MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Virology & Immunology Journal
ISSN: 2577-4379

Past and Current Immunotherapy in Cancer

Demirkaya B[1] and Yalcin S[2]*

[1]Faculty of Medicine, Department of Pediatric Allergy and Immunology, Marmara University, Turkey

[2]Faculty of Medicine, Department of Medical Pharmacology, Kirsehir Ahi Evran University, Turkey

***Corresponding author:** Serap Yalcin, Faculty of Medicine, Department of Medical Pharmacology, Kırsehir Ahi Evran University, Turkey, Email: syalcin@ahievran.edu.tr

Mini Review

Volume 8 Issue 4

Received Date: September 20, 2024

Published Date: October 23, 2024

DOI: 10.23880/vij-16000354

Abstract

Immunotherapy has become a revolutionary method in treating cancer, harnessing the body's immune system to identify and eliminate cancer cells. This review offers an overview of recent advancements and aspects in cancer immunotherapy, covering established treatments such as checkpoint inhibitors and CAR-T cells, as well as emerging innovative approaches and the challenges involved in their clinical application.

Keywords: Immunotherapy; Cancer

Introduction

Cancer is one of the diseases with the highest mortality rate in the world [1]. Cancer research has constantly aimed to develop different treatment methods other than traditional treatment methods. Immunotherapy is one of the most non-traditional treatment systems and aims to kill cancerous cells by ensuring that immune system cells recognize cancerous cells or increasing the cytotoxic effects of cells that have the ability to kill, such as C8T+ or NK cells [2]. In the last years when immunotherapy methods began to be developed, cytokines (especially IFNα and IL-2) were used, but some were replaced by different analogues due to their half-lives, while others were not used due to serious inflammatory side effects. Cancer studies resulted in long-term failures, and although sipuleucel-T was approved for prostate cancer, it was shelved due to difficulties in its production and other reasons. Later, it gained importance in cancer studies thanks to the recent determination of the effectiveness of mABs targeting checkpoint inhibitors. CTLA-4, PD-1/PD-1L are the most commonly used and targeted receptors and ligands. TIL (tumor-infiltrating lymphocytes) and CAR-T treatments have been developed for a long time and follow each other as a system. Although these systems are close to each other, after the CD8T cells taken from patients are grown in vitro, it is aimed to re-administer them to patients or to modify the receptors of these cells and collect both recognition and signal-producing ligands under a single receptor and give them to people. Despite these advances, the effective and safe use of immunotherapies in patients is limited. The reason for this handicap may be difficulties such as predicting the responses of patients and developing biomarkers specifically for individuals based on their expression levels. This article contains information about new strategies and developments.

Trombocytes and Stem Cells

The first innovations in new delivery systems involve the delivery of platelets and hematopoietic stem cells and checkpoint inhibitors, first of all, briefly, platelets are colorless cells found in our blood that stop bleeding by forming clots in case of bleeding, and these cells are known to interact with tumor cells [3]. Studies have found

CC BY

that PD-L1 binding antibodies conjugated to platelets via a binding maleimide reduce recurrence rates and metastasis capabilities in patients after post-operative administration of PD-L1 binding antibodies, and the administration of these PD-L1 binding antibodies with this system has demonstrated an extension of their half-life. In mice treated with this system, recurrence rates were reduced by 75%, while there was no benefit in terms of good prognosis with platelet or PD-L1 administration alone [4].

Hematopoietic stem cells and platelets containing PD-L1 were incubated together and N-azidoacetylgalactosamine-tetraacylated (Ac 4 GalNAz) and dibenzocyclooctinin-PEG 4 -N-hydroxysuccinimidyl ester (BDCO-PEG 4 -NHS ester) were present on these platelets. Targeting cancers with this system results in local release of PD1 and good prognosis in patients [5].

Macrophages

Monocyte cells, which constitute a subpopulation of white blood cells, develop from hematopoietic stem cells in the bone marrow and are called macrophage cells once they enter the tissue [6]. These cells constitute the most important cell group of the innate immune system by performing multiple functions; they perform very effective tasks such as digestion of pathogens (such as digestion of intracellular pathogens), maintaining tissue homeostasis, secretion of cytokines for the initiation and regulation of inflammation.

