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A Comprehensive Review on Cancer Immunotherapy in Veterinary Medicine

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

According to a World Health Organization (WHO) estimate, cancer is one of the leading causes of mortality worldwide, expected to claim the lives of almost 10 million people in 2020. It is estimated that 30% of cancer incidences in low- and lower-middle-income countries are caused by diseases like hepatitis and HPV. Many tumours are treatable if detected early and treated properly. The most common malignancies in dogs include transmissible venereal tumours, mammary gland tumours (breast cancer), spleen cancer, skin cancer, lymphatic cancer, gum tumours (epulis cancer), and eye cancer. The frequency of canine cancer cases in India has been rising quickly.

The fast-developing fields of cancer immunology and immunotherapy have revolutionized how cancer is seen and treated. The process of immunotherapy involves using the body's immune system to locate and destroy cancer cells. New immunotherapy medications that selectively target

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cancer cells while sparing healthy cells have been developed as a result of advancements in immunology. The present study reviews the cause, impacts and effects of Cancer along with the feasibility of Immunotherapy as a cure for the cancer.
Checkpoint inhibitors, monoclonal antibodies, vaccinations, and adoptive cell therapy are a few types of immunotherapies. To more effectively target these malignancies, researchers are exploring novel immunotherapy techniques such as oncolytic virotherapy or CAR T-cell treatment. Researchers are working to develop biomarkers to identify which patients would benefit most from immunotherapy.
Different immunotherapies have been used by veterinary medicine researchers to treat canine neoplasms. These include the use of "caninized" mAb against canine PD-L1 in dogs that have metastatic melanoma, IL-12 electrogene treatment for mast cell tumours in dogs, and hTyr-specific T cells for stage II and III melanoma. This review discusses several immunotherapy approaches for cancer and their outcomes.

Keywords: Cancer; CAR T-cell; dog; immunology; immunotherapy.

1. INTRODUCTION

1.1 Key Facts on Cancer

Cancer is a condition in which some cells in the body develop uncontrolled and spread to other regions of the body. These tumours can be malignant or benign (not cancerous). Normal cells may become cancer cells. Before cancer cells form in tissues of the body, the cells go through abnormal changes called hyperplasia and dysplasia. In hyperplasia, there is an increase in the number of cells in an organ or tissue that appear normal under a microscope. In dysplasia, the cells look abnormal under a microscope but are not cancer. Hyperplasia and dysplasia may or may not become cancer.

According WHO report, around 10 million deaths, or roughly one in six deaths, were caused by cancer in 2020, making it the top cause of death globally. In low- and lower-middle-income nations, cancer-causing infections including the human papillomavirus and hepatitis are thought to be the cause of 30% of cancer cases. If caught early and appropriately treated, many tumours are curable.

While 94 cases of cancer in dogs were reported at the Indian Veterinary Research Institute (IVRI), Uttar Pradesh in 2006-07, the number rose to 209 in 2016-17 more than a two-fold growth [1]. worked based on a retrospective study of 88 biopsies of dogs received over ten years (2005 to 2014). The result revealed that the highest number of tumours was epithelial followed by mesenchymal and mixed ones. The incidence of dog tumours remained consistent from 2005 to 2013, except for a decline in 2011 due to variable reporting by owners (Fig. 1). The increase in neoplastic disease necessitates continuous development from veterinary oncology specialists.

In the Department of Veterinary Pathology, College of Veterinary Science and Animal Husbandry (COVS), Anand, Gujarat, India, a total of 150 biopsy samples and 62 FNAC samples were collected from Canines, Bovines and Equines. Types of cancer in findings were squamous cell carcinoma, TVT, mammary gland tumour, and fibroma. Around 19 cases in dogs were diagnosed with cancer, as detailed in Table 1.

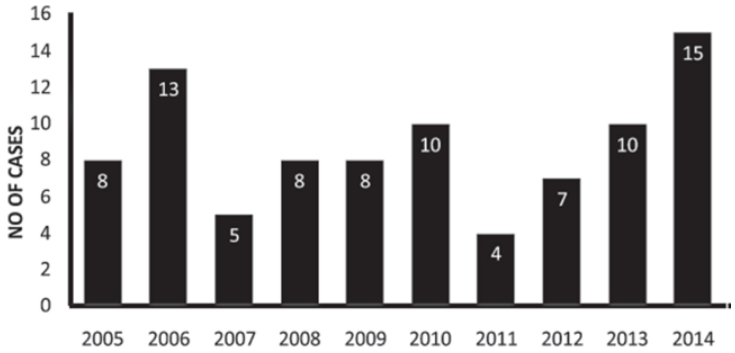

Fig. 1. Year-wise incidence of canine tumours from 2005 to 2014 [1]

Table 1. Annual progress report by COVS, Anand, 2022-23

Sr. No.	Breed	Total	
		Number	Percentage (%)
1	Labrador Retriever	7	36.84
2	Doberman Pinscher	3	15.78
3	German Shepherd	3	15.78
4	Pomeranian	3	15.78
5	Rottweiler	2	10.52
6	Mongrel	1	5.26
	Total	**19**	**100**

According to the American Veterinary Medical Association (AVMA), Neoplasia affects about 1 in 4 dogs at some point in their lives. The incidence of cancer in dogs over the age of 10 is about 50%. According to preliminary estimates of cancer incidence by the National Cancer Institute's Center for Cancer Research (CCR), there are roughly 6 million new cancer diagnoses made each year in dogs and a comparable amount in cats. The incidence of cancer in dogs is nearly the same as that in humans, however, less is known about the incidence of cancer in cats. Some cancers affect cats more frequently than dogs, like lymphoma.

1.2 The Role of Comparative Oncology

Recently, research on cancer in pets is changing our understanding of human cancers and leading to new treatment choices. According to an article by [2], the spontaneous malignancies in pets treated by veterinary oncologists are identical to those in humans. The only two species that naturally produce deadly prostate tumours are dogs and humans. Breast cancer in dogs, like breast cancer in humans, spreads to the bones. and Osteosarcoma, the most common bone cancer in dogs, is the same illness that affects teenagers.

2. CELL CYCLE AND IT's CHECKPOINTS

A checkpoint is one of several locations in the eukaryotic cell cycle (Fig. 2) where a cell might stop progressing to the following stage of the cycle until circumstances are favourable. These checkpoints take place during metaphase, at the G2/M transition, and after G1. The daughter cells that are created must be identical replicas of the parent cell. Errors in chromosomal duplication or distribution result in mutations that might be carried over to every new cell generated from an aberrant cell. There are internal regulatory mechanisms that function at the three main cell cycle checkpoints to stop a damaged cell from continuing to divide. There are checkpoints built into the cycle to ensure everything goes according to plan.

