOJTJoem. Cytolytic granule polarization and degranulation controlled by different receptors in resting NK cells. 2005;202(7):1001-12.

131. Milella M, Gismondi A, Roncaioli P, Palmieri G, Morrone S, Piccoli M, et al. β1 integrin cross-linking inhibits CD16-induced phospholipase D and secretory phospholipase A2 activity and granule exocytosis in human NK cells: role of phospholipase D in CD16-triggered degranulation. 1999;162(4):2064-72.

132. Zompi S, Colucci FJIl. Anatomy of a murder—signal transduction pathways leading to activation of natural killer cells. 2005;97(1):31-9.

133. Boldin MP, Goncharov TM, Goltseve YV, Wallach DJC. Involvement of MACH, a novel MORT1/FADD-interacting protease, in Fas/APO-1-and TNF receptor–induced cell death. 1996;85(6):803-15.

134. Ashkenazi A, Dixit VMJCoicb. Apoptosis control by death and decoy receptors. 1999;11(2):255-60.

135. Pan G, O'Rourke K, Chinnaiyan AM, Gentz R, Ebner R, Ni J, et al. The receptor for the cytotoxic ligand TRAIL. 1997;276(5309):111-3.

136. Varfolomeev EE, Boldin MP, Goncharov TM, Wallach DJTJoem. A potential mechanism of" cross-talk" between the p55 tumor necrosis factor receptor and Fas/APO1: proteins binding to the death domains of the two receptors also bind to each other. 1996;183(3):1271-5.

137. Knight MJ, Riffkin CD, Muscat AM, Ashley DM, Hawkins CJJO. Analysis of FasL and TRAIL induced apoptosis pathways in glioma cells. 2001;20(41):5789-98.

138. O'Leary JG, Goodarzi M, Drayton DL, von Andrian UHJNi. T cell–and B cell–independent adaptive immunity mediated by natural killer cells. 2006;7(5):507-16.

139. Lopez-Vergès S, Milush JM, Schwartz BS, Pando MJ, Jarjoura J, York VA, et al. Expansion of a unique CD57+ NKG2Chi natural killer cell subset during acute human cytomegalovirus infection. 2011;108(36):14725-32.

140. Foley B, Felices M, Cichocki F, Cooley S, Verneris MR, Miller JSJIr. The biology of NK cells and their receptors affects clinical outcomes after hematopoietic cell transplantation (HCT). 2014;258(1):45-63.

141. Hanahan D, Weinberg RAJc. Hallmarks of cancer: the next generation. 2011;144(5):646-74.

142. Fouad YA, Aanei CJAjocr. Revisiting the hallmarks of cancer. 2017;7(5):1016.

143. Kim RJCI. Cancer immunoediting: from immune surveillance to immune escape. 2007:9-27.

144. Burnet MJBmj. Cancer—a biological approach: III. Viruses associated with neoplastic conditions. IV. Practical applications. 1957;1(5023):841.

145. BURNET MJBmb. Immunological factors in the process of carcinogenesis. 1964;20(2):154-8.

146. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RDJNi. Cancer immunoediting: from immunosurveillance to tumor escape. 2002;3(11):991-8.

147. Dunn GP, Bruce AT, Sheehan KC, Shankaran V, Uppaluri R, Bui JD, et al. A critical function for type I interferons in cancer immunoediting. 2005;6(7):722-9.

148. Shankaran V, Ikeda H, Bruce A, White J, Swanson P, Old L, et al. IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity Nature. Nature Publishing Group; 2001.

149. Penn IJDs. Post-transplant malignancy: the role of immunosuppression. 2000;23:101-13.

150. Hollenbeak CS, Todd MM, Billingsley EM, Harper G, Dyer AM, Lengerich EJJCIIJotACS. Increased incidence of melanoma in renal transplantation recipients. 2005;104(9):1962-7.

151. Clemente CG, Mihm Jr MC, Bufalino R, Zurrida S, Collini P, Cascinelli NJCIIJotACS. Prognostic value of tumor infiltrating lymphocytes in the vertical growth phase of primary cutaneous melanoma. 1996;77(7):1303-10.

152. Zhang L, Conejo-Garcia JR, Katsaros D, Gimotty PA, Massobrio M, Regnani G, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. 2003;348(3):203-13.

153. Svennevig J, Lunde O, Holter J, Bjørgsvik DJBjoc. Lymphoid infiltration and prognosis in colorectal carcinoma. 1984;49(3):375.

154. Pagès F, Berger A, Camus M, Sanchez-Cabo F, Costes A, Molidor R, et al. Effector memory T cells, early metastasis, and survival in colorectal cancer. 2005;353(25):2654-66.

155. Smyth MJ, Thia KY, Street SE, MacGregor D, Godfrey DI, Trapani JAJTJoem. Perforin-mediated cytotoxicity is critical for surveillance of spontaneous lymphoma. 2000;192(5):755-60.

156. Mori S, Jewett A, Murakami-Mori K, Cavalcanti M, Bonavida BJCI, Immunotherapy. The participation of the Fas-mediated cytotoxic pathway by natural killer cells is tumor-cell-dependent. 1997;44(5):282-90.

