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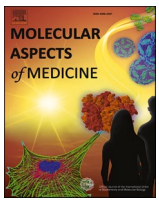

Review

Cancer vaccines: Target antigens, vaccine platforms and preclinical models

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A B S T R A C T

This review provides a comprehensive overview of the evolving landscape of cancer vaccines, highlighting their potential to revolutionize tumor prevention. Building on the success of vaccines against virus-related cancers, such as HPV- and HBV-associated cervical and liver cancers, the current challenge is to extend these achievements to the prevention of non-viral tumors and the treatment of preneoplastic or early neoplastic lesions. This review analyzes the critical aspects of preventive anti-cancer vaccination, focusing on the choice of target antigens, the development of effective vaccine platforms and technologies, and the use of various model systems for preclinical testing, from laboratory rodents to companion animals.

1. The many flavors of tumor prevention

The most straightforward way to reduce cancer incidence is by avoiding human exposure to carcinogens, a strategy known as primary cancer prevention. This is just one of the preventive strategies conceived to control cancer's impact on human health. Malignancy, often resulting from tumor progression leading to metastatic spread, is the principal cause of cancer-related death; secondary cancer prevention aims at preventing neoplastic progression through early diagnosis and treatment.

There are also tertiary and quaternary forms of prevention, but it should be noted that such terms are chiefly used by cancer prevention experts, whereas other health professionals, such as medical oncologists, may use different terminologies. Tertiary prevention aims at limiting tumor extension through the prevention of relapse and metastasis; two effective approaches are prophylactic radiotherapy, which reduces the risk of local relapse after conservative surgery, and adjuvant drug therapy, which is administered to patients at risk of having micrometastases, to prevent their growth and development. Quaternary prevention is a more recent coinage, to denote strategies aimed at the reduction of iatrogenic damage, especially in connection with hypermedicalization.

Another contemporary term is "cancer interception", which was the title of a commentary by Elizabeth Blackburn, published in 2011 by Cancer Prevention Research (Blackburn, 2011). Undoubtedly, cancer interception conveys a more proactive and dynamic feeling than "secondary cancer prevention" – after all, even in cancer prevention, nobody wants to play a secondary role. "Cancer interception" gained traction, particularly in the USA, and is now commonly used in the literature. Domchek and Vonderheide correctly state that "interception is neither primary prevention per se […] nor tertiary prevention" (Domchek and Vonderheide, 2024), clearly equating it with secondary prevention. However, it should be noted that the term is frequently used more broadly, and sometimes ambiguously, especially concerning primary prevention, i.e. in the absence of cancer. Probably "carcinogenesis interception" would provide a clearer meaning of what is really intended with "cancer interception". Still, given the already complex landscape, we will refrain from introducing further terms and prefer to stick with the established concepts of "primary" and "secondary" tumor prevention.

Finally, disease prevention via drug administration is called chemoprevention. Vaccines and other immunological agents are classified

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as drugs, hence tumor prevention by immunological means, i.e. immunoprevention, formally is a subset of chemoprevention. However, the inherent complexity and uniqueness of the molecular and cellular mechanisms set in motion by immunological interventions justifies the attitude of tumor immunologists, who generally regard tumor immunoprevention as a distinct and independent form of prevention.

1.1. The development of human tumor chemoprevention and immunoprevention

In principle, primary prevention is easy: once the carcinogens are identified, they can be altogether avoided. In practice, however, carcinogenic human exposures have been on the rise for the best part of the last century, despite mounting scientific evidence, both in the workplace and in everyday life. A significant global reduction in cancer incidence only began in the 1990s, mainly thanks to the decline in cigarette use among the male population and the elimination of carcinogens from the workplace (De Flora et al., 2005).

The implementation at the population level of vaccines against carcinogenic viruses, beginning with hepatitis B (HBV) in the 1980s, followed by papillomaviruses (HPV) in the 2000s, revolutionized primary prevention and marked the earliest successful example of mass immunoprevention. Long before that, several drugs were shown to effectively reduce the risk of cancer, but their unfavorable toxicological profiles hampered and delayed widespread use. Selective estrogen receptor modulators (SERMs), like tamoxifen and raloxifene, were shown to reduce breast cancer risk by half and were approved for prevention by several regulatory agencies in the late 1990s. However, severe side effects, including the risk of thromboembolism and pro-carcinogenic effects in other organs, restricted their use to women at high risk of breast cancer. Major improvements were obtained with aromatase inhibitors, which have identical efficacy with a reduced set of side effects, extending their use to women at intermediate risk of breast cancer (Cuzick et al., 2014). Non-steroidal anti-inflammatory drugs (NSAIDs) share with anti-estrogens the combination of an effective reduction in cancer incidence, in this case colorectal cancer, with risks (bleeding) unacceptable for the general population, thus limiting their application to high-risk conditions, such as the Lynch syndrome (Bolivar et al., 2023).

Currently available tumor preventive vaccines vastly outperform chemopreventive strategies in terms of efficacy, easily reaching risk reductions close to 100%, *vis-à-vis* percentages in the 10–50% range for anti-inflammatory and anti-estrogenic drugs. However, the most striking difference lies in the absence of severe side effects with vaccines, which exponentially decreases their risk/benefit ratio to negligible levels, thus making them suitable for administration to the entire population.

As papillomaviruses are the sole cause of cervical cancer, and vaccines are nearly 100% effective in preventing chronic infection, epidemiological studies predict a continued reduction in cervical cancer cases (Hall et al., 2019), potentially leading to the eradication of this deadly tumor type - the first such eradication in human history, akin to the elimination of smallpox through vaccination in the last century.

2. Tumor antigens

Cancer vaccines are designed to trigger an immune response against transformed cells by targeting one or more antigens associated with malignancies (Fig. 1). Upon administration, the vaccine aims to stimulate a specific immune response - ideally, both cellular and humoral - against these antigens, thereby restoring the immune system's ability to selectively target and eliminate cancer cells (Fig. 2). However, paradoxically, by activating an anti-cancer immune response, cancer vaccines may also promote immunoediting, a process in which tumor subclones with decreased immunogenicity, such as those that lose antigen expression, are selected, allowing them to evade immune recognition and to proliferate. To minimize the risk of cancer cells loosing antigen expression, becoming resistant to the vaccine-induced immune response, the target antigen must be carefully selected (Cavallo et al., 2011). Additionally, the timing of immunization is crucial. When administered to a healthy individual or during the early stages of cancer, when only a few transformed cells are present, the vaccine-induced immune response can effectively halt cancer development. In such cases, the induction of a strong antibody response may be significant, especially if the targeted antigen is a highly expressed membrane protein or receptor that regulates key intracellular pathways. Indeed, the vaccine-induced antibodies can function as "neutralizing" agents, binding to the antigen and disrupting its function, either directly or through indirect effector mechanisms, potentially blocking cancer progression before it advances (Fig. 2). In contrast, in later stages of cancer, a robust cytotoxic immune response becomes essential to slow or impair tumor progression. At this point, however, tumors may activate immune evasion mechanisms, making it more challenging for the immune system to eliminate cancer cells (Fig. 2). Consequently, a well-timed and comprehensive immune approach, often combining vaccination and the administration of other immunostimulatory approaches, is crucial for effectively controlling and combating cancer progression.

2.1. The ideal tumor antigen: the concept of oncoantigen

An extensively explored approach to overcoming these issues is the use of vaccines targeting multiple, unidentified antigens, such as those derived from the entire protein repertoire of autologous or allogeneic tumor cells, either administered directly or loaded onto dendritic cells. While these vaccines have given promising results in preclinical studies, clinical trials have yielded low response rates and only modest improvements in patient survival (Lin et al., 2022). One of the possible reasons for this limited efficacy is the presence of large quantities of non-immunogenic and tolerogenic self-antigens in tumor cells that can inhibit the immune system and dilute the immune response to the few immunogenic tumor antigens. Consequently, targeting selected tumor antigens may be more effective in eliciting anti-cancer immune responses. To this end, the selection of the appropriate antigen for vaccine development is crucial. To describe such an antigen, we previously introduced the term "oncoantigen", which refers to antigens that are either uniquely or predominantly expressed in cancer cells and are essential for their survival and proliferation. Targeting oncoantigens is a strategic approach, as their indispensable role in cancer cell viability reduces the risk of selecting antigen-loss variants, which would be markedly impaired in their tumorigenic potential (Lollini et al., 2006). Beyond the pivotal role in tumorigenesis, the ideal oncoantigen should avoid triggering autoimmune reactions upon vaccination; thus, its expression in normal tissues should be minimal or absent. Moreover, in the context of cancer prevention, an ideal oncoantigen should be expressed at the pre-neoplastic stage and retained in the eventual tumor. This would enable the immune system, once primed, to eliminate transformed cells, thereby preventing tumor development altogether (Calogero et al., 2008).