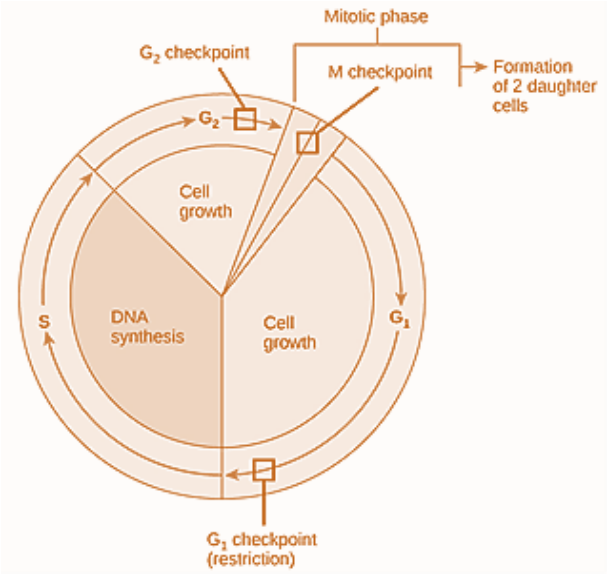

Fig. 2. Cell cycle [3]

In addition to the internally controlled checkpoints, the cell cycle is regulated by two groups of intracellular molecules. These regulatory chemicals can stimulate cell progression to the next phase (positive regulation) or inhibit cell progression (negative regulation). Regulator molecules can either operate independently or impact the activity or synthesis of other regulatory proteins. As a result, the failure of a single regulator may have little impact on the cell cycle, especially if many mechanisms control the same event. The consequence of a poor or non-functioning regulator, on the other hand, can be wide-ranging and even lethal to the cell if many processes are disrupted.

The progression of the cell through multiple checkpoints is regulated by two protein families known as cyclins and cyclin-dependent kinases (Cdks). Throughout the cell cycle, the four cyclin proteins' levels change regularly. The cyclins that were active in the preceding stage of the cell cycle are destroyed after the cell advances to the following stage.

The Cdk/cyclin complex must also be phosphorylated in particular sites to be completely active (Fig. 3). Cdks, like all kinases, are enzymes that phosphorylate other proteins. Phosphorylation activates proteins by altering their structure. Cdk-phosphorylated proteins are important in the cell's progression to the next phase.

Negative regulators halt the cell cycle. Retinoblastoma protein (Rb), p53, and p21 are the most well-studied negative regulatory molecules. Retinoblastoma proteins are a type of tumour suppressor protein found in a variety of cells. The numbers 53 and 21 relate to the functional molecular masses (p) of the proteins in kilo Daltons. All three of these regulatory proteins were found to be damaged or non-functional in malignant cells that had begun to multiply uncontrolled. The main reason for the unregulated progression through the cell cycle in each case was a defective copy of the regulatory protein.

Through the transactivation of its target genes involved in the induction of cell cycle arrest and/or apoptosis, activated p53 promotes cell cycle arrest to allow DNA repair and/or death to limit the proliferation of cells with substantial DNA damage. The genes that code for the positive cell cycle regulators are called proto-oncogenes. Proto-oncogenes are normal genes that, when mutated in certain ways, become oncogenes, genes that cause a cell to become cancerous (Fig. 4).

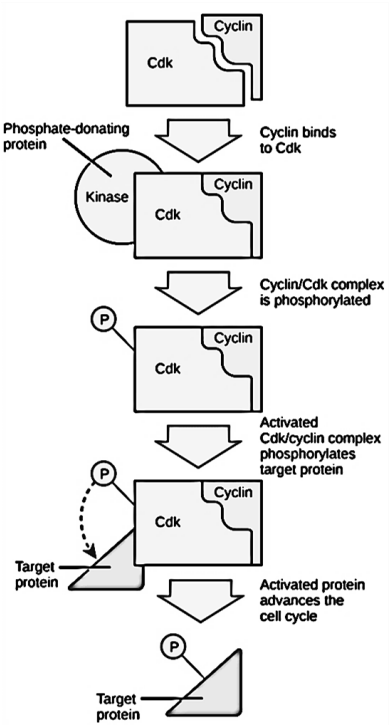

Fig. 3. Cyclin-dependent kinases [3]

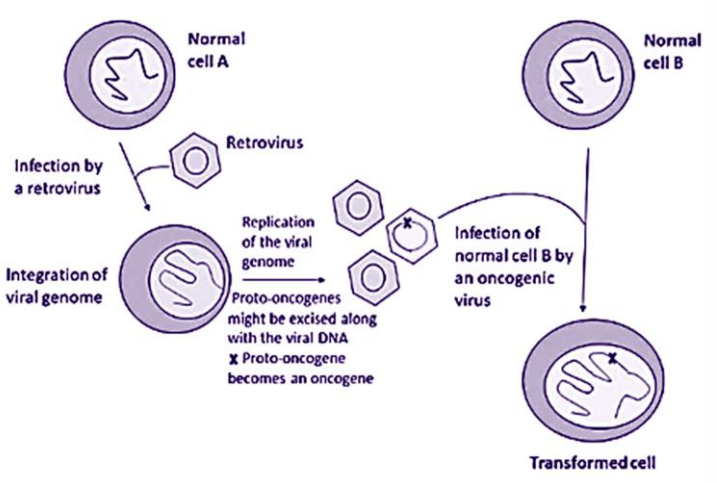

Fig. 4. Proto-oncogenes [4]

3. CANCER AND IMMUNE SYSTEM

A network of biological mechanisms called the immune system guards an organism against illness. It recognises and reacts to a wide range of pathogens, separating them from the organism's healthy tissue, including viruses, parasitic worms, cancer cells, and things like wood splinters. Many animals have two key subsystems of the immune system. The innate immune system responds to a variety of events and stimuli in a predetermined way. The adaptive immune system learns to recognise chemicals it has previously met and responds to each stimulus in a way that is specific to that stimulus. Both rely on molecules and cells to carry out their tasks.

Malignant tumour growth and progression have been demonstrated to be controlled by adaptive immune responses, which are mostly mediated by T cells. Patients and experimental animals can show both innate and adaptive immune responses, and different immune pathways can kill tumour cells in vitro. The difficult task for tumour immunologists is to identify which of these mechanisms may significantly contribute to the defence against tumours and to improve these effector mechanisms in tumour-specific ways.

3.1 CD8+ T and CD4+ T Lymphocytes

“The destruction of tumour cells by CD8+ CTLs is the primary mechanism of adaptive immune defence against tumours. CTLs may operate as a surveillance system, recognising and destroying possibly malignant cells that produce peptides derived from tumour antigens and displayed in conjunction with class I MHC molecules” [6].

“CD4+ cells may contribute to anti-tumor immune responses by supplying cytokines for the development of naïve CD8+ T cells into effector and memory CTLs. Furthermore, helper T cells specific for tumour antigens may produce cytokines such as TNF and IFN-, which might boost tumour cell class I MHC expression and susceptibility to CTL lysis” [6].

3.2 Antibodies, Natural Killer Cells and Macrophages

“Tumour-bearing hosts may produce antibodies against various tumour antigens. Antibodies may kill tumor cells by activating complement or by antibody-dependent cell-mediated cytotoxicity, in which FcR–bearing macrophages or NK cells mediate the killing. However, the ability of antibodies to eliminate tumour cells has been demonstrated largely in vitro, and there is little evidence for effective humoral immune responses against tumours” [7].

Natural Killer (NK) cells destroy a wide variety of tumour cells, particularly those that produce ligands for NK cell activation receptors and have decreased class I MHC expression. Uncertainty surrounds the role of NK cells in tumour immunity in vivo. According to several research, mice without T cells do not develop spontaneous tumours as frequently, and this is ascribed to the existence of normal levels of NK cells, which have an immunological surveillance role.