157. Takeda K, Hayakawa Y, Smyth MJ, Kayagaki N, Yamaguchi N, Kakuta S, et al. Involvement of tumor necrosis factor-related apoptosis-inducing ligand in surveillance of tumor metastasis by liver natural killer cells. 2001;7(1):94-100.

158. Street SE, Trapani JA, MacGregor D, Smyth MJJTJoem. Suppression of lymphoma and epithelial malignancies effected by interferon γ. 2002;196(1):129-34.

159. Zitvogel L, Tesniere A, Kroemer GJNRI. Cancer despite immunosurveillance: immunoselection and immunosubversion. 2006;6(10):715-27.

160. Malmberg K-J, Ljunggren H-G, editors. Escape from immune-and nonimmune-mediated tumor surveillance. Seminars in cancer biology; 2006: Elsevier.

161. Yee C, Thompson J, Byrd D, Riddell S, Roche P, Celis E, et al. Adoptive T cell therapy using antigen-specific CD8+ T cell clones for the treatment of patients with metastatic melanoma: in vivo persistence, migration, and antitumor effect of transferred T cells. 2002;99(25):16168-73.

162. Igney FH, Krammer PHJNRC. Death and anti-death: tumour resistance to apoptosis. 2002;2(4):277-88.

163. Tanaka M, Itai T, Adachi M, Nagata SJNm. Downregulation of Fas ligand by shedding. 1998;4(1):31-6.

164. Jalving M, Heijink D, Koornstra J, Boersma-van Ek W, Zwart N, Wesseling J, et al. Regulation of TRAIL receptor expression by β-catenin in colorectal tumours. 2014;35(5):1092-9.

165. Seliger B, Cabrera T, Garrido F, Ferrone S, editors. HLA class I antigen abnormalities and immune escape by malignant cells. Seminars in cancer biology; 2002: Elsevier.

166. Andersson E, Villabona L, Bergfeldt K, Carlson JW, Ferrone S, Kiessling R, et al. Correlation of HLA-A02* genotype and HLA class I antigen down-regulation with the prognosis of epithelial ovarian cancer. 2012;61(8):1243-53.

167. Hinz S, Trauzold A, Boenicke L, Sandberg C, Beckmann S, Bayer E, et al. Bcl-XL protects pancreatic adenocarcinoma cells against CD95-and TRAIL-receptor-mediated apoptosis. 2000;19(48):5477-86.

168. Salih HR, Rammensee H-G, Steinle AJTJoI. Cutting edge: down-regulation of MICA on human tumors by proteolytic shedding. 2002;169(8):4098-102.

169. Sheen-Chen S-M, Chen H-S, Eng H-L, Chen W-JJWjos. Circulating soluble Fas in patients with breast cancer. 2003;27(1):10-3.

170. Alvarez IB, Pasquinelli V, Jurado JO, Abbate E, Musella RM, de la Barrera SS, et al. Role played by the programmed death-1-programmed death ligand pathway during innate immunity against Mycobacterium tuberculosis. 2010;202(4):524-32.

171. Konishi J, Yamazaki K, Azuma M, Kinoshita I, Dosaka-Akita H, Nishimura MJCcr. B7-H1 expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. 2004;10(15):5094-100.

172. Messal N, Serriari N-E, Pastor S, Nunès JA, Olive DJMi. PD-L2 is expressed on activated human T cells and regulates their function. 2011;48(15-16):2214-9.

173. Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. 2007;13(7):2151-7.

174. Wang B-J, Bao J-J, Wang J-Z, Wang Y, Jiang M, Xing M-Y, et al. Immunostaining of PD-1/PD-Ls in liver tissues of patients with hepatitis and hepatocellular carcinoma. 2011;17(28):3322.

175. Benson Jr DM, Bakan CE, Mishra A, Hofmeister CC, Efebera Y, Becknell B, et al. The PD-1/PD-L1 axis modulates the natural killer cell versus multiple myeloma effect: a therapeutic target for CT-011, a novel monoclonal anti–PD-1 antibody. 2010;116(13):2286-94.

176. Wei B, Wang L, Zhao X, Du C, Guo Y, Sun ZJTB. The upregulation of programmed death 1 on peripheral blood T cells of glioma is correlated with disease progression. 2014;35(4):2923-9.

177. Akbay EA, Koyama S, Carretero J, Altabef A, Tchaicha JH, Christensen CL, et al. Activation of the PD-1 Pathway Contributes to Immune Escape in EGFR-Driven Lung TumorsImmune Escape of EGFR-Mutant Tumors through PD-1. 2013;3(12):1355-63.

178. Derré L, Corvaisier M, Charreau B, Moreau A, Godefroy E, Moreau-Aubry A, et al. Expression and release of HLA-E by melanoma cells and melanocytes: potential impact on the response of cytotoxic effector cells. 2006;177(5):3100-7.

179. Frumento G, Piazza T, Di Carlo E, Ferrini SJE, Metabolic, Targets ID-D. Targeting tumor-related immunosuppression for cancer immunotherapy. 2006;6(3):223-37.

180. Saverino D, Tenca C, Zarcone D, Merlo A, Megiovanni AM, Valle MT, et al. CTLA-4 (CD152) inhibits the specific lysis mediated by human cytolytic T lymphocytes in a clonally distributed fashion. 1999;162(2):651-8.