These cell types are divided into two different classes, M1 and M2, M1 macrophages show cytotoxic effects such as killing cells, while M2 macrophages are generally involved in tissue repair and differentiation of these cells is carried out by different T cell subtypes [7]. M1 macrophages in the tumor microenvironment (TME) are highly effective in initiating the inflammatory response and anti-tumor response because they secrete IFN-γ and TNF-α [6]. At the same time, these cells are able to kill cancerous cells by detecting them by the PRR receptors they have on them, and because of this ability, these cells are effective in cancer treatments [8]. However, the TMJ has developed specific defense strategies, some of which include converting M1 macrophages into M2 macrophages and establishing new oxygen and nutrient transport systems by enabling them to be effective in angiogenesis [8,9]. IL-10, IL-4 and IL-13 released in TME are the most important cytokine group that are effective in the transformation of M2 into macrophages [7]. New strategies have been developed to overcome such problems.

Shen et al. Conducted studies to eliminate these M2 macrophages, namely tumor-associated macrophages (TAM). The BLZ-945 molecule itself is called a colony-stimulating factor and has very important effects on the development, survival and function of macrophages [10]. This molecule specifically targets macrophages and prevents these macrophages from receiving survival signaling, resulting in cell death. In the study by Shen et al, BLZ-945 was combined with a platinum prodrug together with pH-sensitive nanoparticles. This combination provided both a chemotherapeutic effect (platinum prodrug killing tumor cells) and an immunomodulatory effect (BLZ-945 killing TAMs), resulting in a highly improved survival rate in CT26 colon cancer models [11].

Some of the other important strategies are to reconvert these M2 macrophages into M1 macrophages. In this context, many cytokines, TLR antagonists, CpG oligonucleotides are used [12]. Huang, et al. Developed a pH-sensitive nanoparticle that combines CpG oligonucleotides with anti-IL-10 antibodies [13]. TLR detection of these CpGs causes more IL-12 to be secreted into the medium and polarized M2 macrophages to M1 macrophages [13].

Viruses

The binding strategies of viruses to animal cells allow them to bind to different cell lines with varying specificity due to the specific structures they have on them, and targeting strategies have been made with modified or virulence-engineered viruses, and virus-induced cell lysis can also help recruit inflammatory cells and proteins to tumor sites [3]. We investigated the efficacy of small siRNAs as a strategy to inhibit PD-L1 expression before it reaches the translational stage and treated retroviral replication vectors with a hairpin RNA derived from microRNA-30, which resulted in a decrease in PD-L1 expression and increased the activity and number of CD8T cells [14].

In addition, studies have evaluated the effect of oncolytic virotherapy methods and has conducted studies on the effect of both checkpoint inhibitors and co-simulator molecules that have effects on increasing the activity of lymphocytes and discusses their effectiveness. This study investigated the use of oncolytic viruses carrying anti-CTLA-4 monoclonal antibodies and capable of replication for treating subcutaneous lung cancer cells within tumors. The outcomes revealed a decrease in tumor burdens [3,15].

Exosomes

Exosomes are molecular structures forming the smallest group of extracellular vesicles secreted by almost all cells [16]. Exosomes can generally carry proteins of these cells in their membranes depending on the physiology of the cells from which they are secreted [17]. When we examine the exosomes secreted from dendric cells, it is possible to see

Copyright© Yalcin S.

CD80 and CD86 in these exosomes. Although exosomes were thought to be involved in the transport of unwanted waste molecules in general cells when they were first discovered, recent studies have revealed that exosomes have specific and special abilities such as cell differentiation and cell communication [18].

As we explained in detail in the macrophage section, the conversion of TAM cells into M1 cells is very important in the TME to increase the anti-cancer effects. The use of exosomes to reverse the TAM effect without the use of nanoparticles represents an important strategy. In this context, Zhao and colleagues developed an exosome-based delivery system (DTX-M1-Exo) derived from M1 macrophages to reactivate the TME and improve the efficacy of breast cancer therapy [17]. Studies have shown that DTX-M1-Exo can promote the conversion of naive (immature) macrophages to the M1 phenotype. The mechanism of action of the DTX-M1-Exo system is based on reactivation of the immune response in the tumor microenvironment (TME) via exosomes derived from M1 macrophages. By carrying proinflammatory factors, these exosomes convert naïve macrophages to the M1 phenotype, thereby reducing the effect of immunosuppressive M2 macrophages. Cells transformed into M1 macrophages suppress tumor growth in the TMJ by secreting tumor-fighting proinflammatory cytokines and activate other cells of the immune system. Furthermore, DTX-M1-Exo regulates the mitochondrial function of M1 macrophages, allowing these cells to remain active in the long term, which contributes to the maintenance of antitumor efficacy. This mechanism offers a promising approach to cancer therapy, both directly targeting tumor cells and enhancing the immune response. In conclusion, DTX-M1-Exo showed a potent antitumor therapeutic effect and this strategy is considered a promising approach in the fight against tumor [19].