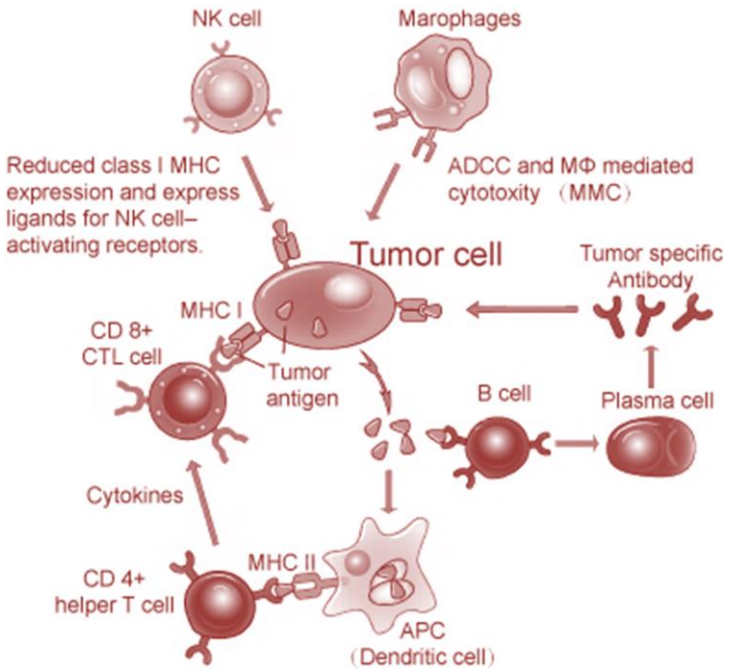

Fig. 5. Immune response against tumour [5]

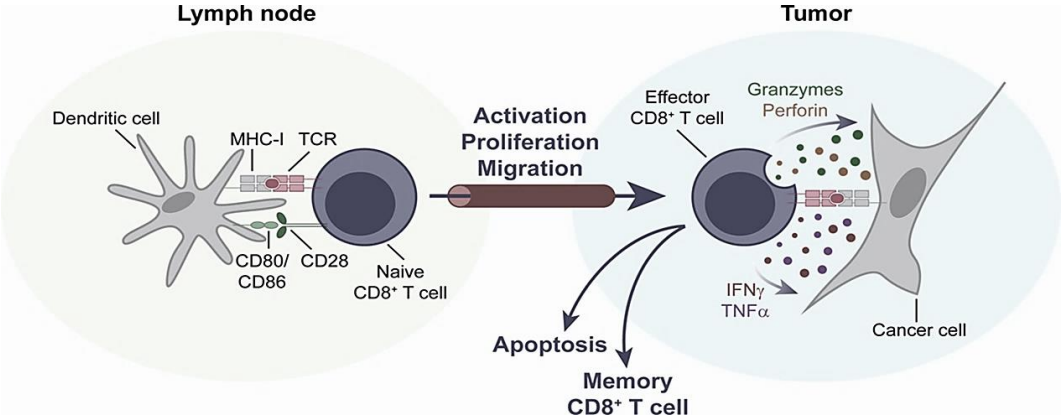

Fig. 6. CD8+ T Lymphocytes [6]

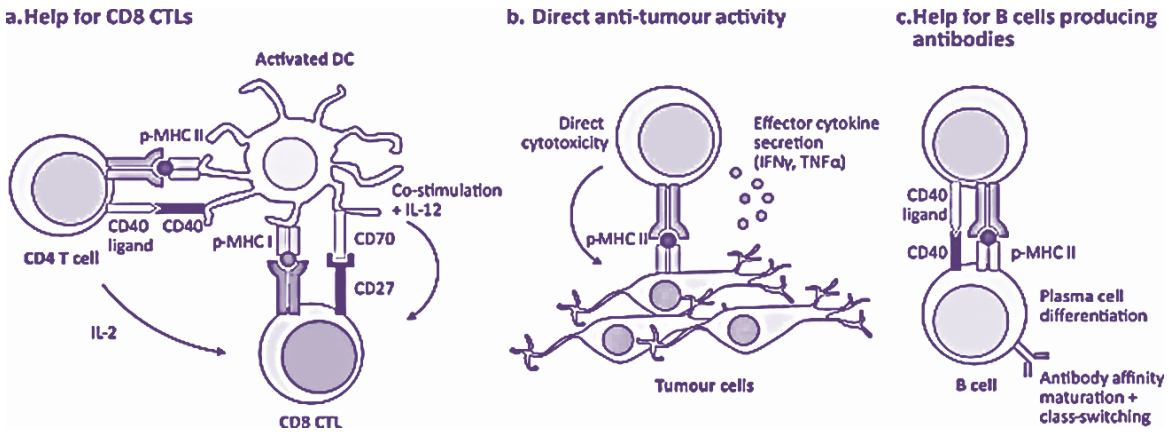

Fig. 7. CD4+ T Lymphocytes [6]

Tumor cells can be inhibited or promoted by macrophages, depending on their activation state. M1 macrophages can kill tumour cells, while M2 macrophages contribute to tumour progression by secreting VEGF, TGF-β, and other factors that promote tumour angiogenesis. The activation state of macrophages by tumours remains unknown.

3.3 Evasion of Immune Responses by Tumours

3.3.1 "Escaping Immune recognition by loss of antigen expression

Tumour cells undergo tumour immunoediting, a process where immune responses pressure them to survive and outgrow variant cells with reduced immunogenicity. This is due to mutations or deletions in genes encoding tumour antigens, which can give antigen-negative tumour cells an advantage over the host immune system" [8]. Tumour cells also show decreased synthesis of class I MHC molecules, β2-microglobulin, and antigen processing machinery, which may allow them to evade T cell-mediated immune responses (Fig. 8).

3.3.2 Active Inhibition of Immune responses

T cells play a crucial role in suppressing immune responses to tumours, with CTLA-4 and PD-1 being key inhibitory pathways. Tumour-associated macrophages may also promote tumour growth and invasiveness by altering the tissue microenvironment and suppressing T-cell responses. Myeloid-derived suppressor cells also play a role.

3.4 Types of Cancer Treatment

Many procedures and drugs are available to treat cancer, with many more being studied. Some are "local" treatments like surgery and radiation therapy, which are used to treat a specific tumour or area of the body. Drug treatments (such as chemotherapy, immunotherapy, or targeted therapy) are often called "systemic" treatments because they can affect the entire body.