181. Tripathi P, Agrawal SJCi. Non-classical HLA-G antigen and its role in the cancer progression. 2006;24(2):178-86.

182. Messina JL, Yu H, Riker AI, Munster PN, Jove RL, Daud AIJCc. Activated stat-3 in melanoma. 2008;15(3):196-201.

183. Yu H, Jove RJNRC. The STATs of cancer—new molecular targets come of age. 2004;4(2):97-105.

184. Wang H, Xie X, Lu W-g, Ye D-f, Chen H-z, Li X, et al. Ovarian carcinoma cells inhibit T cell proliferation: suppression of IL-2 receptor β and γ expression and their JAK-STAT signaling pathway. 2004;74(14):1739-49.

185. Iwata-Kajihara T, Sumimoto H, Kawamura N, Ueda R, Takahashi T, Mizuguchi H, et al. Enhanced cancer immunotherapy using STAT3-depleted dendritic cells with high Th1-inducing ability and resistance to cancer cell-derived inhibitory factors. 2011;187(1):27-36.

186. Terai M, Eto M, Young GD, Berd D, Mastrangelo MJ, Tamura Y, et al. Interleukin 6 mediates production of interleukin 10 in metastatic melanoma. 2012;61(2):145-55.

187. Ogata H, Chinen T, Yoshida T, Kinjyo I, Takaesu G, Shiraishi H, et al. Loss of SOCS3 in the liver promotes fibrosis by enhancing STAT3-mediated TGF-β1 production. 2006;25(17):2520-30.

188. Karavitis J, Hix LM, Shi YH, Schultz RF, Khazaie K, Zhang M. Regulation of COX2 expression in mouse mammary tumor cells controls bone metastasis and PGE2-induction of regulatory T cell migration. 2012.

189. Katz LH, Li Y, Chen J-S, Muñoz NM, Majumdar A, Chen J, et al. Targeting TGF-β signaling in cancer. 2013;17(7):743-60.

190. Liu C-z, Zhang L, Chang X-h, Cheng Y-x, Cheng H-y, Ye X, et al. Overexpression and immunosuppressive functions of transforming growth factor 1, vascular endothelial growth factor and interleukin-10 in epithelial ovarian cancer. 2012;24(2):130-7.

191. Pylayeva-Gupta Y, Lee KE, Hajdu CH, Miller G, Bar-Sagi DJCc. Oncogenic Kras-induced GM-CSF production promotes the development of pancreatic neoplasia. 2012;21(6):836-47.

192. Teng Y, Ghoshal P, Ngoka L, Mei Y, Cowell JKJC. Critical role of the WASF3 gene in JAK2/STAT3 regulation of cancer cell motility. 2013;34(9):1994-9.

193. Song S-S, Yuan P-F, Chen J-Y, Fu J-J, Wu H-X, Lu J, et al. TGF-β favors bone marrow-derived dendritic cells to acquire tolerogenic properties. 2014;43(4):360-9.

194. D'andrea A, Aste-Amezaga M, Valiante NM, Ma X, Kubin M, Trinchieri GJTJoem. Interleukin 10 (IL-10) inhibits human lymphocyte interferon gamma-production by suppressing natural killer cell stimulatory factor/IL-12 synthesis in accessory cells. 1993;178(3):1041-8.

195. Song S, Ling-Hu H, Roebuck KA, Rabbi MF, Donnelly RP, Finnegan AJB, The Journal of the American Society of Hematology. Interleukin-10 inhibits interferon-γ–induced intercellular adhesion molecule-1 gene transcription in human monocytes. 1997;89(12):4461-9.

196. Shono T, Tofilon PJ, Bruner JM, Owolabi O, Lang FFJCr. Cyclooxygenase-2 expression in human gliomas: prognostic significance and molecular correlations. 2001;61(11):4375-81.

197. Kaliński P, Schuitemaker JH, Hilkens CM, Kapsenberg MLJTJoI. Prostaglandin E2 induces the final maturation of IL-12-deficient CD1a+ CD83+ dendritic cells: the levels of IL-12 are determined during the final dendritic cell maturation and are resistant to further modulation. 1998;161(6):2804-9.

198. Coussens LM, Werb ZJN. Inflammation and cancer. 2002;420(6917):860-7.

199. Seno H, Oshima M, Ishikawa T-o, Oshima H, Takaku K, Chiba T, et al. Cyclooxygenase 2-and Prostaglandin E2 Receptor EP2-dependent Angiogenesis in Apc Δ 716 Mouse Intestinal Polyps. 2002;62(2):506-11.

200. Hartigan-O'Connor DJ, Poon C, Sinclair E, McCune JMJJoim. Human CD4+ regulatory T cells express lower levels of the IL-7 receptor alpha chain (CD127), allowing consistent identification and sorting of live cells. 2007;319(1-2):41-52.

201. Berendt MJ, North RJJTJoem. T-cell-mediated suppression of anti-tumor immunity. An explanation for progressive growth of an immunogenic tumor. 1980;151(1):69-80.

202. Woo EY, Chu CS, Goletz TJ, Schlienger K, Yeh H, Coukos G, et al. Regulatory CD4+ CD25+ T cells in tumors from patients with early-stage non-small cell lung cancer and late-stage ovarian cancer. 2001;61(12):4766-72.