2.2. Tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs)

Tumor antigens have traditionally been classified into two main categories: tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs). TAAs are non-mutated self-proteins that are aberrantly expressed in tumor compared to normal cells, either due to overexpression (e.g., HER2, hTERT, MUC-1), re-expression of the so called "retired antigens" - cell lineage differentiation proteins poorly present in adult tissues (e.g., tyrosinase, gp100, MART-1, alpha-lactoglobulin) - or cancer germline antigens, which are normally expressed only in the placenta, germline cells, or during embryonic development, e.g.

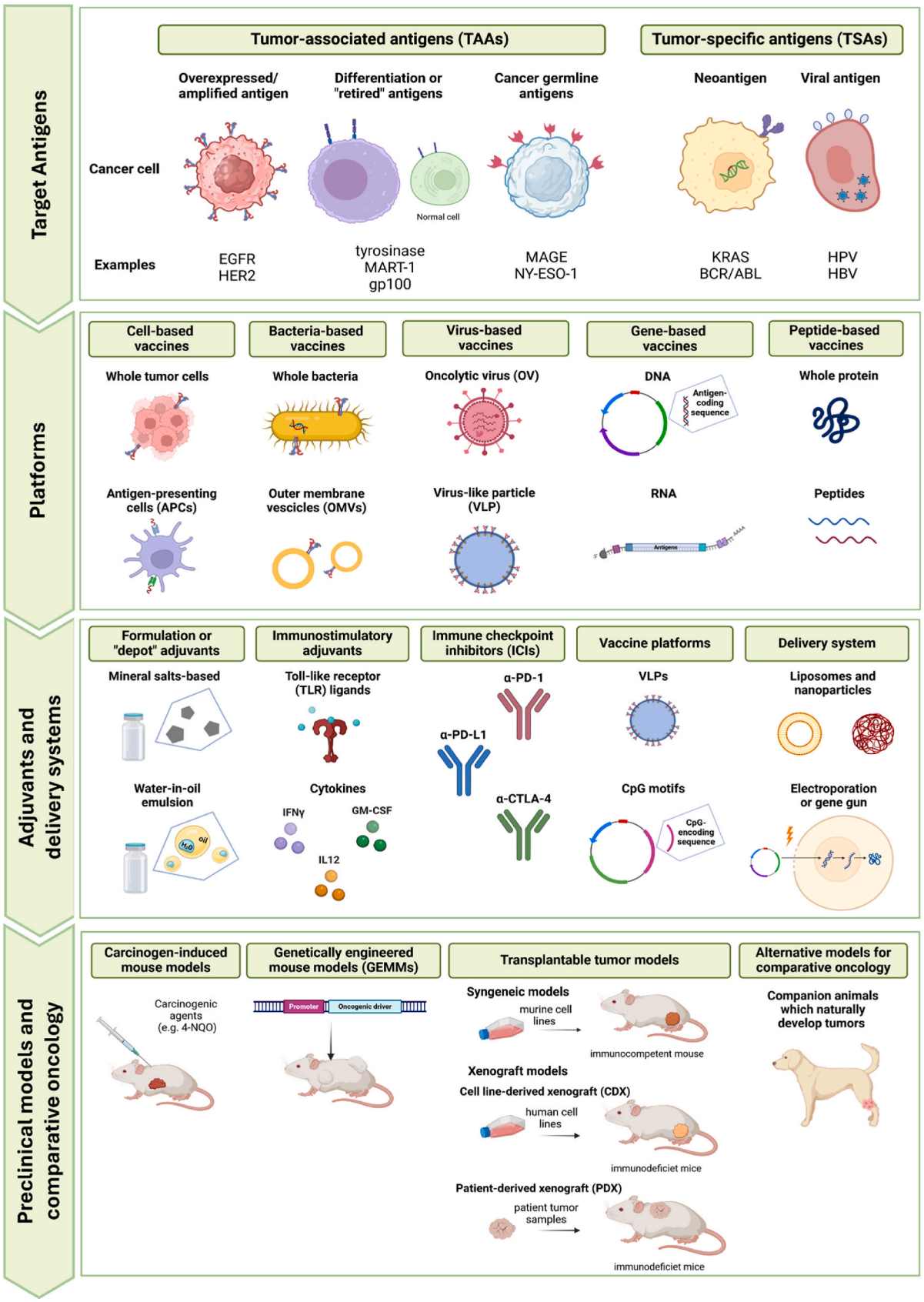

Fig. 1. Building a cancer vaccine. The development of a cancer vaccine includes several crucial steps: starting from the selection of the target antigens to optimizing platforms and delivery systems. Cancer vaccine efficacy is then evaluated in preclinical models, choosing the more representative one.