Studies using other exosomes have enabled the creation of pH-sensitive drug delivery systems in TMEs with acidic properties due to excessive lactate uremia in the TME region. For this system, Kim et al. Developed modified exosomes to facilitate doxorubicin delivery [20]. Thanks to these exosomes, studies on MCF-7 cells have shown that these exosomes may have high anti-cancer properties [20].

DNA-Encoded Monoclonal Antibodies

Some of the most common problems encountered in the application of checkpoint inhibitor therapies are the long-term administration of these inhibitors, production difficulties and cost [21]. To address these challenges to some extent, Duperret et al. developed the DNA-encoded monoclonal antibody (Dmab) technique [21]. In this system, they show that a single dose of Dmabs encoding the anti-CTLA-4 antibody consistently produce this antibody in mice and result in a favorable prognosis in cancers [21]. Other checkpoint inhibitors have also been studied in these systems and the results of their combination therapies are promising with high success rates. However, similar to other cancer treatment studies, there are shortcomings and areas requiring improvement. The primary concern is that these long-term antibodies lack regulatory regions that would guarantee their inhibition. Therefore, the main focus in advancing these systems should be on incorporating regulation or shutdown regions [3].

Bacteria and Bacterial Ghosts

The study and use of bacteria as delivery strategies for checkpoint inhibitors has recently improved but is often limited. In studies, single domain antibodies (nanobodies) with PD-L1 or CTLA-4 inhibitors have been transferred together with a plasmid into mouse models of colorectal cancer with E. *coli* offenses [22]. These plasmids contain both promoter regions that produce checkpoint inhibitors and genes that are linked to promoter regions that cause cell lysis. When E.*coli* reaches a certain number in the cell, it bursts its target cell and releases a large number of inhibitory antibodies to the tumor sites [22].

Bacterial ghosts can be defined as hollow cellular shells created by the expression of the lysis E gene of bacteriophages [23]. These lysis E genes cause the formation of a transmembrane tunnel, which leads to the separation of the cytoplasmic contents of the bacteria. These life forms have been found to retain the ability to interact with cells, making them hypothesized to be very effective in drug or protein transport systems. Studies have also shown that these ghosts are very valuable in their ability to transport molecules such as chemotherapy drugs, proteins, nucleic acids, etc.

However, it is also thought that these structures may be stimulated by TLR structures of immune system cells, which are usually of myeloid origin, and may play important roles in immune system interactions, and may be effective in the activation of naive T cells via dendritic by generating signals via TLR 2/4 [24].

In terms of future significance, immune checkpoint inhibitors loaded on bacterial ghosts may be capable of delivering these systems to tumor sites, or these ghosts injected into tumor sites may be presented with antigens that will enable direct recruitment of B cells and may be effective in initiating humoral or cellular immunity [25] Table 1.

Recent Advances in Immunotherapy

Copyright© Yalcin S.

Systems Used	Advantages	Disadvantages	Source
Herpes Virus	They have the ability to infect cancer cells and multiply rapidly. Anti-HSV drugs are also available to eliminate the virulence effects of these viruses.	Pancreas second line Melanoma Third- line	[26]
Adenovirus	The ability of adenoviruses to destroy cancer stem cells also triggers various cell death signals, resulting in the release of DAMPs, molecular patterns associated with damage.	Glioblastoma	[27]
Rhabdovirus	It has a strong oncolytic activity. In in vitro experiments, it showed high selectivity for tumor cells and low virulence.	Solid Tumors	[28]
LP@BG@CCM	It describes paclitaxel-laden bacterial ghosts that are fused with cancer cell membranes. Promising positive results have been obtained in studies.	Lung Cancer	[29]
Doxorubicin-Loaded Ghosts	Their ability to target a wide range of cells is one of the major advantages of these systems. In this study, instead of *E. Coli*, *M. Haemolytica*, which exhibits a higher binding affinity, was used.	In Vitro Caco-2 Cell Line	[30]

Table 1. Examples of viruses and bacterial ghosts used in cancer therapies in recent years.