203. Ichihara F, Kono K, Takahashi A, Kawaida H, Sugai H, Fujii HJCCR. Increased populations of regulatory T cells in peripheral blood and tumor-infiltrating lymphocytes in patients with gastric and esophageal cancers. 2003;9(12):4404-8.

204. Ormandy LA, Hillemann T, Wedemeyer H, Manns MP, Greten TF, Korangy FJCr. Increased populations of regulatory T cells in peripheral blood of patients with hepatocellular carcinoma. 2005;65(6):2457-64.

205. Fu J, Xu D, Liu Z, Shi M, Zhao P, Fu B, et al. Increased regulatory T cells correlate with CD8 T-cell impairment and poor survival in hepatocellular carcinoma patients. 2007;132(7):2328-39.

206. Sinicrope FA, Rego RL, Ansell SM, Knutson KL, Foster NR, Sargent DJJG. Intraepithelial effector (CD3+)/regulatory (FoxP3+) T-cell ratio predicts a clinical outcome of human colon carcinoma. 2009;137(4):1270-9.

207. Ghiringhelli F, Ménard C, Terme M, Flament C, Taieb J, Chaput N, et al. CD4+ CD25+ regulatory T cells inhibit natural killer cell functions in a transforming growth factor–β–dependent manner. 2005;202(8):1075-85.

208. Gasteiger G, Hemmers S, Firth MA, Le Floc'h A, Huse M, Sun JC, et al. IL-2–dependent tuning of NK cell sensitivity for target cells is controlled by regulatory T cells. 2013;210(6):1167-78.

209. Pandiyan P, Zheng L, Ishihara S, Reed J, Lenardo MJJNi. CD4+ CD25+ Foxp3+ regulatory T cells induce cytokine deprivation–mediated apoptosis of effector CD4+ T cells. 2007;8(12):1353-62.

210. Gabrilovich DI, Bronte V, Chen S-H, Colombo MP, Ochoa A, Ostrand-Rosenberg S, et al. The terminology issue for myeloid-derived suppressor cells. 2007;67(1):425-.

211. Ohki S, Shibata M, Gonda K, Machida T, Shimura T, Nakamura I, et al. Circulating myeloid-derived suppressor cells are increased and correlate to immune suppression, inflammation and hypoproteinemia in patients with cancer. 2012;28(2):453-8.

212. Görgün GT, Whitehill G, Anderson JL, Hideshima T, Maguire C, Laubach J, et al. Tumor-promoting immune-suppressive myeloid-derived suppressor cells in the multiple myeloma microenvironment in humans. 2013;121(15):2975-87.

213. Youn J-I, Nagaraj S, Collazo M, Gabrilovich DIJTJoI. Subsets of myeloid-derived suppressor cells in tumor-bearing mice. 2008;181(8):5791-802.

214. Serafini P, Meckel K, Kelso M, Noonan K, Califano J, Koch W, et al. Phosphodiesterase-5 inhibition augments endogenous antitumor immunity by reducing myeloid-derived suppressor cell function. 2006;203(12):2691-702.

215. Loercher AE, Nash MA, Kavanagh JJ, Platsoucas CD, Freedman RSJTJoI. Identification of an IL-10-producing HLA-DR-negative monocyte subset in the malignant ascites of patients with ovarian carcinoma that inhibits cytokine protein expression and proliferation of autologous T cells. 1999;163(11):6251-60.

216. Hoechst B, Voigtlaender T, Ormandy L, Gamrekelashvili J, Zhao F, Wedemeyer H, et al. Myeloid derived suppressor cells inhibit natural killer cells in patients with hepatocellular carcinoma via the NKp30 receptor. 2009;50(3):799-807.

217. Lin Y, Gustafson MP, Bulur PA, Gastineau DA, Witzig TE, Dietz ABJB, The Journal of the American Society of Hematology. Immunosuppressive CD14+ HLA-DRlow/− monocytes in B-cell non-Hodgkin lymphoma. 2011;117(3):872-81.

218. Poschke I, Mougiakakos D, Hansson J, Masucci GV, Kiessling RJCr. Immature Immunosuppressive CD14+ HLA-DR−/low Cells in Melanoma Patients Are Stat3hi and Overexpress CD80, CD83, and DC-SignCharacterization of Melanoma CD14+ HLA-DR−/low MDSC. 2010;70(11):4335-45.

219. Filipazzi P, Valenti R, Huber V, Pilla L, Canese P, Iero M, et al. Identification of a new subset of myeloid suppressor cells in peripheral blood of melanoma patients with modulation by a granulocyte-macrophage colony-stimulation factor–based antitumor vaccine. 2007;25(18):2546-53.

220. Valenti R, Huber V, Filipazzi P, Pilla L, Sovena G, Villa A, et al. Human tumor-released microvesicles promote the differentiation of myeloid cells with transforming growth factor-β–mediated suppressive activity on T lymphocytes. 2006;66(18):9290-8.

221. Bronte V, Serafini P, Mazzoni A, Segal DM, Zanovello PJTii. L-arginine metabolism in myeloid cells controls T-lymphocyte functions. 2003;24(6):301-5.