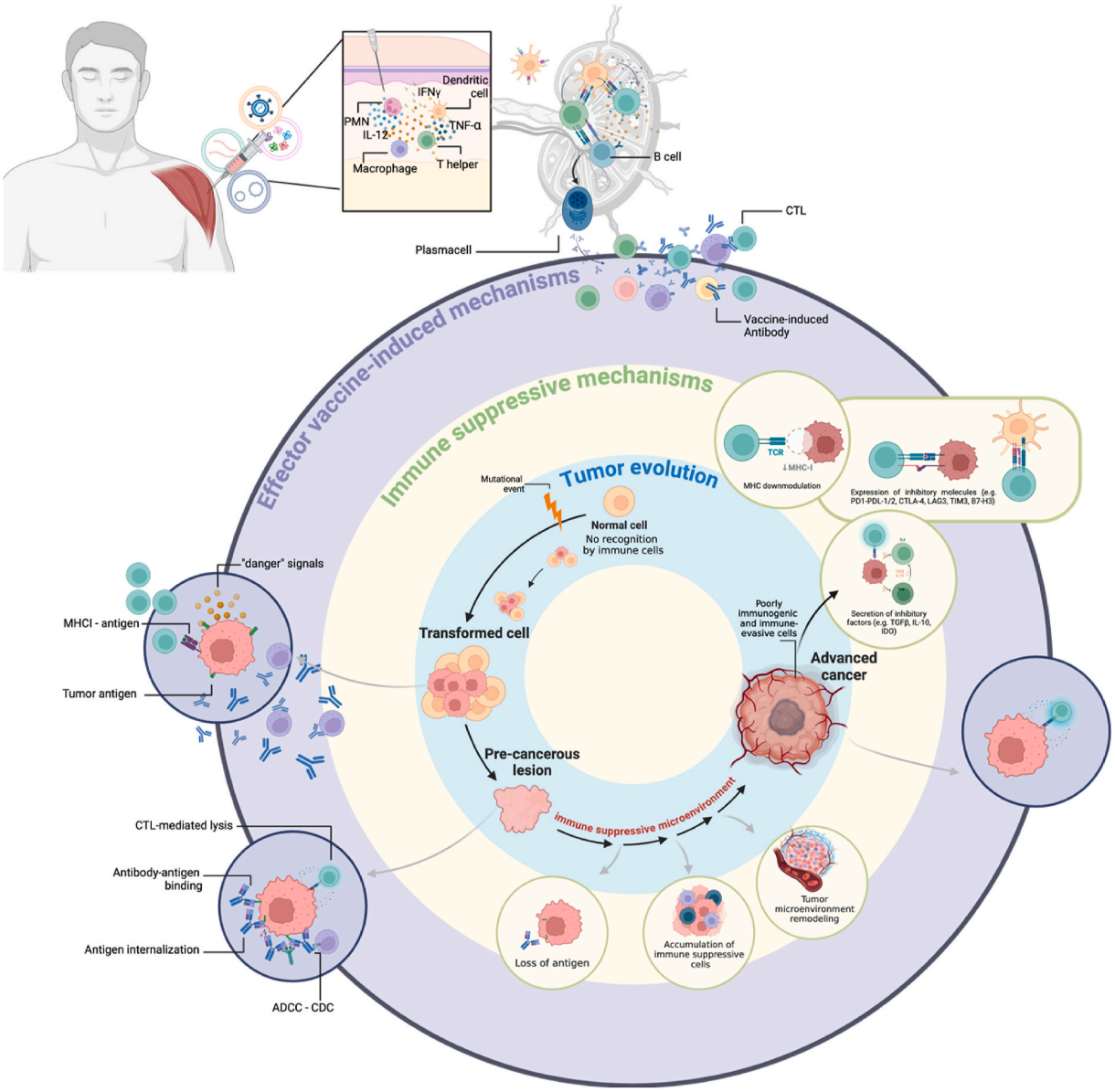

Fig. 2. Cancer vaccine: potential mechanisms of action. Inner circle: tumor evolution. Normal cells that develop sporadic mutations can be recognized by the innate and adaptive immune system that in concert destroy the nascent tumor (elimination phase). If the immune system fails, transformed tumor cells can proliferate to give rise to a pre-cancerous lesion. The progression into advanced tumors involves the interplay between tumor cells, normal healthy cells, and host defense mechanisms. Middle circle: immune suppressive mechanisms. As pre-malignant lesions progress into advanced tumors, cells progressively accumulate genetic mutations and acquire tumor-promoting characteristics; concurrently, the tumor microenvironment (TME) shifts from a tumor-suppressive state to one that supports tumor growth. These events result in immune evasion, supported by tumor antigen and/or MHC-I complex downmodulation, accumulation of immune-suppressive molecules and cells in the TME, and significant remodeling of tumor-stroma interactions. External circle: effector-vaccine-induced mechanisms. Cancer vaccines that deliver tumor antigens, in different formulations (i.e. DNA-, RNA-, peptide-, viral vector-based), are used to trigger a specific anti-cancer vaccine-induced humoral and cellular immunity. Preventive immunization in healthy people or those with pre-malignant lesions enables both antibodies and CTLs to efficiently activate their effector functions against cancer cells. In advanced stages, malignant cells become more resistant to immune attack, and the TME actively counteracts the intervention of the vaccine-induced immune response, limiting the effectiveness of anti-cancer vaccines at this stage.
ADCC, Antibody dependent cellular cytotoxicity; CDC, Complement dependent cytotoxicity; CTL, cytotoxic T cell lymphocyte.

members of the MAGE family, NY-ESO-1, PRAME, hTERT (Kong et al., 2019). In contrast, TSAs are exclusively expressed in tumor cells and include neoantigens generated by mutations or genetic alterations, and oncoviral antigens (Fig. 1). Each category presents unique advantages and challenges for vaccine development, as discussed hereafter.

As mentioned earlier, the introduction of vaccines targeting oncoviruses such as HBV and HPV has resulted in a significant reduction in the incidence of the cancers induced by these viruses. However, the unfortunate reality is that only a minority of cancer types are known to be caused by infectious agents. Therefore, other TSAs or TAAs must be identified to prevent or treat these cancers.

2.3. Off-the-shelf vaccines targeting TAAs for cancer therapy and prevention

TAAs were the first tumor antigens to be identified and tested in clinical trials, beginning in the early 1990s. TAAs are widely expressed across various cancer types, making them attractive targets for off-the-shelf immunotherapies. Numerous TAAs have been identified to date, and many have been evaluated as vaccination targets in patients with

advanced cancer or in the context of tertiary prevention. Most of these trials have shown promising results in terms of safety and immunogenicity, despite the non-tumor-specific nature of TAAs. Preclinical studies and clinical trials across different tumor types have demonstrated that high levels of TAA expression can break central and acquired T cell tolerance, reaching the threshold for T cell activation. A paradigmatic example in this context is HER2, a well-known oncoantigen in various cancer types (Cavallo et al., 2011), including breast cancer (Vinayak et al., 2024). However, in many cases, T cell responses are weak and often fail to correlate with clinical outcomes.

When tested in phase III clinical trials in patients with advanced disease, most TAA-based vaccines did not significantly improve patients' outcomes. As a result, to date, the US Food and Drug Administration (FDA) has approved only one vaccine for tumor therapy, sipuleucel-T (Provenge), which was licensed to treat individuals with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer in 2010 (Cheever and Higano, 2011; Kantoff et al., 2010). Sipuleucel-T consists of the patient's autologous peripheral blood mononuclear cells, including antigen-presenting cells (APCs), which are activated *ex vivo* with a proprietary recombinant fusion protein (PA2024) including the TAA prostatic acid phosphatase (PAP), which is overexpressed in about 95% of prostate cancers, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF). Real-world data show that when sipuleucel-T is administered to patients with castration-resistant metastatic prostate cancer in combination with androgen receptor-targeting agents (ARTAs), it reduces the risk of death by 28.3% compared to ARTAs alone (Hafron et al., 2022). Despite these encouraging results, no other vaccines have showed sufficient clinical efficacy to gain approval for use in patients.

These disappointing outcomes may be attributed to different features of late-stage cancers, including immune ignorance, exclusion, the induction of an immunosuppressive TME, and immune evasion, all of which impair the effector functions of the immune system (Saxena et al., 2021). Given these challenges, the application of TAA-based vaccines in the preventive setting - especially for primary prevention in individuals at high risk, or for cancer interception in subjects with pre-invasive disease - may offer greater potential. In these contexts, the vaccine is administered to a less immunosuppressed individual who has not undergone prior treatments such as chemotherapy, which may impair immune cell function, as is often the case in patients with advanced disease. Consequently, these individuals are more likely to mount an effective immune response. Therefore, vaccines targeting TAAs that are expressed in pre-neoplastic lesions and during the early stages of tumor development may be more effective targets for cancer prevention, a concept highlighted by Olivera J. Finn over 20 years ago (Finn, 2003).

One of the TAAs whose immunotargeting may induce protective immune responses in preventive settings is mucin (MUC)-1, a transmembrane glycoprotein overexpressed in several cancer types, including lung and colon cancers, and already present in premalignant lesions (Saltos et al., 2018). As tumors express aberrantly glycosylated, tumor-specific forms of MUC-1 (Ma et al., 2019; Stanton et al., 2024) that may evade immune tolerance, several vaccines targeting MUC-1 have been developed and successfully tested in preclinical trials. These promising preclinical results have paved the way for the translation of anti-MUC-1 vaccination into the prevention of colon cancer in high risk populations with a recent history of colonic polyps or adenomas (NCT02134925) (Beatty et al., 2010; Finn, 2021; Murwanti et al., 2023; Schoen et al., 2023). A phase I clinical trial demonstrated the safety of a MUC-1 peptide vaccine, which induced a specific immune response in subjects with a low basal frequency of myeloid-derived suppressor cells (MDSCs) (Kimura et al., 2013). A subsequent phase II trial confirmed that the vaccine significantly reduced adenoma recurrence in individuals who mounted an antibody response against MUC-1 (approximatively 25% of vaccinated subjects), and exhibited significantly lower levels of MDSCs and serum interleukin (IL)-6 compared to non-responders (Schoen et al., 2023). These findings demonstrate the feasibility of targeting TAAs in preventive settings, although they also suggest that preventive vaccines may benefit from the association with immunomodulatory drugs when administered in patients with premalignant disease. Since MUC-1 is expressed by many other tumors and their premalignant lesions, additional preventive vaccine trials are being considered, including MUC-1 vaccination in current and former smokers at high risk for lung cancer. The aim is to stimulate the immune system to slow or halt the progression from normal to pre-cancer and cancer cells (NCT03300817) (Finn et al., 2023).

2.4. Targeting cancer stem cells

Another promising category of TAAs for cancer prevention includes those expressed not only in differentiated cancer cells but also in cancer stem cells (CSCs) or cancer initiating cells - cells with self-renewal potential, pluripotency and drug resistance, which are responsible for tumor onset and metastases (Quaglino et al., 2020). Targeting CSC antigens could lead to the early elimination of these cells, preventing tumor initiation or metastasis (Chu et al., 2024). In this context, we have previously identified antigens expressed by breast CSCs, such as Cripto-1 (Witt et al., 2018) and the cysteine-glutamate antiporter xCT (Lanzardo et al., 2016), which are expressed in early lesions and maintained in invasive breast cancer. Various vaccines targeting these antigens have been developed, and preclinical analyses have shown that vaccination significantly inhibits metastasis formation, supporting the idea that immunotherapies directed against CSCs could contribute to cancer prevention (Bolli et al., 2018; Donofrio et al., 2018; Lanzardo et al., 2016; Rolih et al., 2020; Ruiu et al., 2019; Witt et al., 2018), thus opening up new ways for preventive vaccination.