Drug Delivery Methods for Immunotherapy Approach

Lipid-based Nanocarriers

Lipid-based nanocarriers can easily pass through most cellular membranes in the body because of biomimetic properties and also accumulate at high levels. Some of the lipid-based nanocarriers, especially liposomes, show very low toxicity, high level of biodegradation and biocompatibility besides these abilities [31]. The most important properties of liposomes for the delivery of immunotherapeutic agents to specific sites are their hydrophilic and hydrophobic properties [32].

It is aimed to increase the effectiveness of cancer vaccines by combining or filling liposomes with hydrophilic molecules such as proteins, peptides and nucleic acids by transferring these molecules to the spleen or lymph nodes. The primary goal in using this method is to capture and internalise antigenic molecules by antigen-presenting cells densely located in these regions and present them to CD4T cells or to activate CD8T cells called cytotoxic T cells by cross-presentation [33]. In the studies on liposomes, Bayyurt, el al. created a liposomal formulation of ovalbumin antigen with two different adjuvants and delivered it to the target sites. When we examine the adjuvants they used, CpG oligodeoxynucleotide (CpG ODN) was aimed to target receptors called TLR 9 and then to induce the natural defence of the immune system. In the other adjuvant, Poly(I) (polyinosinic-polycytidylic acid) targets TLR3 receptors. In summary, Bayyurt et al. combined ovalbumin antigen and two different adjuvants in a liposomal structure in order to stimulate the immune system more effectively [34].

When we look at other studies with liposomes, we come across two different strategies: studies based on pH differences and those related to checkpoint inhibitors.

The cargo molecules loaded in liposomes designed based on pH are intended to provide a combined effect by activating both TLR9 and STING pathway. While the TLR9 pathway activates the NF-κB pathway, which enables it to act by positively stimulating inflammatory proteins, the STING pathway enables the production of Type 1 interferons. With the disruption of the liposome structure in an acidic PH environment, cargo molecules are released into the environment, and thus the presentation of anigen by APC cells is expected to develop adaptive immunity.

The loading of checkpoint inhibitors as cargo into liposomes may have been done to limit the side effects of these molecules and to facilitate the accumulation of molecules only at tumour sites [31]. Immune control nucleus inhibitors can reverse the effect of tumours escaping the immune system and restore cell death, but they have as many negatives as positives and such toxicities are commonly referred to as immune-related adverse events (irAEs) [35]. To test the aforementioned side effect limitation, Nikpoor et al. evaluated the effect of anti-CTLA4 antibodies loaded into liposomes coated with polyethylene glycol on mice bearing CT26 colon tumours. As a result of this study, it was found that these liposomes were highly permeable and better retained at tumour sites, prolonged the survival of mice and caused tumour growth arrest [31].

Polymer-Based Nanocarriers

Copyright© Yalcin S.

Polymeric nanoparticles have attracted intense interest in immunotherapy studies in recent years due to their unique superior properties and advantages compared to other nanomaterials. These nanoparticles can be synthesised in three different ways: natural, synthetic and semi-synthetic [31]. Polymer-based nanomaterials are easily accepted by organisms thanks to their biocompatibility, offer high cargo carrying capacities and are highly resistant to cellular degradation with their highly stable structures. In addition, the suitability of polymeric nanomaterials for surface modifications has the potential to increase therapeutic efficacy by providing controlled release of immunotherapeutic agents. Therefore, polymeric nanomaterials are considered as promising tools in the field of immunotherapy [36].

Cathepsin B is an enzyme known to play a role in tumour invasion and metastasis and is generally found at high levels in tumour tissues [37]. This enzyme is also known for its ability to cleave the GFLG (Gly-Phe-Leu-Gly) molecule, a synthetic protein used in cancer research and therapeutic developments [38]. Yang et al. added GFLG molecule to the main chain of N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer-doxorubicin (DOX) conjugate in their studies [39]. When these nanoparticles were injected into tumour tissues, high levels of cathepsin B molecules cleaved the GFLG sites before being opsonised by macrophages or innate immune cells, allowing the drug molecules to act on cancer cells [39].