222. Kusmartsev S, Gabrilovich DIJJolb. Inhibition of myeloid cell differentiation in cancer: the role of reactive oxygen species. 2003;74(2):186-96.

223. Mao Y, Poschke I, Wennerberg E, Pico de Coaña Y, Egyhazi Brage S, Schultz I, et al. Melanoma-Educated CD14+ Cells Acquire a Myeloid-Derived Suppressor Cell Phenotype through COX-2–Dependent MechanismsCOX-2/PGE2-Dependent T-Cell Suppression by MDSCs in Melanoma. 2013;73(13):3877-87.

224. Kohanbash G, McKaveney K, Sakaki M, Ueda R, Mintz AH, Amankulor N, et al. GM-CSF Promotes the Immunosuppressive Activity of Glioma-Infiltrating Myeloid Cells through Interleukin-4 Receptor-αIL-4Rα+ Suppressive Myeloid Cells in Gliomas. 2013;73(21):6413-23.

225. Lechner MG, Liebertz DJ, Epstein ALJTJoI. Characterization of cytokine-induced myeloid-derived suppressor cells from normal human peripheral blood mononuclear cells. 2010;185(4):2273-84.

226. Capece D, Fischietti M, Verzella D, Gaggiano A, Cicciarelli G, Tessitore A, et al. The inflammatory microenvironment in hepatocellular carcinoma: a pivotal role for tumor-associated macrophages. 2013;2013.

227. Wyler L, Napoli C, Ingold B, Sulser T, Heikenwälder M, Schraml P, et al. Brain metastasis in renal cancer patients: metastatic pattern, tumour-associated macrophages and chemokine/chemoreceptor expression. 2014;110(3):686-94.

228. Chen C, Qu Q-X, Shen Y, Mu C-Y, Zhu Y-B, Zhang X-G, et al. Induced expression of B7-H4 on the surface of lung cancer cell by the tumor-associated macrophages: a potential mechanism of immune escape. 2012;317(1):99-105.

229. Liu J, Zhang N, Li Q, Zhang W, Ke F, Leng Q, et al. Tumor-associated macrophages recruit CCR6+ regulatory T cells and promote the development of colorectal cancer via enhancing CCL20 production in mice. 2011;6(4):e19495.

230. Helm O, Held-Feindt J, Grage-Griebenow E, Reiling N, Ungefroren H, Vogel I, et al. Tumor-associated macrophages exhibit pro-and anti-inflammatory properties by which they impact on pancreatic tumorigenesis. 2014;135(4):843-61.

231. Manicassamy S, Pulendran BJIr. Dendritic cell control of tolerogenic responses. 2011;241(1):206-27.

232. Talmadge JE, editor Immune cell infiltration of primary and metastatic lesions: mechanisms and clinical impact. Seminars in cancer biology; 2011: Elsevier.

233. Zhong H, Gutkin DW, Han B, Ma Y, Keskinov AA, Shurin MR, et al. Origin and pharmacological modulation of tumor-associated regulatory dendritic cells. 2014;134(11):2633-45.

234. Fioretti D, Iurescia S, Fazio VM, Rinaldi MJJoB, Biotechnology. DNA vaccines: developing new strategies against cancer. 2010;2010.

235. Okamoto I, Arao T, Miyazaki M, Satoh T, Okamoto K, Tsunoda T, et al. Clinical phase I study of elpamotide, a peptide vaccine for vascular endothelial

growth factor receptor 2, in patients with advanced solid tumors. 2012;103(12):2135-8.

236. Pilla L, Valenti R, Marrari A, Patuzzo R, Santinami M, Parmiani G, et al. Vaccination: role in metastatic melanoma. 2006;6(8):1305-18.

237. Negahdaripour M, Vakili B, Nezafat NJII. Exosome-based vaccines and their position in next generation vaccines. 2022;113:109265.

238. Vanmeerbeek I, Sprooten J, De Ruysscher D, Tejpar S, Vandenberghe P, Fucikova J, et al. Trial watch: Chemotherapy-induced immunogenic cell death in immuno-oncology. 2020;9(1):1703449.

239. Sangro B, Sarobe P, Hervás-Stubbs S, Melero IJNrG, hepatology. Advances in immunotherapy for hepatocellular carcinoma. 2021;18(8):525-43.

240. Modjtahedi H, Ali S, Essapen SJBmb. Therapeutic application of monoclonal antibodies in cancer: advances and challenges. 2012;104(1):41-59.

241. Rosenberg SA, Dudley MEJCoii. Adoptive cell therapy for the treatment of patients with metastatic melanoma. 2009;21(2):233-40.

242. Clay TM, Custer MC, Spiess PJ, Nishimura MIJP, Research O. Potential use of T cell receptor genes to modify hematopoietic stem cells for the gene therapy of cancer. 1999;5(1):3-15.

243. Lipowska-Bhalla G, Gilham DE, Hawkins RE, Rothwell DGJCI, Immunotherapy. Targeted immunotherapy of cancer with CAR T cells: achievements and challenges. 2012;61(7):953-62.

244. Sistigu A, Viaud S, Chaput N, Bracci L, Proietti E, Zitvogel L, editors. Immunomodulatory effects of cyclophosphamide and implementations for vaccine design. Seminars in immunopathology; 2011: Springer.