2.5. Hereditary tumors

TAA-based vaccination also represents a promising strategy for preventing tumor onset in patients genetically predisposed to cancer, such as those with Lynch syndrome. These patients show a high lifetime risk of developing colorectal, endometrial, ovarian, or gastric cancers due to inherited mutations/alterations in mismatch repair genes (MSH2, MLH1, MSH6, PMS2), which lead to high genome instability. Extensive genomic analyses have identified TAAs commonly overexpressed in tumors from patients with Lynch syndrome, many of which have been used for the development of vaccines tested in clinical trials for primary cancer prevention in this population. For example, an ongoing clinical trial is evaluating the efficacy of a vaccine targeting three TAAs - Carcinoembryonic antigen (CEA), MUC-1 and brachyury - administered in combination with IL-15 in Lynch syndrome carriers (NCT05419011). Similar approaches are being evaluated in individuals carrying BRCA1/2 mutations, who have a high risk for developing breast and ovarian cancers. A DNA vaccine targeting the TAA human telomerase reverse transcriptase (hTERT), a protein normally expressed during embryogenesis and reactivated as a primary mechanism of cell immortalization, is under investigation. This vaccine, which also targets two additional TAAs (Prostate-specific membrane antigen and WNT1), with or without IL-12 administration, is being evaluated for its ability to prevent tumor onset in BRCA1/2-mutated subjects (NCT04367675). The immunogenicity of hTERT targeting vaccines has been demonstrated in several clinical trials involving patients with advanced tumors or in the adjuvant setting, although their anticancer efficacy was limited, and the vaccination did not control tumor growth or disease progression (Gridelli et al., 2020; Vienot et al., 2023; Zanetti, 2017). The results from ongoing preventive vaccination trials will help determine whether hTERT immunotargeting is effective in less immunosuppressed individuals.

Overall, results from these clinical trials are expected to clarify soon whether TAA-based vaccines are a viable strategy for cancer prevention and whether they can improve the outcomes for individuals at high risk of developing cancer.

2.6. Personalized vaccines targeting TSAs

In addition to TAAs, neoantigens - novel protein sequences not present in normal cells, generated by tumor mutations and genetic alterations - have recently caught attention from oncologists and immunologists. Neoantigens are highly specific to cancer cells, making them an ideal target for vaccines. Their ability to be recognized as non-self by the immune system enables a robust anti-tumor response with minimal risk of autoimmunity. Large-scale sequencing studies have identified single nucleotide variation (SNV)-derived neoantigens in various human cancers, and these are the targets of most anti-cancer vaccines currently being tested in clinical trials (Hu et al., 2024b). However, fewer than 1% of SNVs are immunogenic, limiting the efficacy of vaccination strategies based solely on this approach. This evidence has led to the exploration of alternative neoantigen sources, such as those generated by genomic rearrangements, including DNA insertions and deletions that cause frameshifts. These frameshifts lead to the production of high quantities of neoantigenic peptides capable of inducing specific T cell activation (Turajlic et al., 2017). Gene fusions are another promising source, as they can generate highly immunogenic neoantigens capable of triggering T cell responses. Analysis of TCGA samples across different cancer types revealed that, in approximatively one-third of tumors, the most immunogenic neoepitopes were fusion-derived, highlighting their potential for personalized cancer vaccines (Wei et al., 2019). Recent advances in cancer antigen discovery have uncovered new classes of neoantigens that may represent significant targets in tumors with low mutational burden. These include neoantigens derived from transposable elements (Bonte et al., 2022; Kong et al., 2019), alternative splicing variants such as those produced by exitron (exonic intron) splicing, which increase proteome diversity by creating cryptic introns within protein-coding exons (Wang et al., 2021), and post-translational modifications (Kacen et al., 2023). These neoantigens display greater diversity compared to self-antigens, potentially making them more immunogenic than SNV-derived antigens. However, research in this area is still in its early stages, and the prevalence of these antigens across different cancer types has yet to be fully characterized (Xie et al., 2023a).

The identification of neoantigens typically requires the use of omic technologies to analyze a patient's tumor sample. Consequently, neoantigens have primarily been used to develop personalized vaccines for therapy or tertiary prevention, while their application in primary prevention remains limited. Most vaccines tested to date have combined multiple neoepitopes to increase the probability of inducing immunodominant targets and to address tumor heterogeneity and immune escape mechanisms (Xie et al., 2023a). Several phase I/II clinical trials have demonstrated the safety and immunogenicity of neoantigen-based vaccines, with some showing clinical efficacy in tertiary prevention. As most of these trials have been extensively reviewed elsewhere (Biswas et al., 2023b; Chakraborty et al., 2024; Manoutcharian and Gevorkian, 2024; Xie et al., 2023a), we will only provide some examples. In advanced hepatocellular carcinoma, a phase I/II study of a personalized DNA plasmid-based vaccine encoding 40 tumor antigens, combined with pembrolizumab, showed an objective response rate of 30.6%, compared to 17.0% for pembrolizumab alone (NCT04251117) (Yarchoan et al., 2024). In the phase Ib NCT03558945 trial, personalized neoantigen peptide-based vaccines administered to patients with pancreatic ductal adenocarcinoma following tumor resection yielded a 3-year overall survival rate of 74% (Hu et al., 2024a), indicating the potential of this approach for tertiary prevention. Similarly, the Phase 2b KEYNOTE-942 trial, which tested the efficacy of the personalized mRNA-4157-P201 vaccine developed by Moderna - comprising a long mRNA encoding 9 to 34 neoantigens - in combination with pembrolizumab as adjuvant therapy for high-risk melanoma patients, reduced the risk of disease recurrence by 44% at 18 months (Weber et al., 2024). These promising results led the FDA to grant Breakthrough Therapy Designation to this immunotherapy for the adjuvant treatment of high-risk melanoma following complete resection, sparking the phase III NCT05933577 clinical trial. However, no results from this trial or other ongoing phase III trials are currently available.

It remains to be seen whether neoantigen-based personalized vaccines will outperform TAA-targeted vaccines in tertiary prevention. In therapeutic settings for advanced metastatic cancer, neoantigen-based vaccines have shown limited success. While phase I or II clinical trials have demonstrated the induction of specific T cell responses in patients with advanced disease, tumor regression or long-term survival benefits have been rare (Fan et al., 2023).

2.7. Vaccines targeting shared neoantigens for cancer prevention

A strategy to overcome the challenges associated with the design and production of neoantigen vaccines – such as high costs, long development times, and their personalized nature - is the development of less individualized neoantigen vaccines, which could also be used for primary prevention. One promising approach is to target shared neoantigens arising from common oncogenic driver mutations, such as those in oncogenes or tumor suppressors like KRAS, TP53, and BRAF. These neoantigens, matched appropriately with the patient's human leukocyte antigen (HLA) alleles, could form the basis for other off-the-shelf vaccines. Notably, neoantigens derived from driver mutations are theoretically more likely than those from non-driver mutations to function as oncoantigens. By vaccinating against such oncoantigens, it may be possible to prevent the emergence of antigen-loss variants, leading to effective cancer prevention and treatment (van Dorst et al., 2024). However, clinical trials targeting shared neoantigens have produced mixed results thus far. For example, a phase I trial testing a $KRAS^{G12D}$ mRNA vaccine in patients with metastatic gastrointestinal cancer showed no clinical benefit (Cafri et al., 2020). In contrast, the phase I AMPLIFY-201 trial, which administered a modified peptide vaccine to pancreatic and colorectal cancer patients bearing minimal residual disease, demonstrated that T cell responses correlated with improved relapse-free survival (Pant et al., 2024). Despite the varying outcomes, this strategy could open new ways for the primary prevention of cancer in individuals with high-risk conditions. For instance, a long peptide vaccine targeting multiple KRAS mutations is currently under evaluation (NCT05013216) for cancer prevention in patients at high risk of developing pancreatic cancer due to family history or germline mutations (Haldar et al., 2023). Preclinical studies suggest that a similar approach may also be successful in preventing lung cancer in heavy smokers (Wang et al., 2024).

In addition to driver mutations and oncoviral antigens, other TSAs have recently emerged as putative targets for preventive vaccine development. Extensive sequencing of tumors from patients with Lynch syndrome have revealed recurrent microsatellite mutations that are shared among most patients (Bolivar et al., 2024; Leoni et al., 2020). As discussed by Bolivar A et al. (Bolivar et al., 2023), a genetic vaccine incorporating 209 neoepitopes identified from these mutations has been developed by Nouscom, the sponsor of a currently undergoing a phase I/II clinical trial to assess its potential for cancer prevention in Lynch syndrome patients (NCT05078866).

In the coming years, we expect to see more robust data on the feasibility and efficacy of vaccines for cancer prevention, offering deeper insights into the features of antigens that will be essential for future vaccine development. These advances, combined with ongoing improvements in computational methods and bioinformatics pipelines – especially in neoepitope identification and HLA haplotyping – are likely to accelerate the clinical application of cancer vaccines.

3. Platforms and technologies in cancer vaccine development

A major challenge in developing cancer vaccines is the efficient delivery of antigens to stimulate a potent immune response. Choosing the appropriate platform for cancer vaccines requires careful consideration

of various factors, including the components – antigens and adjuvants - and the delivery systems used.

Based on preparation methods, cancer vaccine platforms can be divided into four principal categories: cell-based, virus/bacteria-based, gene-based, and peptide-based vaccines (Fan et al., 2023; Lopes et al., 2019) (Fig. 1).

