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DEVELOPMENT OF ANTITUMOR DENDRITIC CELL VACCINES WITH ALDH1A2 INHIBITORS TO OVERCOME IMMUNE SUPPRESSION

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ABSTRACT

Vaccines based on dendritic cells have traditionally been considered an exciting field of research in personalized treatment for cancer patients; however, their efficiency has usually been hindered by the same conditions under which the vaccine must be effective. In particular, the tumor microenvironment can be thought of as a hostile area which can disable immune system cells. However, recent discoveries have revealed a definite mechanism that can explain this effect: specifically, the ALDH1A2-retinoic acid (RA) axis. One can describe this process as brakes that prevent dendritic cells from fully maturing. For example, when such cells are isolated from the body and cultured in vitro using common growth factors, a high level of ALDH1A2 may be produced. It is responsible for the synthesis of retinoic acid, which causes the body to produce regulatory T cells, or the peacekeeper cells, rather than the necessary soldier cells required for fighting the tumor. However, to overcome this problem, scientists have started developing the next generation of vaccines along with the use of strong ALDH1A2 inhibitors. With the inhibition of this enzyme, we could essentially release the brake of the immune system. The research shows that with the absence of this signal through the production of retinoic acid, the dendritic cells will once again regain their function, resulting in an extremely aggressive attack on the tumor by CD8+ cytotoxic T cells. By inhibiting the immune suppression caused by the tumor, the inhibitors will enable the vaccine to work more effectively.

Keywords: *Dendritic cells1, Cancer immunotherapy2, DC vaccines3, ALDH1A2 inhibitors, T cells*

Introduction

The way we treat cancer changing very fast, moving toward therapies that rely on the interactions between the tumor and immune system. However, popular treatments like ICBs and ACTs aren't a silver bullet; they can cause harsh side effects and often fail when the tumor creates a shield that suppresses immune activity. This is where cancer vaccines come in. Unlike other therapies that require a pre-existing immune response to work or can only target specific surface markers, DC vaccines can train the immune system from scratch to recognize a much wider variety of threats. This makes them an ideal candidate for multi-stage treatment plans (Hiam-Galvez K.J., Allen B.M., and Spitzer 2024; Hegde P.S., Chen D.S. 2022).

At the heart of this process are Dendritic Cells, the most effective information gatherers in our bodies. They are responsible for alerting the immune system to the presence of cancer. Through a

complex process, these cells capture pieces of the tumor and present them to T cells in the lymph nodes, effectively teaching the body's soldier cells exactly what to attack. While this process is natural, making it efficient enough to completely wipe out a tumor is a major challenge. By better understanding the different types of dendritic cells and improving how they talk to T cells, scientists hope to create vaccines that not only destroy current tumors but also build a long-lasting immune memory to keep the cancer from ever coming back. DC vaccine strategies have been actively investigated as shown in fig 1 (Hiam-Galvez K.J., Allen B.M., and Spitzer 2024).

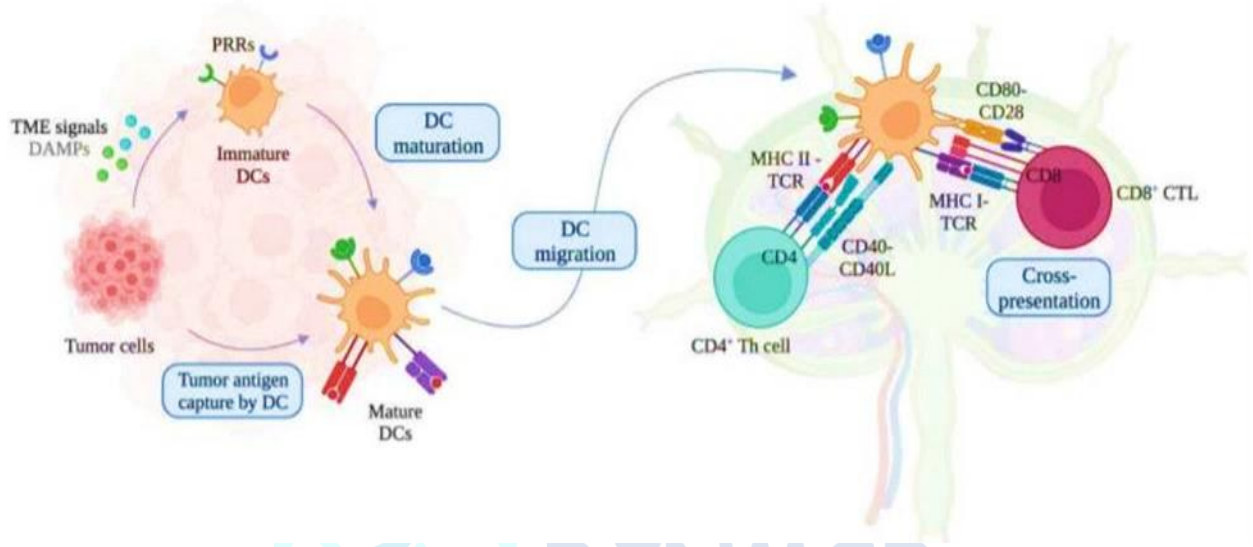

Figure 1: Tumor antigen of cross-presentation by DCs to T cells in TDLNs

Next-generation vaccines

Represent a massive leap forward from traditional methods, shifting from simple germ killing techniques to high tech, precision medicine. Unlike preventative vaccines that shield you from a future infection, these are therapeutic, designed to act as a roadmap for your immune system to find and destroy existing threats like cancer (E. Jenner 2020).

At their heart, these are genetic software for your cells. mRNA vaccines don't carry any part of a virus or tumor; instead, they deliver a temporary set of instructions that tell your body's cells how to build a specific protein (antigen) found on cancer cells. This allows the immune system to recognize the enemy without ever being exposed to the actual disease. (Banchereau, J., et al. 2018).

It is an innovative vaccine that uses the concept of a delivery vehicle. The scientists modify a benign virus (virus vector) and load it up with the genes of the tumor. When inserted into the patient's body, it will find its way to the cells where the genetic code is delivered. Your immune system recognizes the presence of a virus; hence, it responds in the most effective way (Appleton E., Hassan).