245. Vicari AP, Luu R, Zhang N, Patel S, Makinen SR, Hanson DC, et al. Paclitaxel reduces regulatory T cell numbers and inhibitory function and enhances the anti-tumor effects of the TLR9 agonist PF-3512676 in the mouse. 2009;58(4):615-28.

246. Deng Y, Yang J, Qian J, Liu R, Huang E, Wang Y, et al. TLR1/TLR2 signaling blocks the suppression of monocytic myeloid-derived suppressor cell by promoting its differentiation into M1-type macrophage. 2019;112:266-73.

247. Kavanagh B, O'Brien S, Lee D, Hou Y, Weinberg V, Rini B, et al. CTLA4 blockade expands FoxP3+ regulatory and activated effector CD4+ T cells in a dose-dependent fashion. 2008;112(4):1175-83.

248. Tarhini AA, Edington H, Butterfield LH, Lin Y, Shuai Y, Tawbi H, et al. Immune monitoring of the circulation and the tumor microenvironment in patients with regionally advanced melanoma receiving neoadjuvant ipilimumab. 2014;9(2):e87705.

249. Albeituni SH, Ding C, Yan JJCj. Hampering the immune suppressors: therapeutic targeting of myeloid-derived suppressor cells (MDSC) in cancer. 2013;19(6):490.

250. Chalmin F, Ladoire S, Mignot G, Vincent J, Bruchard M, Remy-Martin J-P, et al. Membrane-associated Hsp72 from tumor-derived exosomes mediates STAT3-dependent immunosuppressive function of mouse and human myeloid-derived suppressor cells. 2010;120(2):457-71.

251. Ozao-Choy J, Ma G, Kao J, Wang GX, Meseck M, Sung M, et al. The novel role of tyrosine kinase inhibitor in the reversal of immune suppression and modulation of tumor microenvironment for immune-based cancer therapies. 2009;69(6):2514-22.

252. Eruslanov E, Daurkin I, Ortiz J, Vieweg J, Kusmartsev SJJolb. Pivotal Advance: Tumor-mediated induction of myeloid-derived suppressor cells and M2-polarized macrophages by altering intracellular PGE2 catabolism in myeloid cells. 2010;88(5):839-48.

253. Rodriguez PC, Hernandez CP, Quiceno D, Dubinett SM, Zabaleta J, Ochoa JB, et al. Arginase I in myeloid suppressor cells is induced by COX-2 in lung carcinoma. 2005;202(7):931-9.

254. Veltman JD, Lambers ME, van Nimwegen M, Hendriks RW, Hoogsteden HC, Aerts JG, et al. COX-2 inhibition improves immunotherapy and is associated with decreased numbers of myeloid-derived suppressor cells in mesothelioma. Celecoxib influences MDSC function. 2010;10(1):1-13.

255. Fujita M, Kohanbash G, Fellows-Mayle W, Hamilton RL, Komohara Y, Decker SA, et al. COX-2 Blockade Suppresses Gliomagenesis by Inhibiting Myeloid-Derived Suppressor CellsCOX-2 Blockade and Gliomagenesis. 2011;71(7):2664-74.

256. Hodi FS, O'day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. 2010;363(8):711-23.

257. Robert C, Schadendorf D, Messina M, Hodi FS, O'Day SJCCR. Efficacy and Safety of Retreatment with Ipilimumab in Patients with Pretreated Advanced Melanoma Who Progressed after Initially Achieving Disease ControlIpilimumab Retreatment in Advanced Melanoma. 2013;19(8):2232-9.

258. Taube JM, Anders RA, Young GD, Xu H, Sharma R, McMiller TL, et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. 2012;4(127):127ra37-ra37.

259. Wilgenhof S, Du Four S, Vandenbroucke F, Everaert H, Salmon I, Liénard D, et al. Single-center experience with ipilimumab in an expanded access program for patients with pretreated advanced melanoma. 2013;36(3):215-22.

260. Barber DL, Wherry EJ, Masopust D, Zhu B, Allison JP, Sharpe AH, et al. Restoring function in exhausted CD8 T cells during chronic viral infection. 2006;439(7077):682-7.

261. Rosenblatt J, Avigan DJB. Targeting the PD-1/PD-L1 axis in multiple myeloma: a dream or a reality? 2017;129(3):275-9.

262. Zou GM, Tam YKJEcn. Cytokines in the generation and maturation of dendritic cells: recent advances. 2002;13(2):186-99.

263. Akagawa KS, Komuro I, Kanazawa H, Yamazaki T, Mochida K, Kishi FJR. Functional heterogeneity of colony-stimulating factor-induced human monocyte-derived macrophages. 2006;11:S32-S6.

264. Granelli-Piperno A, Pritsker A, Pack M, Shimeliovich I, Arrighi J-F, Park CG, et al. Dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin/CD209 is abundant on macrophages in the normal human lymph node and is not required for dendritic cell stimulation of the mixed leukocyte reaction. 2005;175(7):4265-73.

265. Gieseler R, Heise D, Soruri A, Schwartz P, Peters JHJDi. In-vitro differentiation of mature dendritic cells from human blood monocytes. 1998;6(1-2):25-39.

266. Ferrantini M, Capone I, Belardelli FJB. Interferon-α and cancer: mechanisms of action and new perspectives of clinical use. 2007;89(6-7):884-93.