3.1. Cell-based vaccines

One of the earliest approaches for developing anti-cancer vaccines involves the use of cell-based technologies. These vaccines leverage whole cells, often derived from a patient's tumor, or immune cells (Fan et al., 2023; Perez-Banos et al., 2023). Cell-based vaccines can be classified into two main types: direct-use, whole-tumor cell vaccines, where tumor cells are directly injected into patients, and antigen-presenting cell (APC)-mediated vaccines, where autologous APCs (commonly dendritic cells; DCs) are loaded with tumor cells or their components before administration. In both cases, cells can be genetically modified to express additional antigens and secrete cytokines or other immune-stimulating factors to increase their efficacy (Perez-Banos et al., 2023; Zhang et al., 2023b).

3.2. Whole tumor cell vaccines

Whole tumor cell (WTC) vaccines, which use either entire "attenuated" tumor cells or lysed tumor cells, are designed to stimulate an immune response against cancer by delivering a broad array of tumor antigens capable of stimulating both CD8 and CD4 T cells (Perez-Banos et al., 2023). These vaccines can be created using the patient's own tumor cells (autologous vaccines) or tumor cells derived from other individuals or cell lines (allogeneic vaccines). By providing specific antigens tailored to the individual cancer, autologous vaccines reduce the risk of immune rejection. However, they are labor-intensive and time-consuming to produce, making them less suitable for patients needing immediate treatment. Additionally, they may induce immune tolerance to dominant antigens, potentially weakening the immune response (Perez-Banos et al., 2023). In contrast, allogeneic vaccines offer quicker production times and broader applicability, although carrying a higher risk of immune rejection (Perez-Banos et al., 2023).

To ensure clinical safety, tumor cells used in WTC vaccines are attenuated to prevent replication. However, this often results in reduced immunogenicity that can be compensated by co-expression of immunostimulatory molecules or through combinatory strategies with other immune-enhancing agents (Chiang et al., 2010). However, clinical trials of WTC vaccines have shown limited success and further research is needed to improve their efficacy as a cancer treatment (Dillman et al., 2018; Faries et al., 2017; Srivatsan et al., 2014). Several factors likely contribute to their limited clinical effectiveness, including suboptimal activation of DCs, which are crucial for inducing a protective CD8 T cell response. Additionally, the biological variability among patient-derived cells used in vaccine preparation has likely contributed to the inconsistent outcomes (Perez-Banos et al., 2023). To address these challenges, various strategies are under investigation, including improving immunologic danger signals, enhancing adjuvants, and optimizing antigen delivery to DCs (Meng et al., 2023; Zhang et al., 2023b).

3.3. Antigen-presenting cells-mediated vaccines

To address the challenge of suboptimal antigen presentation, DCs can be pulsed with tumor antigens or tumor cell lysates. DC-based vaccines are typically created by isolating DC precursors from the patient's blood, culturing and maturing them in a laboratory setting, and then injecting them back into the patient. Once in the body, these cells interact with T cells in the lymph nodes, presenting the tumor antigens they were pulsed with, and potentially triggering a targeted immune response against the cancer cells (Lee et al., 2023b; Najafi and Mortezaee, 2023).

The first demonstration of the efficacy of autologous DC-based vaccines pulsed with tumor antigens in inducing antigen-specific immune responses occurred in 1996 in a clinical trial in patients suffering from B-cell lymphoma (Hsu et al., 1996). Since then, DC-based vaccines have been explored in a wide variety of cancers, including melanoma, prostate cancer, glioblastoma, leukemia, and breast cancer (Gautam et al., 2024; Liau et al., 2023; Najafi and Mortezaee, 2023; Sprooten et al., 2019; Yu et al., 2022).

While sipuleucel-T, as mentioned earlier, remains the only FDA-approved DC-based vaccine, advancements in APC-based vaccine technology and combinatory administration strategies are currently being evaluated to further enhance their therapeutic potential (Perez and De Palma, 2019; Yu et al., 2022).

3.4. Bacteria-based vaccines

Bacteria-based vaccines, traditionally developed to prevent infectious diseases, have recently emerged as innovative platforms for eliciting anti-cancer immune responses. A notable example is *Bacillus Calmette-Guérin (BCG)*. BCG, initially developed as a vaccine against tuberculosis, is now an attenuated bacteria-based immunotherapy (*Mycobacterium bovis*) approved for the treatment of non-muscle invasive bladder cancer (Cardillo et al., 2021; Sylvester et al., 2002).

In the late 19th century, William B. Coley pioneered the use of bacteria for cancer immunotherapy (Coley, 1898). Since then, several bacteria were reported to specifically colonize tumors and trigger immune responses (Zheng et al., 2017; Zhou et al., 2023). In addition, bacteria and their derivatives contain a variety of pathogen-associated molecular patterns (PAMPs) that can trigger immune responses (Yaghoubi et al., 2020). Bacteria can also be easily modified and loaded with tumor antigens (Chen et al., 2024). These characteristics make bacteria a promising platform for anti-cancer vaccine strategies (Derre et al., 2017). Furthermore, incorporation of tumor antigens into bacterial outer membrane vesicles (OMVs) that can be recognized by the host immune system represents another promising platform for cancer vaccines (Caproni et al., 2023; Cheng et al., 2021; Tamburini et al., 2023; Wang et al., 2022).

However, despite their potential, the clinical translation of bacteria-based immunotherapy is currently limited due to biosafety concerns and the lack of standardized production processes (Zhou et al., 2023).

3.5. Virus-based vaccines

Like bacteria-based vaccines, virus-based vaccines were originally developed to prevent infectious diseases. Due to their versatility and ability to be engineered, these vaccines can be modified to express tumor antigens, allowing for their application as both preventive and therapeutic cancer vaccines. The most notable examples in this context are *talimogene laherparepvec* (T-VEC, Imlygic) and the already mentioned virus-like particle (VLP)-based vaccines against HBV and HPV.

T-VEC, a genetically modified oncolytic herpes simplex virus type 1 encoding GM-CSF, was approved by the FDA for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery (Andtbacka et al., 2015; Pol et al., 2016). Oncolytic viruses (OVs) preferentially infect and destroy tumor cells and tumor-associated endothelial cells (Guo et al., 2008; Nemunaitis, 1999). Once the infected tumor cells undergo oncolysis, they release new infectious viral particles along with tumor antigens, contributing to the elimination of residual tumor cells. However, this process sometimes fails to elicit a robust, tumor-specific T-cell response. One strategy to address this issue and enhance T-cell priming efficiency is to genetically modify oncolytic viruses to encode tumor antigens and co-stimulatory factors (Bartlett et al., 2013; Lichty et al., 2014; Vannini et al., 2023).

While clinical trials of OVs as standalone therapies have yielded

controversial results across different cancer types, their efficacy can be improved when used in combination with other therapies or as adjuvant platforms (Roy et al., 2021; Yun et al., 2022). Challenges in OV-based vaccine development include inefficient tumor delivery, limited viral replication in tumor cells, and difficulty in targeting micro-metastases, often requiring combination with conventional treatments to reduce tumor burden (Bartlett et al., 2013; Guo et al., 2019; Yun et al., 2022).

VLP-based vaccines, which have been successful in preventing HBV and HPV infections and their associated cancers, have demonstrated remarkable efficacy as prophylactic cancer vaccines (Tornesello et al., 2022). VLPs are multimeric, self-assembled protein structures that mimic viruses but lack the viral genetic material, making them non-infectious and non-replicative. Their resemblance to native viral capsids enables them to present tumor antigens in a highly immunogenic format, thereby efficiently stimulating the immune system (Caldeira et al., 2020; Mohsen and Bachmann, 2022; Sander and Lollini, 2018). As previously mentioned, VLP-based vaccines have been particularly effective in preventing cancers related to HBV and HPV, such as hepatocellular carcinoma and cervical cancer, respectively (Cuzick, 2015; Harper et al., 2004; Zhou et al., 1991; zur Hausen, 2002). Despite their efficacy in preventing infection and inducing neutralizing antibodies, these vaccines are less effective in treating individuals who are already infected. As a result, research is ongoing to develop therapeutic vaccines for HPV-related cancers (Mo et al., 2022; Skolnik and Morrow, 2023).

VLP platforms are also under investigation to develop both prophylactic and therapeutic cancer vaccines targeting several types of cancer (Ruzzi et al., 2023; Tornesello et al., 2022), including breast cancer and melanoma (Arab et al., 2022; Mohsen et al., 2022; Ruzzi et al., 2022, 2023). Clinical trials focusing on melanoma have produced encouraging results, highlighting the potential of VLP-vaccines to stimulate robust anti-tumor immune responses (Milhem et al., 2020; Mohsen et al., 2020; Speiser et al., 2010).