The extracellular matrix (ECM) consists of various molecules such as collagen, fibronectin, or elastin, but the presence of these molecules in certain ratios is crucial for the cancerisation or metastasis of cells [40]. MMP enzymes are also highly expressed enzyme molecules in tumour tissues, as in cathepsin B. Both MMP-2 and MMP-9 provide ECM degradation by the effect of collagen IV or laminin and indirectly contribute to metastasis [41]. Their ability to be found at high levels in tumour tissues has made these molecules a focal point for targeting nanoparticles [42]. In this context, a peptide molecule (PEG-MP9-Apdl) containing a linker capable of being cleaved by MMP-2 was developed for the treatment of choleraqual cancer [43]. This PEG-MP9-aPDL1 peptide chimera is a molecule designed to bind to PD-L1. This binding inhibits the PD-1/PD-L1 pathway unnecessaty repeat, helping to prevent cancer cells from escaping the immune system. When the PEG-MP9-aPDL1 peptide chimera is cleaved, various molecules are released that allow the immune system to target cancer cells more effectively. For example, the optimised oncolytic peptide MP9 is released. This peptide exerts a direct cytotoxic effect on cancer cells, leading to lysis of tumour cells [44].

The tumour microenvironment contains some specific features for cancer cell growth and development [45]. One of these features is that it has a different redox balance that is not visible compared to normal cells. This redox imbalance leads to DNA damage and protein oxidation in tumour cells and directs the cells to apoptosis, and tumour cells synthesise various antioxidant molecules such as glutathione and catalase to reduce this imbalance. Based on this hypothesis, nanohydrogels are designed based on the redox imbalance in the tumour microenvironment, allowing the presentation of specific proteins to drug molecules or antigen presenting cells (macrophages, dendric cells) loaded into the hydrogels [46].

Conclusion

Innovative delivery systems developed to enhance immunotherapy offer great potential in cancer treatment. By using biological and synthetic structures such as platelets, stem cells, macrophages, viruses, exosomes and nanoparticles, immunosuppressive mechanisms in the tumour microenvironment are targeted and overcome. In particular, the conversion of M2 macrophages into M1 phenotype and the release of specific drugs for tumour sites are among the strategies that increase treatment efficacy. These new systems reduce side effects, inhibit the ability of tumours to escape the immune system and ensure long-term efficacy. Future research should aim to optimise these strategies and use them in clinical applications.

Conflict of Interest

The authors declare no conflicts of interest or financial interests.

References

1. Milroy MJ (2018) Cancer statistics: Global and national. Quality Cancer Care: Survivorship Before, During and After Treatment pp: 29-35.

2. Rosenberg SA, Yang JC, Sherry RM, Kammula US, Hughes MS, et al. (2011) Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clinical Cancer Research 17(13): 4550-4557.

3. Lamichhane P, Deshmukh R, Brown JA, Jakubski S, Parajuli P, et al. (2019) Novel delivery systems for checkpoint inhibitors. Medicines 6(3): 74.

4. Wang C, Sun W, Ye Y, Hu Q, Bomba HN, et al. (2017) In situ activation of platelets with checkpoint inhibitors for post-surgical cancer immunotherapy. Nature Biomedical Engineering, 1(2): 0011.

5. Hu Q, Sun W, Wang J, Ruan H, Zhang X, et al. (2018) Conjugation of haematopoietic stem cells and platelets

Copyright© Yalcin S.

decorated with anti-PD-1 antibodies augments anti-leukaemia efficacy. Nature Biomedical Engineering 2(11): 831-840.

6. Xia Y, Rao L, Yao H, Wang Z, Ning P, et al. (2020) Engineering macrophages for cancer immunotherapy and drug delivery. Advanced Materials 32(40): e2002054.

7. Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, et al. (2018) Macrophage plasticity, polarization, and function in health and disease. Journal of cellular physiology 233(9): 6425-6440.

8. Najafi M, Goradel NH, Farhood B, Salehi E, Nashtaei MS, et al. (2019) Macrophage polarity in cancer: a review. Journal of cellular biochemistry 120(3): 2756-2765.

9. Murray PJ, Wynn TA (2011) Protective and pathogenic functions of macrophage subsets. Nature reviews immunology 11(11): 723-737.