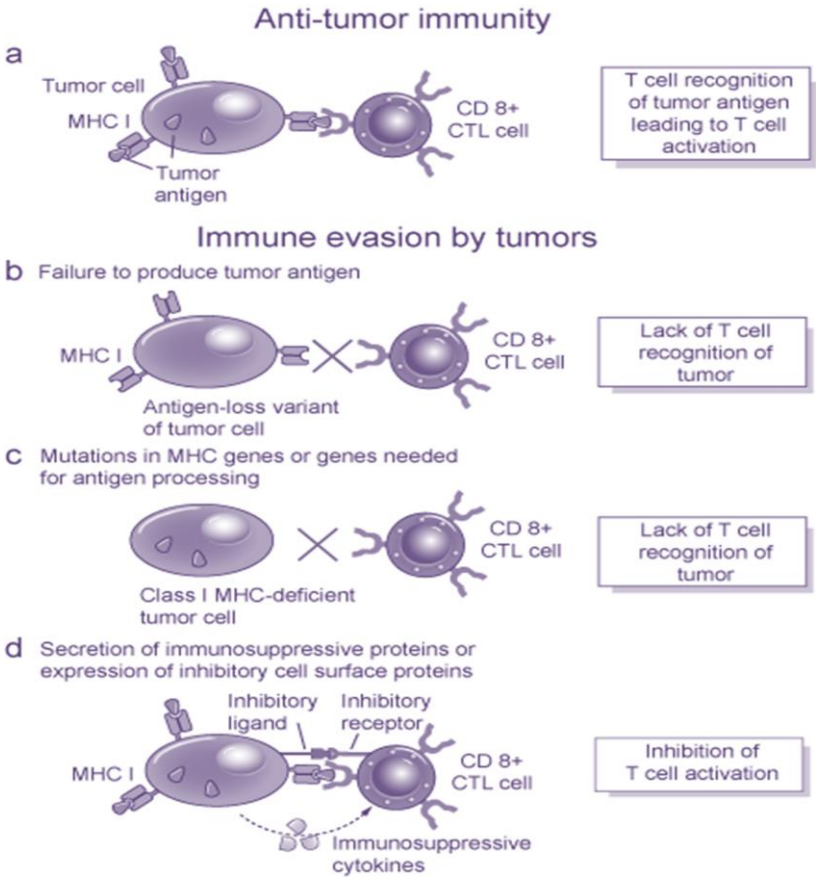

Fig. 8. Evasion of Immune Responses by Tumors [5]

4. IMMUNOTHERAPY

Immunotherapy is a form of cancer treatment that makes use of the patient's immune system. Immunotherapy can alter or enhance the immune system's functioning to enable it to locate and destroy cancer cells

4.1 Immune Checkpoint Inhibitors

“The immune system's capacity to distinguish between bodily normal cells and those it perceives as "foreign" (such as pathogens and cancer cells) is a crucial component of the immune system. As a result, the immune system can target foreign cells while sparing healthy ones. The immune system uses "checkpoint" proteins on immune cells as one method of accomplishing this. These checkpoint proteins can be the target of monoclonal antibodies, which are types of medications”[9].

Immune checkpoint inhibitors (or simply checkpoint inhibitors) are the name given to these medications. Checkpoint inhibitors do not directly kill cancer cells. They function by facilitating the immune system's detection and destruction of cancer cells throughout the body. To initiate an immune response, the checkpoints function as switches that must be switched on (or off). However, cancer cells occasionally manage to circumvent these checkpoints to protect themselves from immune system attacks. All of these medications are infused intravenously (IV).

James P. Allison and.Tasuku Honjowon jointly won the Nobel Prize in Physiology or Medicine in 2018 for their discovery of cancer therapy by inhibition of negative immune regulation [10]. James P. Allison investigated a well-known protein that restrains the immune system. He saw that if we could let go of the brake, our immune system would be free to go after malignancies. He then expanded on this idea to create a whole new method of patient care.

Simultaneously, Tasuku Honjo identified a protein on immune cells and, upon a meticulous investigation of its function, ultimately disclosed that it functions as a brake as well, although in another manner. His findings led to the development of remarkably successful cancer treatments. Allison and Honjo demonstrated the many approaches that may be employed in cancer treatment to suppress the immune system's brakes.

4.2 PD-1, PD-L1, CTLA-4 and LAG-3 inhibitors

“A checkpoint protein on immune cells known as T cells is termed PD-1. It typically functions as a kind of "off switch" to prevent the T cells from attacking other bodily cells. When it binds to the protein PD-L1 on some normal (and malignant) cells, it accomplishes this. In essence, the T cell is instructed to leave the other cell alone when PD-1 attaches to PD-L1”[11].

Large concentrations of PD-L1 in some cancer cells enable them to evade an immunological response. Blocking this binding and enhancing the immune response against cancer cells is possible with monoclonal antibodies that either target PD-1 or PD-L1 [12] (Poole [13]; [14,15–18].

Examples of drugs that target PD-1 include:

- Pembrolizumab (Keytruda)
- Nivolumab (Opdivo)
- Cemiplimab (Libtayo)

“Another checkpoint protein known as CTLA-4 is found on some T cells and functions as a sort of "off switch" to restrain the immune system. Monoclonal antibodies, such as ipilimumab (Yervoy) and tremelimumab (Imjuno), bind to CTLA-4 and prevent it from functioning. This may strengthen the immune system's defences against cancerous cells. PD-1 or PD-L1 inhibitors are frequently used in combination with these medications. Several different cancers can be treated with these mixtures”. [18,20–24].

On some types of immune cells, LAG-3 (lymphocyte activating gene-3) is a checkpoint protein that typically functions as an "off switch" to restrain the immune system. A monoclonal antibody called relatlimab binds to LAG-3 and inhibits its function. This may strengthen the immune system's defences against cancerous cells.

This medication is administered in conjunction with the PD-1 inhibitor nivolumab (Opdualag). In addition to being researched for use in treating various other cancer types, it can be used to treat skin cancer called melanoma.

4.3 Monoclonal Antibodies

Monoclonal antibodies are man-made proteins that function in the immune system similarly to

human antibodies. [25–29] To treat CD20-positive B cell (Blontress®) or CD52-positive T cell lymphoma, the US Department of Agriculture has approved the use of monoclonal antibodies. In the USA and Canada and are marketed under the brand name (Tactress®) [30].

They can be manufactured in four distinct ways and are named based on what they are composed of:

- Murine: These therapies are created from mouse proteins, and their names end in –omab. Chimeric proteins are a cross between mouse and human proteins, and the names of the medicines finish in –ximab.
- Humanized: These medicines are constructed from small bits of mouse proteins linked to human proteins, and their names end in –zumab.
- Human: These are human proteins, and the medicines' names finish in –umab.

4.3.1 Types of Monoclonal Antibodies

Conjugated monoclonal antibodies: Conjugated mAbs are made up of either a radioactive particle or a chemotherapeutic medication. Tagged, labelled, or loaded antibodies are other names for conjugated monoclonal antibodies (mAbs).

The antibody directly delivers radioactivity to cancer cells. It is composed of a mAb medication (rituximab) as well as a radioactive material (Yttrium-90). Radiolabeled mAbs include ibritumomab tiuxetan (Zevalin). This is an antibody against the CD20 antigen, which is found on B cells, which are lymphocytes.

Bispecific monoclonal antibodies: These medications are composed of portions of two separate mAbs, allowing them to bind to two different proteins at the same time. Blinatumomab (Blincyto), for example, is used to treat some kinds of leukaemia.

One component of blinatumomab binds to the CD19 protein present in some leukaemia and lymphoma cells. Another component binds to CD3, a protein found in immune cells known as T cells. This medicine, by attaching to both of these proteins, brings cancer cells and immune cells together, causing the immune system to kill the cancer cells.

4.4 CAR T-cell Therapy

“Chimeric antigen receptor (CAR) T-cell therapy is a method of directing immune cells known as T cells (a kind of white blood cell) to fight cancer by modifying them in the lab so that they can detect and destroy cancer cells”[31]. Because it includes changing the genes inside T cells to help them attack cancer, CAR T-cell therapy is sometimes referred to as a sort of cell-based gene therapy [32–39].