VLPs are particularly appealing as platforms for cancer vaccine due to their intrinsic adjuvant properties, linked to the size and shape features. However, careful evaluation of potential side effects, such as allergic reactions or excessive immune responses, is essential. Additional concerns include pre-existing immunity against the vaccine carrier proteins and the risk posed by unconjugated self-antigen that could bind to healthy cells, leading to unintended consequences (Caldeira et al., 2020; Jegerlehner et al., 2010; Ronzitti et al., 2020).

3.6. Gene-based vaccines

Gene-based or nucleic acid-based vaccines exploit DNA or RNA to deliver the genetic instructions for producing selected antigens. Early developments in gene-based vaccines primarily focused on DNA due to its greater stability and longer persistence in the body compared to RNA (Fan et al., 2023; Kaczmarek et al., 2023). However, following the success of RNA vaccines against COVID-19, RNA has become widely studied as a platform for cancer vaccine development (Guasp et al., 2024).

3.7. DNA vaccines

DNA vaccines utilize bacterial plasmids engineered to encode antigens and immunostimulatory molecules (Fioretti et al., 2010; Lopes et al., 2019; Yang et al., 2014). One advantage of plasmids is their intrinsic adjuvanticity, which can be further enhanced by incorporating sequences of immunostimulatory factors or by employing a specialized delivery system (Yang et al., 2014).

Originally developed and efficiently used to prevent infectious diseases (Ulmer et al., 1993; Yankauckas et al., 1993), DNA vaccines have since been adapted to produce tumor antigens (Yang et al., 2014). For antigen transcription to occur, DNA plasmids must enter the cell nucleus, a process optimized through delivery strategies such as *in vivo* electroporation and gene guns (Paston et al., 2021). The encoded antigens can be presented via major histocompatibility complex (MHC) class I and II pathways, activating CD4 and CD8 T cell responses, as well as establishing immunological memory (Lopes et al., 2019; Tang and Pietersz, 2009; Yang et al., 2014).

Preclinical animal studies have demonstrated that DNA cancer vaccines can elicit immune responses with both preventive and therapeutic effects across various cancer models (Lopes et al., 2017, 2019; Pandya et al., 2023; Quaglino et al., 2004, 2011; Riccardo et al., 2022; Srinivasan and Wolchok, 2004; Tarone et al., 2023). As better discussed in the "*alternative models*" section below, recombinant Listeria monocytogenes-based vaccines may represent a valid approach. However, while human clinical trials have reported good safety profiles, they have shown low immunogenicity and limited therapeutic success (Disis et al., 2023; Lopes et al., 2019).

3.8. RNA vaccines

RNA-based cancer vaccines typically use *in vitro* transcription (IVT) to synthesize RNA from plasmid DNA templates in a cell-free system. RNA is then encapsulated within a delivery system to protect it from degradation. Unlike DNA, which must reach the cell nucleus, RNA only needs to enter the cytoplasm for translation into proteins, resulting in faster and more efficient antigen production (Guasp et al., 2024; Pardi et al., 2018).

RNA has proven to be a very flexible platform, able of encoding multiple proteins simultaneously, with the added benefit of optimized RNA stability and ease of production at scale (Guasp et al., 2024; Wang et al., 2023). The rapid development and global deployment of COVID-19 RNA vaccines further demonstrated the scalability and adaptability of this technology (Thomas et al., 2021; Zhang et al., 2023a).

One of the key advantages of RNA vaccines is their safety profile. Because RNA lacks infectious and integrating capabilities, it degrades naturally through physiological cellular processes, preventing prolonged immune hyperstimulation (Pardi et al., 2018). However, as observed with COVID-19 RNA vaccines, repeated immunizations may be required to induce strong B-cell responses and long-lasting immune memory (Lee et al., 2023a). This is a crucial aspect in the development of RNA vaccines for the treatment of cancer, where the immune system needs to be sufficiently activated to target and eliminate tumors that have escaped immune surveillance. In addition, sustaining an immune response over time is crucial to prevent tumor recurrence and metastasis (Fan et al., 2023). Thus, achieving a balance between immunogenicity and safety in this context will be a key objective.

Numerous clinical trials are underway, exploring the potential of RNA vaccines for various cancer types (Guasp et al., 2024; Sayour et al., 2024). However, currently there are no FDA-approved RNA vaccines for cancer treatment.

3.9. Peptide-based vaccines

Peptide-based cancer vaccines typically consist of epitopes derived from tumor antigens, selected for their immunogenicity and compatibility with HLA alleles. These properties are measured and predicted through several methods (Liu et al., 2021). The length of peptides used plays a crucial role in eliciting an immune response. Short peptides (8–11 amino acids) bind to MHC class I molecules, are easy to synthesize, and are cost-effective, but they may not fully activate T cells due to their capture by non-professional APCs. Additionally, they are HLA-restricted, limiting their use to specific patient populations, and they can be degraded rapidly. In contrast, synthetic long peptides (SLPs) (11–30 amino acids) require processing by professional APCs and can be presented on both MHC class I and II molecules, leading to the activation of both CD8 cytotoxic T cells and CD4 helper T cells, which enhances immune responses. Moreover, SLPs can be modified to improve immunogenicity (Buonaguro and Tagliamonte, 2023; Rabu et al., 2019).

Peptide-based cancer vaccines have shown promising immunogenicity in preclinical studies. However, further progress is needed to improve their clinical effectiveness (e.g., enhancing amino acids stability *in vivo* and selecting appropriate adjuvants) (Abd-Aziz and Poh, 2022; Liu et al., 2021; Stephens et al., 2021). Currently, no peptide-based cancer vaccine has received FDA-approval. However, therapeutic vaccines targeting melanoma, lung cancer, breast cancer, and leukemia are in phase I and II clinical trials, with HER2-positive breast cancer vaccines advancing to phase III (Liu et al., 2021; Swain et al., 2023; You et al., 2021).

4. Strategies to improve cancer vaccine efficacy: adjuvants, delivery systems, and combinatorial approaches

Vaccine efficacy can be reduced by the immunosuppressive tumor microenvironment, which impairs effector T cell activity, or by down-regulated antigen presentation to T cells (Saxena et al., 2021; Zhao et al., 2023). The term "adjuvant" comes from the Latin word "*adjuvare*", which means "to help." Therefore, one of the simplest ways to enhance vaccine immunogenicity is through the appropriate selection of adjuvants. The choice of adjuvants must be optimized for each vaccine formulation to attract immune cells to the injection site and to break immune tolerance, ensuring maximum immune responses and, consequently, clinical efficacy (Cuzzubbo et al., 2020; Marriott et al., 2023; Temizoz et al., 2016) (Fig. 1). Traditional adjuvants, widely used in several licensed vaccines, include both formulation (or “depot”) adjuvants and biological immunostimulatory adjuvants (Cuzzubbo et al., 2020; Zhao et al., 2023). Depot adjuvants, such as mineral salt (alum) and emulsions (e.g., MF59 or AddaVax), are often used in licensed vaccines (Ren et al., 2024; Temizoz et al., 2016; Zhao et al., 2023). Incomplete Freund’s adjuvant and Montanide (ISA 720 or ISA 51) are examples of water-in-oil emulsions frequently used in clinical trials. These emulsions form a depot at the injection site, capturing the antigen and preventing its rapid trafficking to local lymph nodes, thereby inducing inflammation and a gradual release of the antigen, which elicits both CD4 and CD8 T cell responses (Kenter et al., 2009; Paston et al., 2021; Zhao et al., 2023).

Biological immunostimulatory adjuvants exploit the intrinsic properties of cytokines (e.g. INFα, IFNγ, IL2, IL12 or GM-CSF) and toll-like receptor (TLR) ligands to enhance vaccine efficacy. A widely used immunostimulatory adjuvant is GM-CSF, a cytokine that stimulates the bone marrow to produce granulocytes and macrophages, which are released into the bloodstream (Tay et al., 2017; Zhao et al., 2018). In preclinical studies, GM-CSF showed promise by recruiting DCs to the injection site, promoting their maturation, and facilitating antigen presentation. However, clinical trial results have been inconsistent (Cuzzubbo et al., 2020; Parmiani et al., 2007).

Immune checkpoint inhibitors (ICIs), such as antibodies targeting programmed cell death protein-1 (PD-1), its ligand (PDL-1), or cytotoxic T-lymphocyte antigen-4 (CTLA-4), can also function as adjuvants when administered concurrently with cancer vaccines. ICIs enhance T cell responses, reduce the influence of immune suppressive cells, and counteract tumor immune evasion (Batista-Duharte et al., 2022; Cuzzubbo et al., 2020; Soares et al., 2015).