The technology can be seen as the best package to use in any vaccine. Using nanoscale packaging techniques, the antigen or the genes will be wrapped in tiny droplets referred to as nanoparticles. The nano-vaccines created will be in the right sizes to fit into the immune cells, thus enhancing effectiveness and reducing side effects of the vaccine since it reaches where it matters the most (Appleton E., Hassan J., Chan Wah Hak C 2020).

As each tumor in an individual is distinct, therefore, the treatment will vary from one individual to another. In personalized cancer vaccines, scientists use DNA sequencing technologies to discover mutations in the tumor called neoantigen markers that cannot be found anywhere else except within that individual's tumor cells. In turn, a vaccine will be tailored to recognize this red flag so that the tumor can be targeted with precision (Appleton E., Hassan J., and Chan Wah Hak C 2020).

The dendritic cells are described as intelligence officers of the immune system. The process entails harvesting specialized dendritic cells from the bloodstream of a patient, training these cells in the laboratory through exposure to antigens or markers of cancerous tumors, and then re-administering the trained cells to the patient. Upon reintroduction into the body, the intelligent cells coach the body's T cells on how the cancer appears, resulting in a targeted search and destroy mission (Gutiérrez-Martínez E., Planès R., Anselmi G., and Reynolds 2020).

In the vast majority of cases (in more than 97% of all clinical trials), researchers use one of two strategies of producing DC vaccines – ex vivo cultivation and training of the cells and/or their transfer of markers in a living body (in vivo). The overwhelming majority of research studies utilize an ex vivo strategy of generating DC vaccines. (Bazewicz, C. G., et al. 2018).

This strategy consists in the isolation of precursor cells from a patient's blood. Usually, CD14+ monocytes or CD34+ progenitor cells are selected for the experiment. After that, the cells are trained in a laboratory using special growth factors such as GM-CSF and IL-4 in order to transform precursors into immature dendritic cells. While being cultivated, the cells undergo an introduction of various antigens from tumors or fragmented cancer cells. In the end, there comes an application of so-called maturation cocktail which serves as a sort of activation factor for the vaccine. (Brown C.C., Gudjonson H., Pritykin Y., Deep D., Lavallée V.P 2019).

Because there isn't one standard way to make these vaccines yet, different labs use different recipes and methods. So far, the only major success story is Sipuleucel-T (Provenge), which was approved by the FDA for treating advanced prostate cancer. Recently, doctors have seen even better results by pairing Provenge with other treatments, like immune checkpoint inhibitors or immune-boosting proteins (IL-7), to give the patient's defenses an extra edge as shown in fig 2 (Boudousquie C., Gannon P.O., Kandalaft L.E 2019).

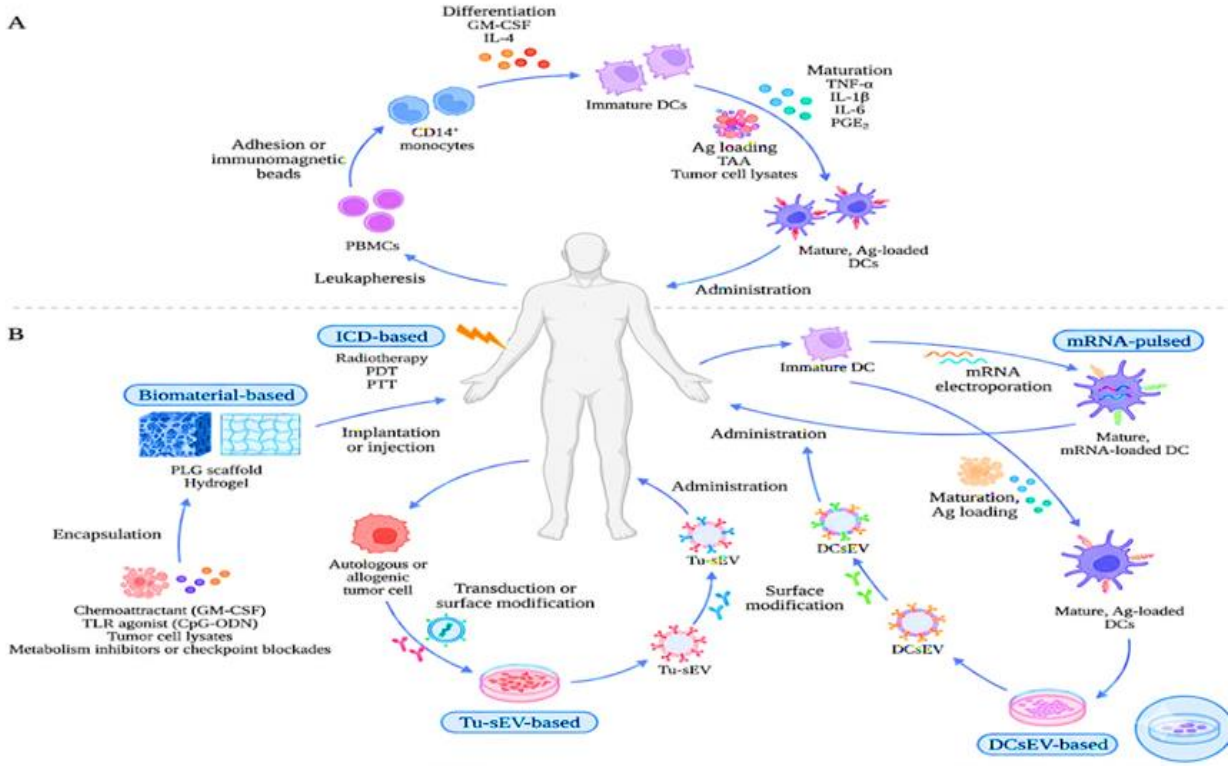

Figure 2: Conventional ex-vivo dendritic cell vaccine production versus next-generation biomaterial, mRNA, and extracellular vesicle-based delivery strategies

Most scientists opt for using CD14+ monocytes since they are easier to obtain from blood samples. Although CD34+ cells have proven to perform better in preparing the body's soldiers (CTLs) for their tasks, the rarity of such cells, constituting less than 0.1 percent of blood cells, makes the process hard to apply on a large scale (Kumbhari A., Kim P.S2021).

However, in order to overcome these problems, scientists tried to train dendritic cells in situ by employing targeting antibodies (such as Clec9A or CD40), which serve as a tracker delivering tumor antigens straight to the dendritic cell receptors circulating in the bloodstream or residing in various tissues (Boudousquie C., Gannon P.O., Kandalaft L.E 2019).