10. Almahariq MF, Quinn TJ, Kesarwani P, Kant S, Miller CR, et al. (2021) Inhibition of colony-stimulating factor-1 receptor enhances the efficacy of radiotherapy and reduces immune suppression in glioblastoma. In Vivo 35(1): 119-129.

11. Shen S, Li HJ, Chen KG, Wang YC, Yang XZ, et al. (2017) Spatial targeting of tumor-associated macrophages and tumor cells with a pH-sensitive cluster nanocarrier for cancer chemoimmunotherapy. Nano Letters 17(6): 3822-3829.

12. Rodell CB, Arlauckas SP, Cuccarese MF, Garris CS, Li R, et al. (2018) TLR7/8-agonist-loaded nanoparticles promote the polarization of tumour-associated macrophages to enhance cancer immunotherapy. Nature biomedical engineering 2(8): 578-588.

13. Huang Z, Zhang Z, Jiang Y, Zhang D, Chen J, et al. (2012) Targeted delivery of oligonucleotides into tumor-associated macrophages for cancer immunotherapy. Journal of controlled release 158(2): 286-292.

14. Lin AH, Twitty CG, Burnett R, Hofacre A, Mitchell LA, et al. (2017) Retroviral replicating vector delivery of miR-PDL1 inhibits immune checkpoint PDL1 and enhances immune responses in vitro. Molecular Therapy-Nucleic Acids 6: 221-232.

15. Du T, Shi G, Li YM, Zhang J, Tian H, et al. (2014) Tumor-specific oncolytic adenoviruses expressing granulocyte macrophage colony-stimulating factor or anti-CTLA4 antibody for the treatment of cancers. Cancer gene therapy 21(8): 340-348.

16. Marar C, Starich B, Wirtz D (2021) Extracellular vesicles in immunomodulation and tumor progression. Nature immunology 22(5): 560-570.

17. Zhang H, Wang S, Sun M, Cui Y, Xing J, et al. (2023) Exosomes as smart drug delivery vehicles for cancer immunotherapy. Frontiers in immunology 13: 1093607.

18. Wang J, Sun X, Zhao J, Yang Y, Cai X, et al. (2017) Exosomes: a novel strategy for treatment and prevention of diseases. Frontiers in pharmacology 8: 300.

19. Zhou W, Zhou Y, Chen X, Ning T, Chen H, et al. (2021) Pancreatic cancer-targeting exosomes for enhancing immunotherapy and reprogramming tumor microenvironment. Biomaterials 268: 120546.

20. Kim JY, Song J, Jung H, Mok H (2018) I-motif-coated exosomes as a pH-sensitive carrier for anticancer drugs. Applied Biological Chemistry 6: 599-606.

21. Duperret EK, Trautz A, Stoltz R, Patel A, Wise MC, et al. (2018) Synthetic DNA-encoded monoclonal antibody delivery of Anti–CTLA-4 antibodies induces tumor shrinkage in vivo. Cancer research 78(22): 6363-6370.

22. Gurbatri CR, Lia I, Vincent R, Coker C, Castro S, et al. (2020) Engineered probiotics for local tumor delivery of checkpoint blockade nanobodies. Science translational medicine 12(530): eaax0876.

23. Hutchison III CA, Sinsheimer RL (1966) The process of infection with bacteriophage phi-X174: X. Mutations in a phi-X lysis gene. Journal of Molecular Biology 18(3): 429-447.

24. Khan N, Vidyarthi A, Pahari S, Negi S, Aqdas M, et al. (2016) Signaling through NOD-2 and TLR-4 bolsters the T cell priming capability of dendritic cells by inducing autophagy. Scientific reports 6(1): 19084.

25. Ebensen T, Paukner S, Link C, Kudela P, de Domenico C, et al. (2004) Bacterial ghosts are an efficient delivery system for DNA vaccines. The Journal of Immunology 172(11): 6858-6865.

26. Ma W, He H, Wang H (2018) Oncolytic herpes simplex virus and immunotherapy. BMC immunology 19: 40.

27. Sato-Dahlman M, LaRocca CJ, Yanagiba C, Yamamoto M (2020) Adenovirus and immunotherapy: advancing cancer treatment by combination. Cancers 12(5): 1295.