Some vaccine platforms, such as DNA plasmids containing CpG motifs (which act as TRL9 agonists) or VLPs with geometrical structures conducive to a strong B cell response, possess intrinsic adjuvant properties (Zhao et al., 2023). Nevertheless, combined strategies - using a traditional adjuvant alongside a platform with intrinsic adjuvanticity - may be necessary to maximize the therapeutic efficacy of cancer vaccines (Ruzzi et al., 2022).

Some vaccine delivery systems, such as electroporation, can also be considered as adjuvants, as they enhance cellular uptake. Electroporation, by creating transient pores in cell membranes, can increase DNA uptake by up to 1000-fold, while also inducing an adjuvant effect through local tissue damage and the stimulation of proinflammatory cytokines (Paston et al., 2021; van Drunen Littel-van den Hurk and Hannaman, 2010). However, patient compliance may be a concern with this approach (Aurisicchio and Ciliberto, 2012; Baryakova et al., 2023).

Combining a delivery system with an immunostimulant adjuvant is a common strategy to enhance cancer vaccine efficacy (Marriott et al., 2023). For instance, combining Montanide (for its depot effect) with a TLR ligand (to enhance APC stimulation) is a widely used approach in anti-cancer vaccines (Cuzzubbo et al., 2020). However, this approach should be carefully evaluated since TLR activation may also exert detrimental effects in some cancer types (Di Lorenzo et al., 2022). Additionally, combining cancer vaccines with other therapeutic modalities employed in clinical practice offers a promising strategy to enhance vaccine effectiveness. Approaches such as reducing regulatory T cells with chemotherapeutic agents, incorporating radiotherapy, or using ICIs can improve vaccine efficacy by targeting different aspects of the immune response and tumor microenvironment, potentially leading to better clinical outcomes (Cuzzubbo et al., 2020; Ghiringhelli et al., 2007; Golden et al., 2012; Reits et al., 2006; Saxena et al., 2021).

5. Preclinical models for anti-cancer vaccination studies

Building upon the advances in vaccine design and immunotherapeutic strategies discussed above, a critical step in cancer vaccine development is their preclinical evaluation phase. This stage involves testing the efficacy and safety of vaccines in controlled laboratory settings. A major challenge is identifying predictive preclinical models that accurately mimic human cancer biology and immune responses to ensure successful translation of research findings into clinical practice. The significance of preclinical models for cancer prevention has been underscored by the National Cancer Institute (NCI), which launched the PREVENT program to support the testing of innovative strategies in preclinical models, with a high translational potential for clinical trials.

To address the complexity of cancer and its interaction with the immune system, various *in vivo* preclinical mouse models have been extensively used (Bosenberg et al., 2023; Le Magnen et al., 2016; Palladini et al., 2018) (Fig. 1). Each model offers distinct advantages depending on the specific oncological questions, such as modeling tumor immune evasion, testing vaccine-induced immunity, or assessing the therapeutic potential of vaccine-adjuvant combination.

Although initially most anti-cancer vaccine trials have focused on established or late-stage tumors, these conditions often present thorny challenges. Advanced tumors typically create an immunosuppressive microenvironment that shackles the immune system’s ability to respond effectively to the vaccine (Labani-Motlagh et al., 2020; Liu et al., 2023; Xie et al., 2023b). This immunosuppressive soil poses a significant barrier to therapeutic success, contributing to the limited efficacy observed in human clinical trials. Shifting the focus of vaccination strategies to preventive or early-stage settings, either before malignancy develops or during the onset of pre-invasive disease, could enhance vaccine efficacy by acting in a less immunosuppressive environment (Domchek and Vonderheide, 2024; Finn, 2018; Stanton et al., 2024). This approach underscores the importance of developing and utilizing preclinical models that can simulate early cancer development and immune interception. In this context, mouse models that spontaneously develop tumors in an immunocompetent system offer significant potential for advancing preventive strategies. These models are designed to mimic spontaneous tumorigenesis, either through carcinogens exposure or genetic engineering, by inducing specific somatic mutations that activate oncogenes or deactivate tumor suppressors, or by inducing the overexpression of oncogenes or the loss of tumor suppressor expression.

5.1. Carcinogen-induced mouse models

Carcinogen-induced mouse models are valuable tools for studying cancer development and prevention. These models are created by exposing mice to cancer-causing agents, such as chemicals or biological toxins, to simulate the processes of tumor initiation, promotion, and

progression in humans. They mimic spontaneous tumor formation, making them particularly useful for investigating therapeutic interventions and immune mechanisms involved in cancer development (Bareham et al., 2021). For example, 4-nitroquinoline 1-oxide (4-NQO) -induced cancer mouse models have been instrumental in advancing head and neck cancer prevention efforts by revealing critical insights into oral carcinogenesis. Transcriptomic analysis of these models has identified key genes associated with the transition from oral dysplasia to invasive cancer, leading to the development of vaccines targeting non-canonical peptides overexpressed during this process (Foy et al., 2016).

Despite their contributions to understanding immune surveillance and immune editing mechanisms, carcinogenesis models do have limitations. The use of carcinogens can result in extensive DNA damage, leading to the accumulation of somatic mutations, which does not entirely reflect the development of most human cancers that arise independently of carcinogen exposure (Bareham et al., 2021; Olson et al., 2018). Nonetheless, immunization strategies that focus on proteins and non-canonical peptides overexpressed during carcinogenesis have shown protective effects in preclinical models (Patel et al., 2019; Twitty et al., 2011; Yu et al., 2016). This approach is now moving into clinical trials for high-risk populations, such as tobacco users (Hilton et al., 2022).

5.2. Genetically engineered mouse models (GEMMs)

A wide variety of genetically engineered mouse models (GEMMs) that reflect the development of common human cancers have been established (Hill et al., 2021; Kersten et al., 2017). These GEMMs replicate the sequential process of tumorigenesis, from premalignant lesions to invasive disease, offering a valuable opportunity to interrogate the earliest stages of spontaneous carcinogenesis, which are often inaccessible in human studies (Finn and Beatty, 2016; Keenan and Jaffee, 2013; Le Magnen et al., 2016; Young, 2017). These models are particularly valuable as they are exploitable to test specific target approaches against a known oncogenic driver. The value of GEMMs lies also in the possibility to evaluate the efficacy of vaccination either halting cancer onset or impeding the progression of premalignant lesions. Furthermore, GEMMs enable the identification of deregulated molecular pathways in preinvasive lesions that may be leveraged for novel immunopreventive vaccines.

One well-studied example of a cancer prevention vaccine targeting a driver mutation in premalignancy, involves the KRAS oncogene. KRAS mutations are the earliest genetic alterations in human pancreatic tumors, among others, occurring in premalignant pancreatic intraepithelial neoplasia and being conserved in advanced pancreatic cancers, making them an ideal target for primary and secondary prevention. In KRAS-driven GEMMs, which spontaneously develop pancreatic tumors, numerous anti-KRAS vaccination strategies have demonstrated promising potential in preventing cancer development and progression (Haldar et al., 2024; Huff et al., 2023; Keenan et al., 2014; Zaidi et al., 2022). The success of these studies highlights the substantial translational potential of such vaccines, particularly given that pancreatic cancer often progresses gradually after the initial oncogenic event, providing a critical window for early intervention. Notably, several KRAS-based vaccines are now under clinical investigation, including trials in genetically predisposed individuals with pancreatic cysts (NCT05013216), further reinforcing the relevance of early-stage prevention.

Similarly, the MUC-1 antigen has been a focal point in preventive anti-cancer vaccine research, due to its expression in premalignant lesions across multiple cancer types, including colon and lung cancer. Various MUC-1-based vaccines have demonstrated efficacy in GEMM preclinical models of colon cancer, reducing inflammation and preventing progression to colitis-associated cancer (Beatty et al., 2012; Lakshminarayanan et al., 2016; Murwanti et al., 2023). It is precisely following these promising results that MUC-1 vaccination is being explored for cancer prevention in high-risk populations, such as individuals with a history of colonic polyps or adenoma (NCT02134925) (Beatty et al., 2010; Finn, 2021; Kimura et al., 2013; Murwanti et al., 2023; Schoen et al., 2023). Moreover, preventive trials are being considered for former smokers at high risk for lung cancer (NCT03300817), demonstrating the broad applicability of this antigen in cancer prevention (Finn et al., 2023).