267. Le DT, Pardoll DM, Jaffee EMJCj. Cellular vaccine approaches. 2010;16(4):304.

268. Palma M, Hansson L, Choudhury A, Näsman-Glaser B, Eriksson I, Adamson L, et al. Vaccination with dendritic cells loaded with tumor apoptotic bodies (Apo-DC) in patients with chronic lymphocytic leukemia: effects of various adjuvants and definition of immune response criteria. 2012;61(6):865-79.

269. Salcedo M, Bercovici N, Taylor R, Vereecken P, Massicard S, Duriau D, et al. Vaccination of melanoma patients using dendritic cells loaded with an allogeneic tumor cell lysate. 2006;55(7):819-29.

270. Schuler-Thurner B, Schultz ES, Berger TG, Weinlich G, Ebner S, Woerl P, et al. Rapid induction of tumor-specific type 1 T helper cells in metastatic melanoma patients by vaccination with mature, cryopreserved, peptide-loaded monocyte-derived dendritic cells. 2002;195(10):1279-88.

271. Meidenbauer N, Harris D, Spitler L, Whiteside TJTP. Generation of PSA-reactive effector cells after vaccination with a PSA-based vaccine in patients with prostate cancer. 2000;43(2):88-100.

272. Ricupito A, Grioni M, Calcinotto A, Hess Michelini R, Longhi R, Mondino A, et al. Booster vaccinations against cancer are critical in prophylactic but detrimental in therapeutic settings. 2013;73(12):3545-54.

273. Shen C-H, Talay O, Mahajan VS, Leskov IB, Eisen HN, Chen JJPotNAoS. Antigen-bearing dendritic cells regulate the diverse pattern of memory CD8 T-cell development in different tissues. 2010;107(52):22587-92.

274. Berger TG, Haendle I, Schrama D, Lüftl M, Bauer N, Pedersen LØ, et al. Circulation and homing of melanoma-reactive T cells to both cutaneous and visceral metastases after vaccination with monocyte-derived dendritic cells. 2004;111(2):229-37.

275. Wilgenhof S, Corthals J, Heirman C, van Baren N, Lucas S, Kvistborg P, et al. Phase II study of autologous monocyte-derived mRNA electroporated dendritic cells (TriMixDC-MEL) plus ipilimumab in patients with pretreated advanced melanoma. 2016;34(12):1330-8.

276. Palucka K, Banchereau JJNRC. Cancer immunotherapy via dendritic cells. 2012;12(4):265-77.

277. H. Yi D, Appel SJSjoi. Current Status and Future Perspectives of Dendritic Cell–Based Cancer Immunotherapy. 2013;78(2):167-71.

278. Mazumder AJLr. Lymphokine-activated killer cells: in vitro and in vivo studies. 1985;4(3):215-20.

279. Walewski J, Paietta E, Dutcher J, Wiernik PJJocr, oncology c. Evaluation of natural killer and lymphokine-activated killer (LAK) cell activity in vivo in patients treated with high-dose interleukin-2 and adoptive transfer of autologous LAK cells. 1989;115(2):170-4.

280. Lee J-C, Lee K-M, Kim D-W, Heo DSJTJoI. Elevated TGF-β1 secretion and down-modulation of NKG2D underlies impaired NK cytotoxicity in cancer patients. 2004;172(12):7335-40.

281. Parkhurst MR, Riley JP, Dudley ME, Rosenberg SAJCCR. Adoptive Transfer of Autologous Natural Killer Cells Leads to High Levels of Circulating Natural Killer Cells but Does Not Mediate Tumor RegressionNK Adoptive Transfer in Cancer Patients. 2011;17(19):6287-97.

282. Iliopoulou EG, Kountourakis P, Karamouzis MV, Doufexis D, Ardavanis A, Baxevanis CN, et al. A phase I trial of adoptive transfer of allogeneic natural killer cells in patients with advanced non-small cell lung cancer. 2010;59(12):1781-9.

283. Frohn C, Doehn C, Durek C, Böhle A, Schlenke P, Jocham D, et al. Feasibility of the adoptive transfusion of allogenic human leukocyte antigen-matched natural killer cells in patients with renal cell carcinoma. 2000;23(4):499-504.

284. Miller JS, Soignier Y, Panoskaltsis-Mortari A, McNearney SA, Yun GH, Fautsch SK, et al. Successful adoptive transfer and in vivo expansion of human haploidentical NK cells in patients with cancer. 2005;105(8):3051-7.

285. Pfeiffer M, Schumm M, Feuchtinger T, Dietz K, Handgretinger R, Lang PJBjoh. Intensity of HLA class I expression and KIR-mismatch determine NK-cell mediated lysis of leukaemic blasts from children with acute lymphatic leukaemia. 2007;138(1):97-100.

286. Giebel S, Locatelli F, Lamparelli T, Velardi A, Davies S, Frumento G, et al. Survival advantage with KIR ligand incompatibility in hematopoietic stem cell transplantation from unrelated donors. 2003;102(3):814-9.

287. Beelen DW, Ottinger HD, Ferencik S, Elmaagacli AH, Peceny R, Trenschel R, et al. Genotypic inhibitory killer immunoglobulin-like receptor ligand

incompatibility enhances the long-term antileukemic effect of unmodified allogeneic hematopoietic stem cell transplantation in patients with myeloid leukemias. 2005;105(6):2594-600.