Although this approach yielded impressive results when used experimentally in laboratories due to its high efficacy in activating immunity, its practical implementation failed to produce significant success because it faced two problems: firstly, the presence of the appropriate receptor must be confirmed on target immune cells, and, secondly, at the same time, there is a need to provide additional stimuli for these cells. Otherwise, the result will either be negative or worse – tolerance development toward the tumor (Sprooten J., Ceusters J 2020).

The ongoing challenges associated with insufficient cell migration and temporary effects of previous techniques can be overcome using biomaterials scaffolds, such as PLG (poly lactide-co-glycolide)) and injectable hydrogels. The purpose of these biomaterials is to create an artificial niche, meaning that immune stimulation will occur within an artificially engineered body structure. Rather than being cultured in the lab, these structures will be infused with specific molecules that recruit the body's dendritic cells to this location, such as recruitment protein (GM-CSF) and danger signals (CpG-ODN), in order to stimulate the immune response. Cabeza-Cabrerizo M., Cardoso A., Minutti C.M. In situ means that cells can undergo the process in their normal biological setting, staying at the location for up to two weeks while collecting important information. Biomaterial scaffolds provide better and more prolonged activation of T-cells compared to liquid-based vaccines because these biomaterials control antigen release according to the biological rhythm (Cytlak U., Resteu A 2018).

Dendritic Cells in Cancer Immunotherapy

Cancerous tumors have shown remarkable ability to evade the immune system response through the creation of an environment that is immunosuppressive. This is done by producing cytokines such as IL-10 and TGF-b, inducing the expansion of regulatory T cells, and using metabolically suppressive substances that render normal functioning immune cells unable to respond. Moreover, tumors can hijack the very defense mechanism of the body by creating tolerogenic dendritic cells that simply ignore the presence of the tumor. To overcome this, researchers use an ex vivo technique whereby the precursors from the patient's body are isolated, modified, and trained to respond to cancer antigens away from the immune-suppressive environment, and then re-injected to the body (Villani A.-C., Satija R 2021).

Immunogenic Cell Death (ICD)

A powerful new strategy involves using stress-inducing treatments to transform cold tumors which the immune system typically ignores into hot tumors that trigger a massive immune response. This is achieved through a process called Immunogenic Cell Death (ICD). By using clinical tools like radiotherapy, photodynamic therapy (PDT), or photothermal therapy (PTT), doctors can kill a portion of the tumor in a way that causes the dying cells to explode with stress signals. (Zheng S., Lazo S., et al.2023).

These signals, such as Calreticulin (CRT) and HMGB1, act like high-visibility red flags that tell the immune system to find me and eat me. This helps to signal the dendritic cells about the presence of cancer and provides them with the whole library of the tumor antigens. The approach guarantees that the body will receive a full picture of the tumor antigens because the tumor serves as the immunization source (Zheng S., Lazo S., et al.2023).

Modern vaccines are also exploring the use of genetic instructions and tiny biological messengers to bypass traditional logistical hurdles. mRNA pulsed vaccines involve electroporating or essentially opening the pores of dendritic cells to deliver the genetic blueprint of the tumor directly into the cell. This allows the DCs to produce and present tumor markers with incredible efficiency. On the other hand, researchers are utilizing small extracellular vesicles (sEVs) microscopic droplets naturally released by cells. Calmeiro J., Carrascal M., Gomes C (2019).

These vesicles can be harvested from both DCs and tumors and then engineered to carry high concentrations of tumor markers and immune-boosting signals. Because these vesicles are so small, they can travel directly to the lymph nodes, bypassing the need for a whole dendritic cell to navigate through dense body tissues, which speeds up the immune system's training process (Brown C.C., Gudjonson H., Pritykin Y., and Deep D. 2024).

Synergistic and Systemic Effects

The ultimate goal of these next-generation vaccines is to work in harmony with other modern treatments, such as Immune Checkpoint Blockades (ICBs), to create a multi-pronged attack. By combining the training power of a DC vaccine which teaches the immune system who to fight with the brake-releasing power of ICBs which allows the immune system to fight harder doctors can overcome the tumor's natural defenses. Carreno B.M., Magrini V (2015).

The interaction does more than remove the primary tumor; it can cause the abscopal effect, which is quite amazing because it means that after the immune system is re-educated in its function, it starts to attack other metastatic tumors far away from the treatment site. Most importantly, it should be stated that advanced vaccines ensure the development of immunological memory in the body's immune system, which will guarantee a high level of preparedness for a possible cancer recurrence (Marmonti E., Oliva-Ramirez J., and Haymaker C. (2015).

Advanced Delivery: mRNA-Pulsed DC Vaccines

Dendritic cell pulsing with mRNA has become an example of high technology compared to conventional approaches of using tumor particles and synthetic peptides. Using peptides for vaccinations may be frequent but involves complex matching with the immune characteristics of the patient (HLA restriction) and does not provide a long-lasting effect. On the other hand, the mRNA-pulsed vaccine is used similarly to software, which orders the dendritic cells to express all necessary tumor-specific antigens inside out. Hildebrand W.H., Mardis E.R., et al (2015).

This approach is highly preferable due to its natural decomposition and inability to alter the genetic makeup of the patient while being considered as danger signals that activate the innate immunity through the stimulation of TLR3, TLR7, and TLR8 receptors (Petti A.A., Ly A., Lie W.-R., Hildebrand W.H., Mardis E.R., et al. 2024). Dendritic cell pulsing with mRNA has become an example of high technology compared to conventional approaches of using tumor particles and synthetic peptides. Using peptides for vaccinations may be frequent but involves complex matching with the immune characteristics of the patient (HLA restriction) and does not provide a long-lasting effect. (Petti A.A., Ly A., Lie W.-R., Hildebrand W.H., Mardis E.R., et al. 2024).

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To get this genetic information into the cells effectively, researchers often use a technique called electroporation, which uses a tiny, precise electric pulse to open temporary pores in the cell membrane. This allows the mRNA to slide directly into the cell's engine room (the cytosol) before it

can be degraded by external enzymes. (Cheever M.A., Higano C.S 2011).

Once inside, the mRNA can be derived from two sources: it can either be a complete mirror of the patient's specific tumor (whole tumor-derived mRNA) or specifically engineered in a lab (in vitro transcribed mRNA). In order to introduce genetic information efficiently into cells, electroporation is usually used (Becker-Hapak M 2021).