This form of treatment can be quite beneficial in the treatment of certain types of cancer, even when other treatments are no longer effective. Because various tumours have distinct antigens, each CAR is tailored to that cancer's antigen.

“For example, cancer cells in certain types of leukaemia or lymphoma have an antigen called CD19. CAR T-cell treatments for these tumours are designed to connect to the CD19 antigen and will not work on tumours that lack the CD19 antigen” [39–41].

4.5 Cytokines

“Cytokines are small proteins that regulate the growth and function of other immune systems and blood cells. They alert the immune system to start working when they are released. They also contribute to anti-cancer activities by transmitting signals that cause abnormal cells to perish and normal ones to live longer” [43].

A chemokine is a specific sort of cytokine. A chemokine can direct immune cells toward a certain target. Chemokines are classified into several types, including interleukins, interferons, tumour necrosis factors, and growth factors. Cytokines influence the formation of all blood cells and other cells that aid in the immunological and inflammatory responses of the body.

Interleukins: Interleukins are cytokines that serve as chemical messengers between white blood cells. Interleukin-2 (IL-2) promotes the growth and division of immune system cells. A synthetic form of IL-2 has been approved for the treatment of advanced kidney cancer and metastatic melanoma. For these tumours, IL-2 can be given alone or in combination with chemotherapy or other cytokines such as interferon-alfa.

Interferons: Interferons are substances that aid the body's defences against virus infections and cancer. Interferon (IFN) types are called after the first three letters of the Greek alphabet: IFN-alfa, IFN-gamma & IFN-beta. Cancer is only treated with IFN-alfa.

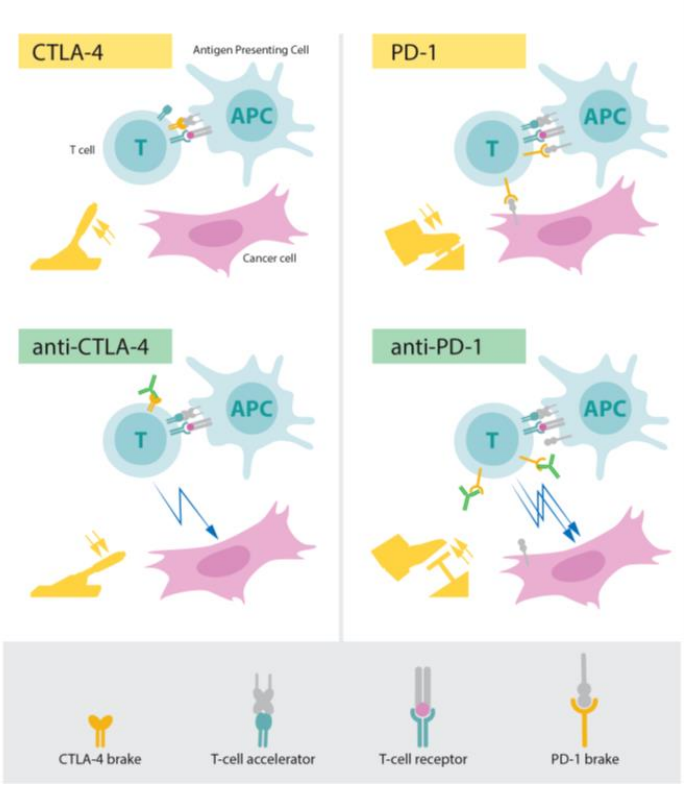

Fig. 9. Upper left: Activation of T cells requires that the T-cell receptor binds to structures on other immune cells recognised as" non-self". A protein functioning as a T-cell accelerator is also required for cell activation. CTLA-4 functions as a brake on T cells that inhibits the function of the accelerator

Lower left: *Antibodies (green) against CTLA-4 block the function of the brake leading to activation of T cells and attack on cancer cells.*

Upper right: *PD-1 is another T-cell brake that inhibits T-cell activation*

Lower right: *Antibodies against PD-1 inhibit the function of the brake leading to activation of T cells and highly efficient attack on cancer cells [19]*

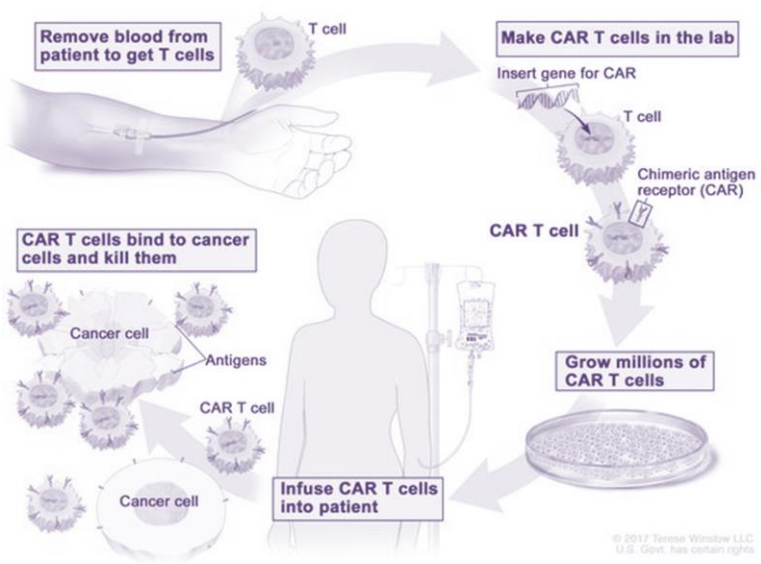

Fig.10. CAR T-cell Therapy [42]

4.6 Cancer Vaccines

Vaccines are substances put into the body to start an immune response against certain diseases. Usually, vaccines are thought to be given to healthy people to help prevent infections. But few vaccines can help prevent or treat cancer.

4.6.1 Dendritic cell vaccines

A novel treatment approach for cancer patients is the dendritic cell-based cancer vaccination. To trigger an antigen-specific T-cell response, dendritic cells (DCs) transmit antigens to the body.

Immunotherapy based on DCs is a safe and effective way to support immune responses against tumours and extend cancer patients' lives. Inducing cellular immunity is the primary objective of therapeutic vaccinations. Priming naïve T cells and causing the shift from chronically activated non-protective CD8+ T cells to healthy CD8+ T cells is important because they can generate cytotoxic T lymphocytes (CTLs), which can identify and destroy cancer cells by identifying certain antigens. Long-lived memory CD8+ T cells are also produced by this process, and they will function to stop relapses.

The most important stage in vaccination is successfully presenting cancer antigens to T cells. Since DCs are highly potent cells to deliver antigens, they provide a viable alternative for enhancing therapeutic vaccinations [44].

4.6.2 Oncolytic Virus

Viral infection and subsequent destruction of cells is known as "oncolytic virus therapy." Viruses are small, invading particles that enter or infect our cells. They then exploit the genetic machinery of the cell to replicate, spreading to neighbouring, uninfected cells.

Several viruses, including the human papillomavirus (HPV), which causes the cervical head and neck cancer, and the hepatitis B virus (HBV), which causes liver cancer, have been linked to the development of certain malignancies [46].