28. Conrad DP, Tsang J, Maclean M, Diallo J-S, Le Boeuf F, et al. (2013) Leukemia cell-rhabdovirus vaccine: personalized immunotherapy for acute lymphoblastic leukemia. Clinical Cancer Research 19(14): 3832-3843.

Copyright© Yalcin S.

29. Ling D, Jia X, Wang K, Yan Q, Yuan B, et al. (2024) Cancer cell membrane-coated bacterial ghosts for highly efficient paclitaxel delivery against metastatic lung cancer. Acta Pharmaceutica Sinica B 14(1): 365-377.

30. Paukner S, Kohl G, Lubitz W (2004) Bacterial ghosts as novel advanced drug delivery systems: antiproliferative activity of loaded doxorubicin in human Caco-2 cells. Journal of controlled release 94(1): 63-74.

31. Pérez-Herrero E, Lanier OL, Krishnan N, D'Andrea A, Peppas NA (2024) Drug delivery methods for cancer immunotherapy. Drug Delivery and Translational Research 14(1): 30-61.

32. Gao A, Hu XL, Saeed M, Chen BF, Li YP, et al. (2019) Overview of recent advances in liposomal nanoparticle-based cancer immunotherapy. Acta Pharmacologica Sinica 40(9): 1129-1137.

33. Barati N, Nikpoor AR, Razazan A, Mosaffa F, Badiee A, et al. (2017) Nanoliposomes carrying HER2/neu-derived peptide AE36 with CpG-ODN exhibit therapeutic and prophylactic activities in a mice TUBO model of breast cancer. Immunology letters 190: 108-117.

34. Bayyurt B, Tincer G, Almacioglu K, Alpdundar E, Gursel M, et al. (2017) Encapsulation of two different TLR ligands into liposomes confer protective immunity and prevent tumor development. Journal of controlled release 247: 134-144.

35. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, et al. (2019) Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nature reviews Clinical oncology 16(9): 563-580.

36. Pérez-Herrero E, Fernández-Medarde A (2015) Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. European journal of pharmaceutics and biopharmaceutics 93: 52-79.

37. Mort JS, Buttle DJ (1997) Cathepsin b. The international journal of biochemistry & cell biology 29(5): 715-720.

38. Zhang C, Pan D, Li J, Hu J, Bains A, et al. (2017) Enzyme-responsive peptide dendrimer-gemcitabine conjugate as a controlled-release drug delivery vehicle with enhanced antitumor efficacy. Acta biomater 55: 153-162.

39. Yang Y, Pan D, Luo K, Li L, Gu Z (2013) Biodegradable and amphiphilic block copolymer–doxorubicin conjugate as polymeric nanoscale drug delivery vehicle for breast cancer therapy. Biomaterials 34(33): 8430-8443.

40. Berthier C, Marti HP (2006) Metzincins, including matrix metalloproteinases and meprin, in kidney transplantation. Swiss medical weekly 136(49-50): 789-794.

41. Malemud CJ (2006) Matrix metalloproteinases (MMPs) in health and disease: an overview. Front Biosci 11(1): 1696-1701.

42. Roomi MW, Monterrey JC, Kalinovsky T, Rath M, Niedzwiecki A (2009) Patterns of MMP-2 and MMP-9 expression in human cancer cell lines. Oncology reports 21(5): 1323-1333.

43. Yu Z, Shen X, Yu H, Tu H, Chittasupho C, et al. (2023) Smart polymeric nanoparticles in cancer immunotherapy. Pharmaceutics 15(3): 775.

44. Lu L, Zhang H, Zhou Y, Lin J, Gao W, et al. (2022) Polymer chimera of stapled oncolytic peptide coupled with anti-PD-L1 peptide boosts immunotherapy of colorectal cancer. Theranostics 12(7): 3456-3473.

45. Chen M, Xiang R, Wen Y, Xu G, Wang C, et al. (2015) A whole-cell tumor vaccine modified to express fibroblast activation protein induces antitumor immunity against both tumor cells and cancer-associated fibroblasts. Scientific reports 5(1): 14421.

46. Doskey CM, Buranasudja V, Wagner BA, Wilkes JG, Du J, et al. (2016) Tumor cells have decreased ability to metabolize H2O2: Implications for pharmacological ascorbate in cancer therapy. Redox biology 10: 274-284.

Copyright© Yalcin S.