During this procedure, there is a delivery of short electrical pulses which create temporary pores in the membrane allowing the introduction of the mRNA straight into the cytosol before it could be digested by extracellular enzymes. As a source of mRNA, it can come from one of two options. First, mRNA can be an exact copy of the tumor of the patient (whole tumor-derived mRNA). Second, mRNA can be generated in a laboratory (in vitro transcribed mRNA). (Becker-Hapak M 2021).

The first option allows targeting all mutations of the tumor to prevent its immune escape. In the second case, additional modifications are added to the mRNA, which include lysosomal sorting signals. It provides guidance for the tumor antigen processing to allow the presentation of tumor marker peptides via MHC I and MHC II to activate CD8 and CD4 helper T-cells correspondingly. (Constantino J., Gomes C 2011). This is what makes the procedure the gold standard in activating complete adaptive immunity to ensure extended response. It was confirmed during the trials of glioblastoma treatment when patients had a much increased survival time (Zilionis R., Engblom C2020).

Ex Vivo Dendritic Cell Vaccination

Using ex vivo technique for generating DC vaccines is the most studied method, which at present accounts for about 97% of all clinical trials. The ex vivo method relies on extracting certain cells from the body of a patient in order to educate them under controlled conditions in the laboratory without being hindered by the immunosuppressive TME of the tumor. (Falcão A., Cruz M.T., Neves B.M. 2016).

In vivo, the tumor generates stop signs, such as IL-10 and TGF-β, which transform the naturally occurring DCs to tolerogenic cells, thus rendering them oblivious to cancer. By conducting the education process outside of the body, researchers will ensure that the DCs are mature and equipped with appropriate cancer-related information when introduced into the body to initiate an immune attack against the cancer (Oliveira M.M.S., D'Aulerio R., and Yong T 2019).

The Step-by-Step Production Process

The production of the ex vivo vaccine requires following a certain biological process that will convert regular blood cells into highly efficient cancer-fighting cells:

Leukapheresis & Isolation: To start the process of production, the patient's Peripheral Blood Mononuclear Cells (PBMCs) need to be harvested through a process of leukapheresis. The cells harvested can then be isolated by using such methods as plastic adherence or immunomagnetic beads, resulting in CD14+ monocytes (Cabeza-Cabrerizo M 2019).

Differentiation: These isolated monocytes are then put in a culture with specific medium containing growth factors, namely GM-CSF and IL-4. This leads to the differentiation of the cells into immature dendritic cells after a period of 6 days (Curtsinger J.M., Mescher M.F. 2020).

Maturation & Antigen Presentation: On day seven, these immature cells are pulsed or loaded with TAAs and tumor cell lysates, along with a maturation cocktail made of TNF-α, IL-1β, IL-6, and PGE2, which lasts for 48 hours (Joffre O.P., Segura E., Savina A 2021).

Reinfusion: After the process of maturation and training is complete, the cells are introduced back into the body and move to the lymph nodes.The production of an ex vivo vaccine follows a precise biological sequence designed to transform ordinary blood cells into high-performance cancer hunters (Calmeiro J., Carrascal M., Gomes C 2020).

Real research has established ALDH1A2 as a critical metabolic node. Via its conversion of retinal to RA, the cancer produces a tolerogenic microenvironment that dampens any active response by T cells. Research Findings: Recent research (2025-2026) indicates that ALDH1A2

inhibitors reduce levels while boosting the presence of $CD8^+$ T cells. Vaccines Combinations: By using ALDH1A2 inhibitors alongside modern mRNA vaccines, the tolerogenic status of dendritic cells can be turned around to allow proper antigen presentation from the vaccines. Fang, X. & Kang, Y. (2026).

The most successful next-gen data comes from personalized neoantigen platforms. Unlike traditional vaccines, these are custom-built for each patient's unique tumor mutations. Clinical Data: In ongoing Phase IIb/III trials (2024–2025), the combination of the mRNA-4157 vaccine and anti-PD-1 therapy showed a 44% improvement in recurrence-free survival in patients with resected high-risk melanoma compared to immunotherapy alone. (Tawor, A. 2024).

The vaccine encodes up to 34 synthetic neoantigens, forcing the immune system to recognize multiple faulty proteins on the tumor surface simultaneously, making it harder for the tumor to hide via immune suppression: Weber, J. S., et al. (2024). Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab alone in resected melanoma: a randomised, open label, phase 2b trial. The Lancet, 403(10427), 632-644.

A major hurdle in vaccine research is ensuring the vaccine reaches the lymph nodes and penetrates the dense, suppressive TME Research Data: Data from 2025 indicates that Intelligent Nanocarriers (lipid nanoparticles or LNPs) can be engineered to release their cargo only in the acidic environment of the tumor. This localized release helps flip macrophages from a pro-tumor (M2) state to an anti-tumor (M1) state. Corogeanu, D., & Diebold, S. S. (2022).

Humanized Models: Using humanized mice and ex vivo human tumor samples, researchers demonstrated that these nanoparticles bypass the suppressive effects of retinoic acid by delivering Toll like receptor (TLR) agonists directly to the dendritic cells. Wu, L., Zhang, H., & Liu, P. (2025). Nanoparticle based cancer vaccines: Overcoming the suppressive barrier of the tumor microenvironment. Journal of Nanobiotechnology, 23(1), 89-104. PMC11717780.

The first major issue associated with the current paradigm of DC-based vaccination lies in the metabolic brake present in the tumor microenvironment (TME). The latest evidence reveals that solid tumors, especially hepatic metastasis, rely on ALDH1A2 protein activity for conversion of Vitamin A into retinoic acid (RA). Although RA serves as a signaling molecule during development, its role within the TME has a profoundly immunomodulating effect by inducing regulatory T cells (Tregs) and inhibiting CTL activation (Jones & Von Hoff, 2024).

In advanced-generation strategies, ALDH inhibitors (e.g., Disulfiram or selective RALDH antagonists) are added directly to the process of DC maturation. As a result, this intervention will prevent any accidental tolerance induction caused by even the most sophisticated combinations of activators such as GM-CSF or IL-4, both of which were reported to cause upregulation of ALDH1A2 in some scenarios (Badillo et al., 2024). In other words, this approach ensures that the vaccine will lock the DCs in a stimulatory state, preventing the formation of tolerogenic T cells (Gupta et al., 2022).