For several reasons, oncolytic viruses are a potentially effective cancer treatment method:

1. Immunodeficiency of cancer cells frequently results in compromised antiviral defences.
2. These naturally occurring viruses can be modified to have beneficial traits, such as a reduced capacity to infect healthy cells, the capacity to target tumours with therapeutic payloads, and the capacity to release immune-stimulating compounds once they have infected tumour cells.
3. These oncolytic viruses can infect cancer cells and induce them to "burst," releasing cancer antigens and destroying cancer cells. The immune systems that these antigens trigger may then search for and destroy any residual tumour cells in the area and maybe elsewhere in the body.

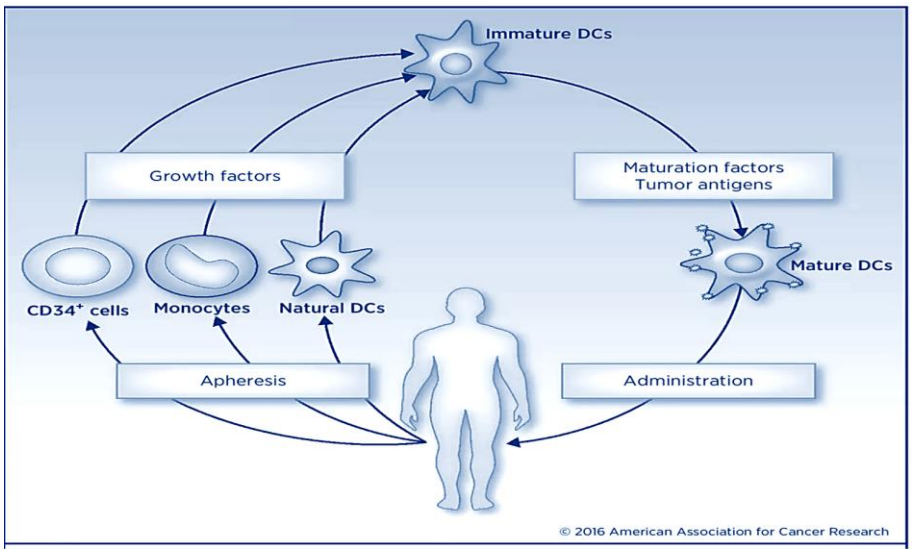

Fig. 11. Dendritic cell vaccines [45]

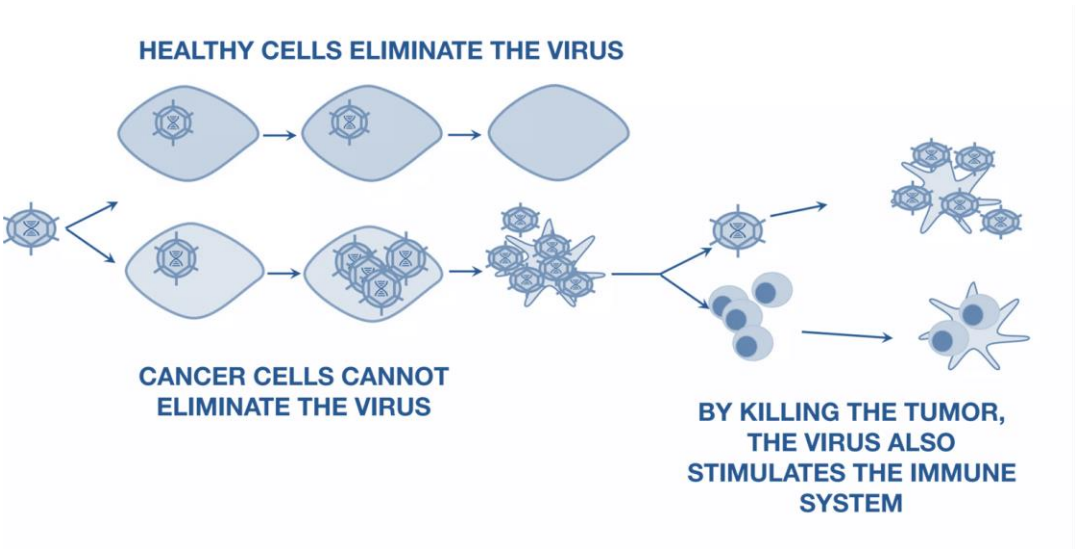

Fig. 12. Oncolytic viruses [3]

4.7 BTLA/HVEM Axis Dysregulation

"In recent years, interest in B-and T-Lymphocyte Attenuator (BTLA), an inhibitory immunological checkpoint expressed on B, T, and NK cells, has grown. HVEM functions as BTLA's binding partner and is distinguished by a more widespread expression because it is also found in neuronal, hematopoietic, epithelial, and endothelial cells. HVEM functions as a bidirectional switch that may both initiate its signal transduction and act as a ligand for various co-stimulatory and co-inhibitory substances. The preservation of the immune response's equilibrium depends on this implica network " [47]. "Chronic lymphocytic leukaemia (CLL) patients develop immunosuppression, affecting their antitumor responses. The BTLA/HVEM axis plays a role in promoting defects in T cell-mediated responses against leukemic cells. Increased BTLA expression on CD4+ and CD8+ T lymphocytes correlates with diminished treatment time. BTLA activation leads to decreased IL-2 and IFN-γ production, while BTLA/HVEM binding disruption enhances IFN-γ+CD8+ T lymphocytes. Treatment with anti-BLTA blocking monoclonal antibodies and ibrutinib can induce leukemic cell depletion. This dysregulation has a prognostic role and limits T-cell-driven antitumor responses" [48].

4.7.1 TIM-3 Immunoregulatory role and its interactions.

T cell immunoglobulin and mucin domain-containing protein 3 (TIM3) is a member of the TIM family that was first shown to be expressed on CD4+ and CD8+ T cells that produced interferon-γ. Because there was no discernible inhibitory signalling motif, it was also hypothesised that TIM3 might operate as a co-stimulatory receptor. Initially, findings suggested that TIM3 operated as a "co-inhibitory" or "checkpoint" receptor. TIM3 is a component of a module that also includes other co-inhibitory receptors, or "exhausted" T cells, which are co-expressed and co-regulated in cancer and persistent viral infections [49].

5. CANCER IMMUNOTHERAPY IN VETERINARY MEDICINE

Veterinarian immunotherapy is not as advanced as it might be, and there are several reasons why, the most important being financial. Biotechnology companies are aware that the veterinary industry has limited access to costly immunotherapies; as a result, they are hesitant to contribute enough funding for clinical studies, which can be prohibitively expensive due to the immunotherapy's high costs. Immunotherapy is a significant challenge to the area of veterinary medicine due to the lack of comprehensive evaluation of the canine immune system and the unknown cellular biology of tumours in dogs. Even if the previous several years have seen an increase in clinical studies, financial support, and attitudinal changes, we are still a long way off.