288. Miller JS, Cooley S, Parham P, Farag SS, Verneris MR, McQueen KL, et al. Missing KIR ligands are associated with less relapse and increased graft-versus-host disease (GVHD) following unrelated donor allogeneic HCT. 2007;109(11):5058-61.

289. Vey N, Bourhis J-H, Boissel N, Bordessoule D, Prebet T, Charbonnier A, et al. A phase 1 trial of the anti-inhibitory KIR mAb IPH2101 for AML in complete remission. 2012;120(22):4317-23.

290. Benson Jr DM, Hofmeister CC, Padmanabhan S, Suvannasankha A, Jagannath S, Abonour R, et al. A phase 1 trial of the anti-KIR antibody IPH2101 in patients with relapsed/refractory multiple myeloma. 2012;120(22):4324-33.

291. Anderson D, Grillo-Lopez A, Varns C, Chambers K, Hanna NJBST. Targeted anti-cancer therapy using rituximab, a chimaeric anti-CD20 antibody (IDEC-C2B8) in the treatment of non-Hodgkin's B-cell lymphoma. 1997;25(2):705-8.

292. Gluck WL, Hurst D, Yuen A, Levine AM, Dayton MA, Gockerman JP, et al. Phase I studies of interleukin (IL)-2 and rituximab in B-cell non-hodgkin's lymphoma: IL-2 mediated natural killer cell expansion correlations with clinical response. 2004;10(7):2253-64.

293. Dall'Ozzo S, Tartas S, Paintaud G, Cartron G, Colombat P, Bardos P, et al. Rituximab-dependent cytotoxicity by natural killer cells: influence of FCGR3A polymorphism on the concentration-effect relationship. 2004;64(13):4664-9.

294. Hunter TB, Manimala NJ, Luddy KA, Catlin T, Antonia SJJAr. Paclitaxel and TRAIL synergize to kill paclitaxel-resistant small cell lung cancer cells through a caspase-independent mechanism mediated through AIF. 2011;31(10):3193-204.

295. Lundqvist A, Abrams SI, Schrump DS, Alvarez G, Suffredini D, Berg M, et al. Bortezomib and Depsipeptide Sensitize Tumors to Tumor Necrosis Factor–Related Apoptosis-Inducing Ligand: A Novel Method to Potentiate Natural Killer Cell Tumor Cytotoxicity. 2006;66(14):7317-25.

296. Sarhan D, Wennerberg E, D'Arcy P, Gurajada D, Linder S, Lundqvist AJCI, Immunotherapy. A novel inhibitor of proteasome deubiquitinating activity renders tumor cells sensitive to TRAIL-mediated apoptosis by natural killer cells and T cells. 2013;62(8):1359-68.

297. VanOosten RL, Moore JM, Karacay B, Griffith TJCb, therapy. Histone deacetylase inhibitors modulate renal cell carcinoma sensitivity to TRAIL/Apo-2L-induced apoptosis by enhancing TRAIL-R2 expression. 2005;4(10):1104-12.

298. Wennerberg E, Sarhan D, Carlsten M, Kaminskyy VO, D'Arcy P, Zhivotovsky B, et al. Doxorubicin sensitizes human tumor cells to NK cell-and T-cell-mediated killing by augmented TRAIL receptor signaling. 2013;133(7):1643-52.

299. Meropol NJ, Porter M, Blumenson LE, Lindemann MJ, Perez RP, Vaickus L, et al. Daily subcutaneous injection of low-dose interleukin 2 expands natural killer cells in vivo without significant toxicity. 1996;2(4):669-77.

300. Phillips JH, Gemlo BT, Myers WW, Rayner AA, Lanier LLJJoCO. In vivo and in vitro activation of natural killer cells in advanced cancer patients undergoing combined recombinant interleukin-2 and LAK cell therapy. 1987;5(12):1933-41.

301. Burns L, Weisdorf D, DeFor T, Vesole D, Repka T, Blazar B, et al. IL-2-based immunotherapy after autologous transplantation for lymphoma and breast cancer induces immune activation and cytokine release: a phase I/II trial. 2003;32(2):177-86.

302. Sarhan D, D'Arcy P, Wennerberg E, Lidén M, Hu J, Winqvist O, et al. Activated monocytes augment TRAIL-mediated cytotoxicity by human NK cells through release of IFN-γ. 2013;43(1):249-57.

303. Jungkunz-Stier I, Zekl M, Stühmer T, Einsele H, Seggewiss-Bernhardt RJL, lymphoma. Modulation of natural killer cell effector functions through lenalidomide/dasatinib and their combined effects against multiple myeloma cells. 2014;55(1):168-76.

304. Ni J, Miller M, Stojanovic A, Garbi N, Cerwenka AJJoEM. Sustained effector function of IL-12/15/18–preactivated NK cells against established tumors. 2012;209(13):2351-65.

305. Rosental B, Y Appel M, Yossef R, Hadad U, Brusilovsky M, Porgador AJCmc. The effect of chemotherapy/radiotherapy on cancerous pattern recognition by NK cells. 2012;19(12):1780-91.