The evolution towards next-gen vaccines is marked by the increase in antigenic specificity highlight the development towards using personalized neoantigens in mRNA vaccines. mRNA platforms allow for the precise expression of multiple epitopes, expanding the repertoire of T cells, thus making it harder for the tumor to evade due to antigenic drift. Nonetheless, even with highly specific T cells (Lee et al. 2023) and Kebabçıoğlu et al. (2024)).

T cell silencing can occur once they enter the tumor microenvironment. Hence, the need for the synergistic use of Immune Checkpoint Inhibitors (ICIs). For instance, anti-PD-1. According to (Zanotta et al. (2024), DC vaccines act like the ignition for activating T cells while ICIs act as fuel to prevent T cell exhaustion. Such an approach works well for cold tumors since the vaccine enables T cells to enter the tumor site while ICIs ensure T cells remain functional within the tumor microenvironment. (Curtsinger J.M., Mescher M.F2010).

The recent scRNA-seq analysis has shed light on the intricacies of DC subsets, unveiling a problem called mature regulatory DCs (mregDCs). As described by Badillo et al. (2024), despite being mature, they still produce a number of inhibitory signals such as PD-L1 and IDO1. The new approach involves the employment of agonist antibodies (e.g., anti-CD40) to circumvent the regulatory circuits and trigger an efficient stimulatory pathway (Corogeanu & Diebold, 2022).

Additionally, the review will discuss Cancer Stem Cells (CSCs). As noted by Gupta et al. (2022), the isoforms of ALDH not only impair immune response but preserve the stemness of CSCs. Thus, the targeting of specific antigens of CSCs via DC vaccines and their simultaneous inhibition will help get rid of both the bulk tumor and the seeds that might lead to relapse. This is facilitated by using biomimetic nanoparticles ensuring a direct delivery of these payloads to the lymph nodes, thereby facilitating the contact between DCs and naive T cells (Zanotta et al., 2024).

Development of Antitumor DC Vaccines with ALDH1A2 Inhibitors

A significant transition from first generation methodologies to ''next generation'' metabolic reprogramming has been observed in the evolution of dendritic cell (DC) vaccines. The inherent plasticity of DCs, which are frequently switched to a tolerogenic state within the tumor microenvironment (TME), is considered the primary challenge in traditional DC therapy (Wculek et al., 2020). Aldehyde Dehydrogenase 1A2 (ALDH1A2) has been identified in recent studies as a key metabolic checkpoint through which immune evasion is facilitated via the production of retinoic acid (RA), by which regulatory T cells (Tregs) are induced (Bazewicz et al., 2018; Marcut et al., 2023).

This high specificity is achieved by the use of peptides, mRNA, or tumor lysates to load these genetically engineered DCs with tumor-specific antigens (Stevens et al., 2022). An improved phenotype profile with upregulated costimulatory molecules (CD80, CD86) and low PD-L1 is demonstrated in ALDH1A2 blocked DCs and not in the conventional vaccines (Zanoni et al., 2022; Xia et al., 2023). The ''tolerogenic'' nature of the vaccine on re-infusion is avoided using this metabolic blockage. Synergy with immune checkpoint blockade therapy using anti-PD-1 antibodies is also shown through this technology where effective T-cell priming is achieved initially, followed by sustained stimulation through checkpoint blockades (Sallusto & Lanzavecchia, 2021; Zhou et al., 2025).

Figure 3 illustrates the entire process of generating these reprogrammed vaccines in an ex vivo setting, which consists of blocking the ALDH1A2 activity at the maturation stage of the vaccine production pipeline.

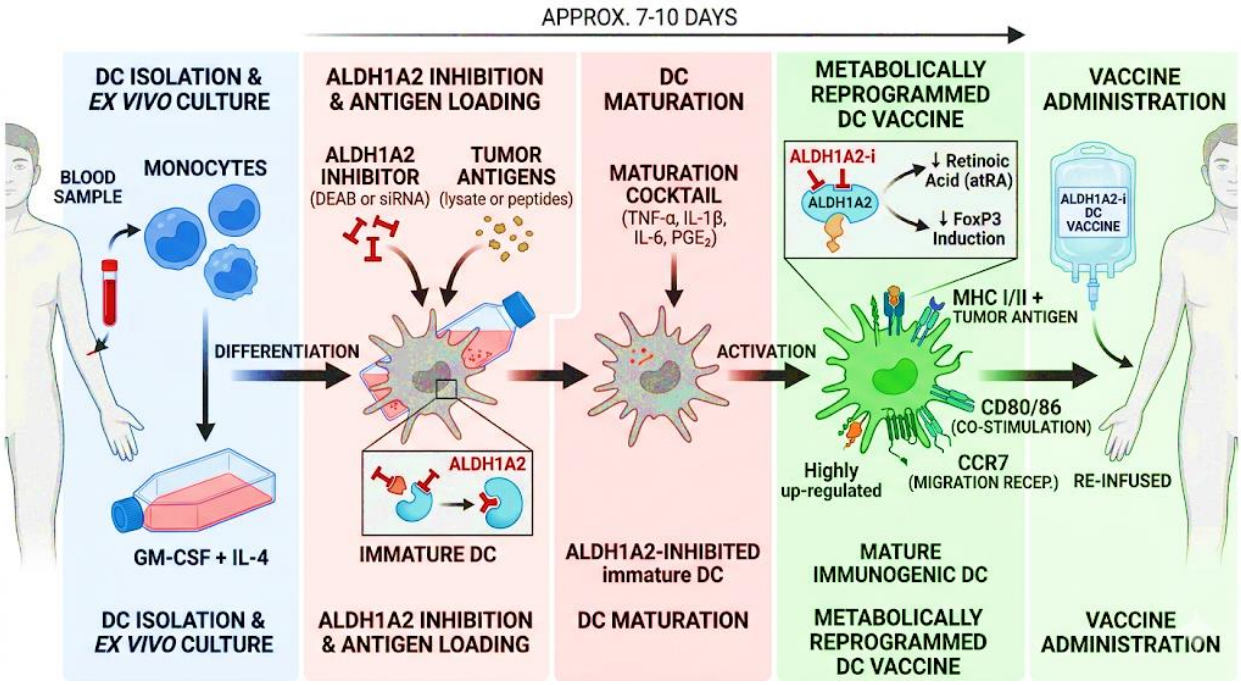

Figure 3: Ex-vivo technique of Development of ALDH1A2-Inhibited Antitumor DC Vaccines