Table 2. Advancements in Cancer Immunotherapy

Advancements	Reference
hTyr-specific T cell (plasmid DNA encoding human tyrosinase) permitted for the treatment of stage II and III melanoma	[50]
In canine transmissible venereal tumour (TVT), IL-12 electrogene treatment resulted in a considerable delay in tumour development and subsequently, total tumour remission	[51]
Interlekin-12 (IL-12) stimulates NK cells and causes IFN-gamma to be released. Numerous clinical studies testing the efficacy of IL-12 gene therapy in various veterinary animals have been conducted	[52,53]
In dogs with mast cell tumours, IL-12 electrogene treatment led to a 50% decrease in tumour volume	[54]
PDL1 expression has been found on a variety of canine tumours in studies employing canine tumour biopsy samples and a human mAb with cross-reactivity with canine PD-L1	[17]
In dogs with metastatic melanoma, a recent clinical trial employing a “canonised” mAb against canine PD-L1 showed a limited response	[14]
The United States Department of Agriculture recently granted full (CD20) or conditional (CD52) licenses for clinical use in the treatment of canine B-cell and T-cell lymphomas, respectively	[30]

6. CONCLUSIONS

Various studies indicate that year-wise incidence of cancer is increasing in dogs and cats. In India, the number of canine cancer cases has been rapidly increasing due to a lack of systematic research and an animal cancer registry.

The cell cycle checkpoints take place during metaphase, at the G2/M transition, and after G1, to ensure whether the cell cycle goes normal or not. T cells play a central role in immune responses to cancer. Immunotherapy is a form of cancer treatment that uses the patient's immune system to identify and combat cancer cells. Types of Immunotherapies are checkpoint inhibitors, monoclonal antibodies, CAR T-cell therapy, Cancer vaccines and Oncolytic viruses.

In Veterinary medicine, the use of Immunotherapeutic agents is increasing day by day i.e. IL-12 gene therapy, "caninized" mAb against canine PD-L1, and hTyr-specific T cell therapy in canine cancer. Tumour immunotherapy is most likely to be acknowledged as the fourth weapon in the battle against cancer in veterinary medicine soon, joining surgery, chemotherapy, and radiation treatment, given the growing interest and modern research in the field.

7. FUTURE PROSPECTS

There are still many cancer types that do not react to existing immunotherapy treatments, but researchers are striving to understand how cancer cells interact with the immune system and create novel treatments to stop cancer from spreading. We can explore ways to combine immunotherapy with other treatments, such as chemotherapy or radiation therapy, to improve outcomes. Nowadays immunotherapy is costly, but it should be cost effective in future. The future scope of cancer in Veterinary medicine is, to establish separate branches of veterinary oncology and immunotherapy for effective treatment.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Lather D, Gupta R, Sharma D. Retrospective studies on tumour conditions in Dogs over ten years (2005-2014). The Haryana Veterinarian. 2017 Jun 30; 56:47–9.
2. Bergman PJ, McKnight J, Novosad A, Charney S, Farrelly J, Craft D, et al. Long-term survival of dogs with advanced malignant melanoma after DNA vaccination with xenogeneic human tyrosinase: A phase I trial. Clin Cancer Res. 2003 Apr;9(4):1284–90.
3. Lumen Learning [Internet]. Cell Cycle Checkpoints.

Available:https://courses.lumenlearning.com/suny-wmopen-biology1/chapter/cell-cycle-checkpoints/
4. Oncogene. In: Britannica
5. Murphy KM. Janeway's immunobiolog. Garland Science; 2011.
6. Drijvers JM, Sharpe AH, Haigis MC. The effects of age and systemic metabolism on anti-tumor T cell responses. Kaeberlein M, Tyler JK, editors. Elife. 2020;9:e62420.
7. Cooper MA, Fehniger TA, Caligiuri MA. The biology of human natural killer-cell subsets. Trends Immunol. 2001 Nov;22(11):633–40.
8. Kim SK, Cho SW. The evasion mechanisms of cancer immunity and drug intervention in the tumor microenvironment. Front Pharmacol. 2022 May 24;13.
9. Shiravand Y, Khodadadi F, Kashani SMA, Hosseini-Fard SR, Hosseini S, Sadeghirad H, et al. Immune Checkpoint Inhibitors in Cancer Therapy. Current Oncology. 2022 Apr 24;29(5):3044–60.
10. The Nobel Foundation [Internet]. 2018. The Nobel Prize in Physiology or Medicine 2018. Available:https://www.nobelprize.org/prizes/medicine/2018/summary/
11. Sun Q, Hong Z, Zhang C, Wang L, Han Z, Ma D. Immune checkpoint therapy for solid tumours: Clinical dilemmas and future trends. Signal Transduct Target Ther. 2023 Aug 28;8(1):320.
12. Coy J, Caldwell A, Chow L, Guth A, Dow S. <scp>PD</scp> -1 expression by canine T cells and functional effects of <scp>PD</scp> -1 blockade. Vet Comp Oncol. 2017 Dec 25;15(4):1487–502.
13. Poole RM. Pembrolizumab: First Global Approval. Drugs. 2014 Oct 21;74(16):1973–81.
14. Maekawa N, Konnai S, Ikebuchi R, Okagawa T, Adachi M, Takagi S, et al. Expression of PD-L1 on Canine Tumor Cells and Enhancement of IFN-γ Production from Tumor-Infiltrating Cells by PD-L1 Blockade. Shiku H, editor. PLoS One. 2014 Jun 10;9(6):e98415.
15. Riley JL. Combination Checkpoint Blockade — Taking Melanoma Immunotherapy to the Next Level. New England Journal of Medicine. 2013 Jul 11;369(2):187–9.
16. Robert C, Soria JC, Eggermont AMM. Drug of the year: Programmed Death-1 receptor/Programmed Death-1 Ligand-1 receptor monoclonal antibodies. Eur J Cancer. 2013 Sep;49(14):2968–71.
17. Scharf VF, Farese JP, Coomer AR, Milner RJ, Taylor DP, Salute ME, et al. Effect of bevacizumab on angiogenesis and growth of canine osteosarcoma cells xenografted in athymic mice. Am J Vet Res. 2013 May;74(5):771–8.
18. Wang Q, Wu X. Primary and acquired resistance to PD-1/PD-L1 blockade in cancer treatment. Int Immunopharmacol. 2017 May;46:210–9.
19. The Nobel Foundation [Internet]. 2018. The Nobel Prize in Physiology or Medicine; 2018. Available:https://www.nobelprize.org/prizes/medicine/2018/summary/
20. Allison JP, Chambers C, Hurwitz A, Sullivan T, Boitel B, Fournier S, et al. A Role for CTLA-4-Mediated Inhibitory Signals in Peripheral T Cell Tolerance? In. 2007;92–102.
21. Lebbé C, Weber JS, Maio M, Neyns B, Harmankaya K, Hamid O, et al. Survival follow-up and ipilimumab retreatment of patients with advanced melanoma who received ipilimumab in prior phase II studies. Annals of Oncology. 2014 Nov;25(11):2277–84.
22. KAWANO M, ITONAGA I, IWASAKI T, TSUMURA H. Enhancement of antitumor immunity by combining anti-cytotoxic T lymphocyte antigen-4 antibodies and cryotreated tumor lysate-pulsed dendritic cells in murine osteosarcoma. Oncol Rep. 2013 Mar;29(3):1001–6.
23. Shin JH, Park HB, Oh YM, Lim DP, Lee JE, Seo HH, et al. Positive conversion of negative signalling of CTLA4 potentiates antitumor efficacy of adoptive T-cell therapy in murine tumour models. Blood. 2012 Jun 14;119(24):5678–87.
24. Son CH, Bae JH, Shin DY, Lee HR, Choi YJ, Jo WS, et al. CTLA-4 Blockade Enhances Antitumor Immunity of Intratumoral Injection of Immature Dendritic Cells into Irradiated Tumor in a Mouse Colon Cancer Model. Journal of Immunotherapy. 2014 Jan;37(1):1–7.
25. Maleki LA, Baradaran B, Majidi J, Mohammadian M, Shahneh FZ. Future prospects of monoclonal antibodies as magic bullets in Immunotherapy. Hum Antibodies. 2013 Nov 18;22(1–2):9–13.
26. Miller MJ, Foy KC, Kaumaya PTP. Cancer immunotherapy: Present status, future perspective, and a new paradigm of