Diagrammatic representation of the ex vivo technique that involves isolation and differentiation of monocytes to generate metabolically reprogrammed immunogenic DCs through ALDH1A2 inhibition (using siRNA and small-molecule inhibitors) with maturation cocktails shown in figure 3 (Banchereau et al., 2018; Villablanca et al., 2011; Wculek et al., 2020 The metabolic conversion of Vitamin A is considered the primary factor governing the molecular basis of dendritic cell (DC) mediated immune suppression. It has been established that retinal is converted into all-trans-retionic acid (atRA) by the enzyme Aldehyde Dehydrogenase 1A2 (ALDH1A2) within the cytoplasm of the DC (Manicassamy & Pulendran, 2009). Under standard conditions or within the tumor microenvironment, the translocation of this generated atRA to the nucleus is observed, where the Retinoic Acid Receptor (RAR) and Retinoid X Receptor (RXR) complex is bound (Villablanca et al., 2011).

The expression of the transcription factor FoxP3 in native T cells is directly induced by this signaling pathway, through which their differentiation into immunosuppressive Regulatory T cells (Tregs) is promoted (Bazewicz et al., 2018). In the absence of an inhibitor, the expansion of these Tregs leads to the suppression of effector T-cell functions, by which tumor immune evasion is facilitated (Badillo et al., 2024). However, the production of atRA is significantly diminished when ALDH1A2 blockers are introduced, which subsequently results in the inhibition of the RAR and RXR mediated induction of FoxP3 (Galvin et al., 2013).

The T-cell balance is shifted from a tolerogenic to an immunogenic state as a result of this metabolic blockade. The induction of tumor cell apoptosis and the overall enhancement of vaccine induced antitumor immunity are considered essential outcomes of this mechanical shift (Xia et al., 2023). Furthermore, the resistance of solid tumors to immunotherapy is often attributed to this axis, by which ALDH1A2 is rendered a high-priority therapeutic target (Zanoni et al., 2022).

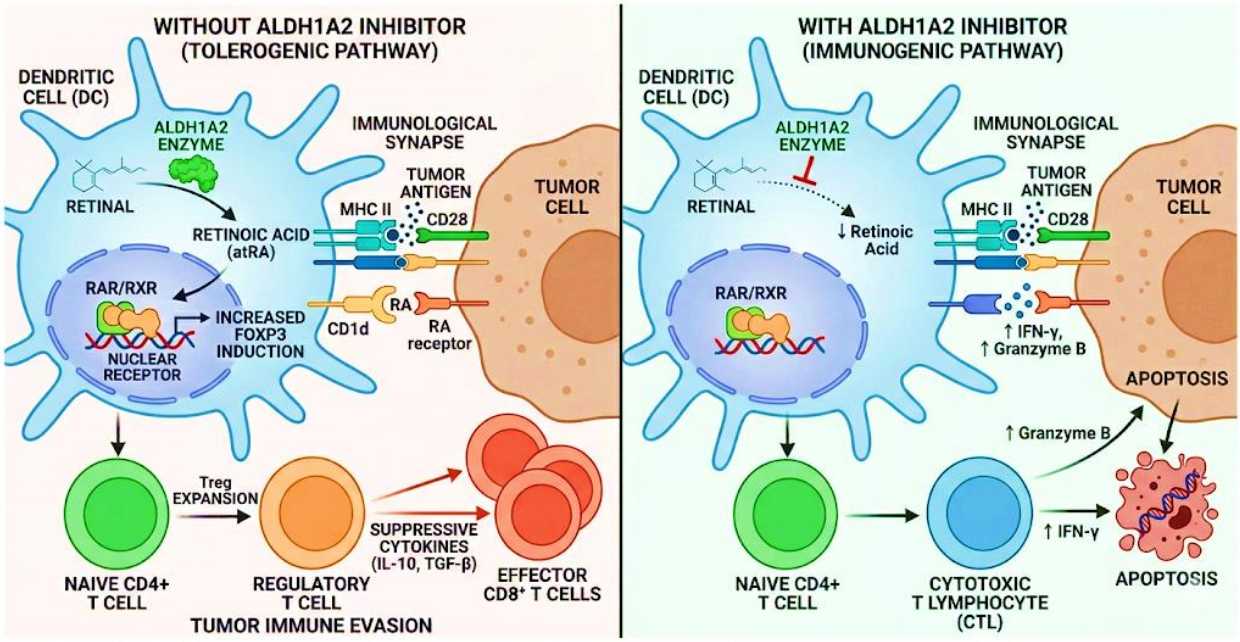

Figure 4: Molecular Mechanism of ALDH1A2-Mediated Immune Regulation in DC Vaccines.

Fig 4 shows the left panel illustrates the tolerogenic pathway where ALDH1A2 converts retinal into retinoic acid, leading to FoxP3 induction and Treg expansion. The right panel demonstrates the immunogenic shift following ALDH1A2 inhibition, resulting in increased CTL activation and tumor cell apoptosis (Galvin et al., 2013; Villablanca et al., 2011; and Xia et al., 2023).

Several distinct therapeutic advantages over conventional immunotherapy are offered by the integration of ALDH1A2 inhibitors into antitumor dendritic cell (DC) vaccines. Primary among these is the ability to overcome tumor induced immune tolerance, through which the zone of protection created by the tumor is effectively disrupted by metabolic reprogramming (Wculek et al., 2020).

Consequently, the vaccine is allowed to function in environments previously characterized as cold or immunosuppressed. Furthermore, a significant reduction in Treg-mediated suppression is achieved through this approach. The inadvertent expansion of FoxP3+ regulatory T cells a common cause of failure in first-generation DC vaccines is prevented by blocking the ALDH1A2 retinoic acid axis (Bazewicz et al., 2013).

This shift is directly linked to an improved cytotoxic T-cell response, as a substantial increase in the infiltration of T-cells into the tumor mass is observed upon the inhibition of ALDH1A2 (Targeting autocrine retinoic acid signaling..., 2025; Xia et al., 2023).

Another critical advantage is found in the potential for synergy with immune checkpoint inhibitors, such as anti-PD-1 and anti-CTLA-4. It is suggested that while the ''brakes'' on the immune system are released by checkpoint blockers, the necessary ''accelerator'' is provided by the ALDH1A2-inhibited DC vaccine through the generation of a robust pool of high quality effector T cells (Zhou et al., 2025).

Overall vaccine efficacy is shown to be enhanced by this dual strategy, which may overcome resistance in patient's non-reponsive to monotherapy (Zanoni et al., 2022; Stevens et al., 2022). Finally, an immunogenic state is ''locked'' into the DCs through the use of siRNA or small molecule blockers during the *ex vivo* maturation phase, by which their reversal into a tolerogenic phenotype upon re-infusion is prevented (Villablanca et al., 2011; Badillo et al., 2024).

The core differences between traditional methodologies and the proposed metabolic reprogramming strategy are summarized in Table

1. As shown, the transition from a tolerogenic to an immunogenic state is facilitated by the precise inhibition of the ALDH1A2-retinoic acid axis (Wculek et al., 2020; Zanoni et al., 2022).

Table 1: Comperative Analysis of ALDH1A2 DC Vaccines

Feature	Conventional DC Vaccines	ALDH1A2-Inhibited DC Vaccines	References
Developmental Strategy	Standard maturation using GM-CSF and IL-4; high risk of tolerogenicity.	Integration of small molecule inhibitors (DEAB) or siRNA-mediated knockdown.	Banchereau et al. (2018); Villablanca et al. (2011)
Molecular Mechanism	Retinal is converted to atRA, leading to RAR/RXR binding and FoxP3 induction.	Blockade of atRA production, preventing FoxP3 expression in naive T cells.	Manicassamy & Pulendran (2009); Galvin et al. (2013)
Therapeutic Advantages	Limited efficacy due to Treg expansion and tumor immune evasion.	Enhanced CTL infiltration, IFN-γ/Granzyme B release, and synergy with anti-PD-1.	Xia et al. (2023); Zhou et al. (2025)

Combination with other Next Generation approaches

Another area to be explored in the development of the next-generation DC vaccines is the reprogramming of the Vitamin A metabolism in the TME. Studies have demonstrated that the liver and some tumors are immune-tolerant environments wherein Vitamin A metabolism occurs through the action of the enzyme ALDH1A2, resulting in the production of retinoic acid (Jones & Von Hoff, 2024).

This axis is a critical pathway in the context of vaccine development wherein, in the presence of RA, the DCs become tolerogenic, resulting in Tregs and not CTLs. By incorporating inhibitors of ALDH, such as Disulfiram, or RALDH inhibitors in the vaccine protocol, researchers can prevent the accidental induction of immune suppression (Jones & Von Hoff, 2024; Gupta et al., 2022).

This ensures that the maturation of the DCs, which is induced through the action of GM-CSF and IL-4, is not hijacked by the TME to induce regulatory immune cells (Badillo et al., 2024).

The limitation of first-generation DC vaccines is thought to be related to the cold nature of many tumors. Next-generation approaches overcome this limitation through the integration of ignition and fuel to generate a synergistic effect. Ignition is provided by the DC vaccine, while fuel is supplied by ICIs, such as anti-PD-1 and anti-CTLA-4, to prevent T cells from being exhausted by the TME (Zanotta et al., 2024; Lee et al., 2023).

Next-generation approaches also utilize the high-fidelity expression of neoantigens through the application of mRNA technology, which ensures the expression of a spectrum of neoantigens, thus minimizing off-target effects and resulting in a poly-specific immune response, which is very difficult for the tumor to evade (Lee et al., 2023; Badillo et al., 2024).

Advanced DC vaccinology has now accepted the concept of the heterogeneity of DCs, particularly the role of mreg DCs. These cells, identified through scRNA-seq, are a unique population of DCs, which, although mature in terms of cell surface phenotype, are suppressive in terms of high expression of PD-L1 and IDO1. Expression (Badillo et al., 2024). This is addressed by the next-generation vaccines, which employ agonistic antibodies, e.g., anti-CD40, to impose a strictly stimulatory program of maturation (Corogeanu & Diebold, 2022). Moreover, the approach to Cancer Stem Cells (CSCs), which are often chemoresistant, using DC-mediated immunity is proposed to prevent relapse (Gupta et al., 2022). Using biomimetic nanoparticles, it is now possible to target the lymph nodes, thereby protecting unstable antigens and ensuring stimulatory signals reach the appropriate niches for an effective systemic immune response (Zanotta et al., 2024).

Challenges

The major problem in the current DC vaccinology is the metabolic brake present in the tumor microenvironment and other immune-tolerant organs such as the liver. A study by Jones & Von Hoff (2024) showed that the liver and other solid tumors use the enzyme ALDH1A2 to convert Vitamin A into retinoic acid. Although retinoic acid is known to be a developmental signaling molecule, in the tumor microenvironment, it is known to act as a very powerful immunomodulator that induces regulatory T cells and suppresses the activation of CTLs.The next-generation approach is to incorporate the ALDH inhibitors such as Disulfiram or the RALDH inhibitors into the DC maturation process. (Jones & Von Hoff 2024)

This is to prevent the accidental induction of tolerance that is often seen even in the case of the standard DC maturation cocktail such as GMCSF and IL-4, which has been shown to inadvertently induce the expression of the ALDH1A2 enzyme (Badillo et al., 2024). By blocking the expression of the ALDH1A2 enzyme, the vaccine is able to lock the DCs into a stimulatory phenotype and ensure that the immune response is always effector-oriented and not suppressive (Gupta et al., 2022).

The shift from 1st generation to next-generation vaccines is characterized by an improved antigenic specificity, or resolution, and the application of molecular accelerators. (Lee et al. 2023 and Kebabçıoğlu et al. 2024) highlight the trend toward personalized neoantigens, or tumor-specific mutations, that are specific to the patient's tumor, using mRNA-based platforms. This permits the precise expression of tumor-specific antigens, thereby creating an expanded T-cell repertoire that makes it harder for tumors to undergo antigenic drift. Nevertheless, it is still possible for T-cells, no matter how precisely primed, to become anergic upon entering the TME. In this context, the synergy with Immune Checkpoint Inhibitors (ICIs) such as anti-PD-1 or anti-CTLA-4 is considered vital. In their research, (Zanotta et al. 2024)

While the DC vaccine is responsible for the ignition or T-cell priming, the fuel is provided by the ICI, which prevents T-cell exhaustion. This combination is particularly effective against cold tumors, where the vaccine induces T-cells to enter the tumor, while the ICI ensures that they remain functional within the hostile tumor microenvironment (Zanotta et al., 2024).