peptide immunotherapeutics. Discov Med. 2013 Mar;15(82):166–76.
27. Sliwkowski MX, Mellman I. Antibody Therapeutics in Cancer. Science (1979). 2013 Sep 13;341(6151):1192–8.
28. Zigler M, Shir A, Levitzki A. Targeted cancer immunotherapy. Curr Opin Pharmacol. 2013 Aug;13(4):504–10.
29. Zhou L, Xu N, Sun Y, Liu X (Margaret). Targeted biopharmaceuticals for cancer treatment. Cancer Lett. 2014 Oct;352(2):145–51.
30. Regan D, Guth A, Coy J, Dow S. Cancer immunotherapy in veterinary medicine: Current options and new developments. The Veterinary Journal. 2016 Jan;207:20–8.
31. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. Blood Cancer J. 2021 Apr 6;11(4):69.
32. Aldrich JF, Lowe DB, Shearer MH, Winn RE, Jumper CA, Kennedy RC. Vaccines and Immunotherapeutics for the Treatment of Malignant Disease. Clin Dev Immunol. 2010; 2010:1–12.
33. Casucci M, Bondanza A, Falcone L, Provasi E, Magnani Z, Bonini C. Genetic engineering of T cells for the immunotherapy of haematological malignancies. Tissue Antigens. 2012 Jan 12;79(1):4–14.
34. Cieri N, Mastaglio S, Oliveira G, Casucci M, Bondanza A, Bonini C. Adoptive immunotherapy with genetically modified lymphocytes in allogeneic stem cell transplantation. Immunol Rev. 2014 Jan 13;257(1):165–80.
35. Cheadle EJ, Gornall H, Baldan V, Hanson V, Hawkins RE, Gilham DE. <scp>CAR</scp> T cells: driving the road from the laboratory to the clinic. Immunol Rev. 2014 Jan 13;257(1):91–106.
36. O'Connor CM, Wilson-Robles H. Developing T Cell Cancer Immunotherapy in the Dog with Lymphoma. ILAR J. 2014 Jan 1;55(1):169–81.
37. McCormack E, Adams KJ, Hassan NJ, Kotian A, Lissin NM, Sami M, et al. Bi-specific TCR-anti CD3 redirected T-cell targeting of NY-ESO-1- and LAGE-1-positive tumours. Cancer Immunology, Immunotherapy. 2013 Apr 22;62(4):773–85.
38. Raval RR, Sharabi AB, Walker AJ, Drake CG, Sharma P. Tumor immunology and cancer immunotherapy: summary of the 2013 SITC primer. J Immunother Cancer. 2014;2(1):14.
39. Riches JC, Gribben JG. Advances in chimeric antigen receptor immunotherapy for chronic lymphocytic leukaemia. Discov Med. 2013 Dec;16(90):295–302.
40. Cruz CRY, Micklethwaite KP, Savoldo B, Ramos CA, Lam S, Ku S, et al. Infusion of donor-derived CD19-redirected virus-specific T cells for B-cell malignancies relapsed after allogeneic stem cell transplant: a phase 1 study. Blood. 2013 Oct 24;122(17):2965–73.
41. Dotti G, Gottschalk S, Savoldo B, Brenner MK. Design and development of therapies using chimeric antigen receptor-expressing T cells. Immunol Rev. 2014 Jan 13;257(1):107–26.
42. National Cancer Institute (NCI) [Internet]. CAR T cells: Engineering patients' immune cells to treat their cancers. Available: https://www.cancer.gov/about-cancer/treatment/research/car-t-cells
43. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012 Apr 22;12(4):252–64.
44. Calmeiro J, Carrascal MA, Tavares AR, Ferreira DA, Gomes C, Falcão A, et al. Dendritic Cell Vaccines for Cancer Immunotherapy: The Role of Human Conventional Type 1 Dendritic Cells. Pharmaceutics. 2020 Feb 15;12(2):158.
45. American Society of Clinical Oncology (ASCO) [Internet]. Understanding immunotherapy. Available:https://www.cancer.net/navigating-cancer-care/how-cancer-treated/immunotherapy-and-vaccines/understanding-immunotherapy
46. Lin D, Shen Y, Liang T. Oncolytic virotherapy: Basic principles, recent advances and future directions. Signal Transduct Target Ther. 2023 Apr 11;8(1):156.
47. Sordo-Bahamonde C, Lorenzo-Herrero S, Gonzalez-Rodriguez AP R, Payer Á, González-García E, López-Soto A, et al. BTLA/HVEM Axis Induces NK Cell Immunosuppression and Poor Outcome in Chronic Lymphocytic Leukemia. Cancers (Basel). 2021 Apr 7;13(8):1766.
48. Sordo-Bahamonde C, Lorenzo-Herrero S, Martínez-Pérez A, Gonzalez-Rodriguez AP, Payer ÁR, González-García E, et al. BTLA dysregulation correlates with poor outcome and diminished T cell-mediated antitumor responses in chronic lymphocytic

leukemia. Cancer Immunol Immunother. 2023 Jul;72(7):2529–39.
49. Wolf Y, Anderson AC, Kuchroo VK. TIM3 comes of age as an inhibitory receptor. Nat Rev Immunol. 2020 Mar 1;20(3):173–85.
50. Goubier A, Fuhrmann L, Forest L, Cachet N, Evrad-Blanchard M, Juillard V, et al. Superiority of needle-free transdermal plasmid delivery for the induction of antigen-specific IFNγ T cell responses in the dog. Vaccine. 2008 Apr;26(18):2186–90.
51. Chuang T, Lee S, Liao K, Hsiao Y, Lo C, Chiang B, et al. Electroporation-mediated IL-12 gene therapy in a transplantable canine cancer model. Int J Cancer. 2009 Aug 8;125(3):698–707.
52. Reed SD, Fulmer A, Buckholz J, Zhang B, Cutrera J, Shiomitsu K, et al. Bleomycin/interleukin-12 electrochemogene therapy for treating naturally occurring spontaneous neoplasms in dogs. Cancer Gene Ther. 2010 Jul 12;17(7):457–64.
53. Siddiqui F, Li CY, LaRue SM, Poulson JM, Avery PR, Pruitt AF, et al. A phase I trial of hyperthermia-induced interleukin-12 gene therapy in spontaneously arising feline soft tissue sarcomas. Mol Cancer Ther. 2007 Jan 1;6(1):380–9.
54. Pavlin D, Cemazar M, Cör A, Sersa G, Pogacnik A, Tozon N. Electrogene therapy with interleukin-12 in canine mast cell tumors. Radiol Oncol. 2011 Jan 1;45(1).

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