Recent studies on single-cell RNA sequencing have revealed the intricacy of Dendritic Cells (DCs), where there is a problematic state referred to as mature regulatory DCs (mregDCs). mregDCs are technically mature but have high levels of inhibitory factors like PD-L1 and IDO1, which truncate the immune response (Badillo et al.,2024). The review also includes the discussion on Cancer Stem Cells (CSCs) in relation to therapeutic resistance. According to Gupta et al. (2022).

Aside from inhibiting immunity through ALDH isoforms, these also play a significant role in maintaining the 'stemness' and drug-resistance properties of CSCs. Targeting antigens on CSCs using DC vaccines while inhibiting ALDH isoforms will result in a two-fold effect, tumor elimination and removal of recurrence 'seeds.' This is also in line with using biomimetic nanoparticles in ensuring that complex molecular loads are delivered directly to the lymph nodes to maximize interaction with naive T-cells (Zanotta et al., 2024).

Future perspectives

One of the major hurdles faced by modern DC vaccinology is the concept of a metabolic brake inherent in the tumor microenvironment (TME) as well as other immune-tolerant sites like the liver. A study by Jones & Von Hoff (2024) showed that the liver, as well as many solid tumors, utilizes the enzyme ALDH1A2 for the metabolism of Vitamin A into Retinoic Acid (RA).

While RA is a developmental signaling molecule, it assumes a pro-immunosuppressive role when present in the tumor microenvironment, promoting the development of regulatory T-cells (Tregs) and inhibiting the activation of cytotoxic T-lymphocytes (CTLs). The emerging strategies of next-generation DC vaccines involve the direct addition of ALDH inhibitors, like Disulfiram or

RALDH inhibitors, during the DC maturation step. (Xia, J., et al. 2023).

This circumvents the unintended induction of immune tolerance, which can even be seen when using conventional DC maturation cocktails like GM-CSF and IL-4, which have been shown to inadvertently induce ALDH1A2 (Badillo et al., 2024). This allows the vaccine to circumvent this metabolic checkpoint, thereby locking the DCs into a purely stimulatory phenotype, ensuring a purely effector-oriented immune response rather than a suppressive one (Gupta et al., 2022).

The shift from first-generation to second- or next-generation vaccines is characterized by improved antigenic accuracy and the application of molecular 'boosters highlight this shift toward more 'personalized neoantigens,' or tumor-specific mutations unique to the patient's tumor, using mRNA platforms. This strategy enables accurate expression of multiple antigens and an expanded T-cell repertoire, making it more difficult for tumor antigens to 'drift' and escape T-cell recognition. Yet, even T-cells that have been optimally primed in vitro may become anergic upon entry into the TME' (Lee et al. 2023 and Kebabçıoğlu et al. 2024).

Thus, the 'synergy' with Immune Checkpoint Inhibitors (ICIs), including anti-PD-1 and anti-CTLA-4 agents, is critical in this approach. Zanotta et al. (2024) highlight that while DC vaccines offer 'ignition,' ICIs offer 'fuel,' or T-cell activation and prevention of exhaustion. This combination is particularly effective in 'cold' tumor models, in which T-cells are recruited to the tumor but also remain 'functional' in this hostile metabolic environment (Zanotta et al., 2024).

In a recent study, Badillo et al. (2024) used scRNA-seq to study the complexity of DCs and found a problematic state of Mature Regulatory DCs (mregDCs), which is technically mature but overexpresses inhibitory checkpoints like PD-L1 and IDO1, which truncate the immune response. However, the next-generation approach is to modulate the immune response using agonist antibodies, like anti-CD40, to circumvent the regulatory response and induce a strong stimulatory response (Corogeanu & Diebold, 2022). Moreover, the review should highlight the role of CSCs in therapeutic resistance.

Aside from suppressing the immune response, ALDH has a major role in maintaining the stem cell-like stemness and drug resistance of CSCs. By targeting CSC-specific antigens in a DC vaccine and simultaneously targeting ALDH (Gupta et al. 2022), clinicians can achieve a two-pronged effect in cancer therapy eliminating the bulk of the tumor and simultaneously eliminating the seeds of recurrence. This is further enhanced by the use of biomimetic nanoparticles, which ensure the targeting of these complex molecular payloads to the lymph nodes, maximizing the interaction of engineered DCs and naive T cells (Zanotta et al., 2024).

Conclusion:

Cancer immunotherapy has advanced to a point whereby conventional therapies such as immune checkpoint blockade therapy (ICB) and adoptive cell therapy (ACT) have been complemented by the next generation of dendritic cell (DC) vaccines. Although the first DC vaccine, Sipuleucel-T, provided proof of concept of this therapy approach, it faced some challenges related to the tumor-induced cold environment. Metabolic Locking: Another advancement includes the targeting of metabolic checkpoints through the inhibition of the ALDH1A2 enzyme, whose function is to convert vitamin A into retinoic acid. Since retinoic acid creates a tolerogenic environment which inhibits T-cell activation, targeting ALDH1A2 leads to metabolic locking, hence maintaining DCs in a stimulatory environment. Precision and Personalization: The development of mRNA neoantigen vaccines is a significant step forward in the realm of precision medicine. Such customized vaccines, which target unique mutations within an individual's tumor cells, have been found to be effective in increasing recurrence-free survival by up to 44% when combined with anti-PD-1 treatment.

Advanced Delivery Systems: Utilizing biomaterials, lipids, and extracellular vesicles (sEVs) has overcome numerous historical limitations. In this context, the biomaterials can be viewed as the GPS of delivery vehicles for

antigenic proteins that effectively target lymph nodes and ensure strong immune response without side effects. The ultimate effectiveness of these therapies hinges on their synergism with other therapies. While DC vaccines serve as the starter to ignite the T-cells, ICIs provide the fuel needed to avoid T-cell exhaustion. With these therapies combined, not only is there tumor elimination in the primary site, but an abscopal effect can be elicited in distant metastasis sites.

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