The potential of cancer prevention vaccines has also been extensively explored in the context of breast cancer, where well-established preclinical models of stepwise HER2-dependent mammary tumor progression are available. GEMMs, such as mouse mammary tumor virus (MMTV)-neu/HER2 transgenic mice, closely mimic human HER2-positive breast cancer progression, from preneoplastic lesions to invasive carcinomas and metastasis (De Giovanni et al., 2014; Quaglino et al., 2008). These models have been pivotal in demonstrating the efficacy of immune-mediated anti-HER2 vaccines in preventing mammary tumor progression (De Giovanni et al., 2014; Gil et al., 2014; Jacob et al., 2010; Lollini et al., 2013; Piechocki et al., 2003; Quaglino et al., 2010). In contrast, sporadic triple-negative breast cancer (TNBC) lacks a single driving mutation, making GEMMs especially useful for identifying novel vaccine targets. The C3(1)/Tag transgenic mouse model, which mirrors human TNBC progression, enabled researchers to target TOP2A, a molecule identified in TNBC lesions, via vaccination, significantly reducing tumor incidence when administered in a prophylactic setting (Green et al., 2000). Such findings provide a proof-of-concept for the potential efficacy of preventive immunization in high-risk individuals.

5.3. Expanding the scope of GEMMs: Lynch syndrome and hereditary cancers

Several GEMMs of hereditary cancers have been developed, including models for Lynch syndrome and hereditary BRCA1/2-associated breast and ovarian cancer syndromes, that may serve as proof-of-concept to explore vaccine-based strategies aimed at preventing cancer in defined high-risk populations (Biswas et al., 2023a). As mentioned earlier, individuals with Lynch syndrome, who carry mismatch repair mutations that lead to recurrent frameshift mutations, often develop colon cancer (Lepore Signorile et al., 2021). Lynch syndrome preclinical models have shown that vaccines targeting these recurrent frameshift mutations can reduce tumor burden and improve survival (Gebert et al., 2021), opening new avenues for colorectal cancer prevention in this population before the formation of an immunosuppressive environment and the acquisition of other key oncogenic mutations in genes such as APC, BRAF, and TP53.

5.4. Transplantable tumor models

Spontaneous tumor development in GEMMs normally requires longer periods of time when compared to other preclinical models, such as non-autochthonous, transplantable tumor models. These models are therefore more advantageous when the research intends the evaluation vaccine efficacy, alone or in combinatorial approaches, particularly in tertiary prevention and therapy.

Transplantable tumor models can be categorized into syngeneic and xenograft models (either cell line- or patient-derived) (Westwood et al., 2014). Syngeneic models involve injecting murine tumor cells into immunocompetent mice of the same genetic background. These models are easily established through subcutaneous injections (for tumor development and eventually spontaneous metastases) or intravenous and intracardiac injections (for experimental metastasis models) of murine tumor cells. These models are widely used for evaluating cancer vaccine efficacy and mechanisms of action in established and advanced tumors. However, a key limitation is that tumor development is frequently induced in non-native anatomical locations, lacking organ-specific features like tissue architecture and immune recruitment,

which can affect the accuracy of immune response assessments. To overcome these challenges, syngeneic orthotopic models have been developed by injecting tumor cells into the appropriate anatomical site. These models have been used in various cancer types, including bladder carcinoma (intravesical tumor implantation), breast cancer (injection into mammary adipose tissue), colon cancer (cecal injection), glioblastoma (intracranial injection), hepatocellular carcinoma (subcapsular implantation), renal cancer (kidney injection), lung cancer (direct lung injection or tracheal instillation) and pancreatic cancer (intrapancreatic injection) (Chulpanova et al., 2020; Devaud et al., 2014).

Although syngeneic orthotopic models aim to improve upon traditional approaches, murine cancer cell lines are often poorly differentiated, proliferate rapidly, are inoculated into healthy organs, and are characterized by a low heterogeneity. To better capture the complexity of human cancers, human xenograft models were developed, which imply transplanting human immortalized cancer cells (cell lines-derived xenografts, CDX) or fresh tumor fragments from patients (patient-derived xenografts, PDX) into immunodeficient mice (Jin et al., 2023; Landuzzi et al., 2021; Nanni et al., 2019). However, to study anti-cancer vaccines, a functional immune system is critical, requiring complex artificial interventions to generate mice with a humanized immune system capable of mounting effective immune responses (Choi et al., 2018; Chuprin et al., 2023; De Giovanni et al., 2012; Yan et al., 2023).

One promising alternative is the use of transgenic mice expressing the human HLA-A2 molecule (Conforti et al., 2009; McArdle, 2009; Salio et al., 1999; Sher et al., 2016). These immunocompetent mice allow researchers to study immune responses in a humanized context. By vaccinating HLA-A2 mice, both T cell and antibody responses specific to antigens in the vaccine can be generated. These responses can be transferred into immunodeficient mice bearing HLA-A2-matched human tumors, either as CDX or PDX, offering the possibility to dissect the contribution of both arms of the adaptive immune system against established human tumors (Sher et al., 2016; Tarone et al., 2023).

Despite these advancements, several limitations persist in mouse models, including high costs, long latency periods following tumor graft implantation, variability in tumor development among animals, and HLA-A2 haplotype restriction in the case of adoptive transfer experiments with HLA-A2 mice. Moreover, while human tumor cells are inoculated in these mice, the surrounding stromal components remain murine, which can impact the tumor microenvironment's relevance to human disease.

5.5. *Alternative models: the role of comparative oncology in anti-cancer vaccine development*

The transition from mouse studies to human clinical trials often yields disappointing results, with only about 10% of successful treatments in mice advancing to approval for human oncology. This is particularly evident in anti-cancer vaccine research. Key factors contributing to this translational failure include the use of young, healthy animals, the challenge of replicating the heterogeneity and microenvironment of human tumors, and the fundamental differences in immune responses between conventional preclinical cancer models and humans (Finn, 2018; Maeng et al., 2018; Morse et al., 2021; Prasad, 2016).

To bridge this gap, researchers are increasingly turning to alternative models, with a growing focus on companion animals, particularly dogs, which naturally develop tumors (Fig. 1). These models capture the complexity of cancer more accurately compared to mouse models and offer significant predictive value for evaluating anti-cancer vaccines. Tumors in pet dogs develop spontaneously, evolve, and often metastasize and recur in relevant anatomical sites, mimicking the stepwise progression and clinical presentation of human tumors. Canine tumors also share many genetic and molecular features with human tumors, further enhancing the predictive value of these models for evaluating immunotherapies (Bryan and Maitz, 2024; Oh and Cho, 2023; Stevenson et al., 2022; Tarone et al., 2019, 2022a, 2022b).

Importantly, while there are broad similarities in immune responses to activation between dogs and humans (Li et al., 2022), some key quantitative and qualitative differences in immune cell behavior have been demonstrated (Chow et al., 2024). For example, major leukocyte subsets and phenotypes are comparable in dogs and humans, but canine T cells exhibit lower overall transcriptional activity compared to human T cells. Although both species show similar proliferative responses upon activation, canine T cells produce significantly less interferon-gamma (IFN-γ) than their human counterparts, indicating a less pronounced Th1 bias of CD4 T cells (Chow et al., 2024). Similarly, canine NK cells show a reduced expression of IFN-γ and other effector molecules compared to human NK cells (Gingrich et al., 2021). Conversely, canine macrophages demonstrate greater responsiveness to IFN-γ stimulation, as seen through higher co-stimulatory molecule expression and increased tumor necrosis factor-alpha (TNF-α) production, compared to human macrophages (Chow et al., 2022, 2024).

These immunological differences do not diminish the value of canine models for cancer research, which has been validated over years of study. Assessing immune responses in dogs with cancer offer insights that can guide the design of immunotherapy trials. Understanding the differences between canine and human contexts helps in selecting appropriate immunological biomarkers and endpoints for evaluating the efficacy of cancer vaccines in canine trials, ultimately improving the translatability of findings to human cancer research.

The field of veterinary oncology offers a unique advantage: faster tumor progression in canine patients allows researchers to conduct trials more efficiently. For example, the Vaccination Against Canine Cancer Study (VACCS) trial investigates the safety, immunogenicity, and efficacy of a cancer-preventive vaccine in dogs. This study, initiated in May 2019, had enrolled 804 dogs by October 2022 and is the first clinical study evaluating a preventative prime-boost vaccination combining a DNA plasmid and a peptide-based vaccine, targeting neoantigens generated by RNA-processing errors in tumor cells (Burton et al., 2024).

For treating advanced tumors, canine cancer patients are often treated with the same conventional therapies used in humans, yielding comparable clinical responses. This overlap enables researchers to evaluate combinations of standard therapies and novel vaccines within a relatively short timeframe. Additionally, the flexibility in veterinary oncology allows for innovative treatment approaches to be explored earlier in the therapeutic process.

Among the cancers being studied in comparative oncology are melanoma, lymphoma, and sarcoma (LeBlanc et al., 2016b; Oh and Cho, 2023). In some cases, veterinary studies could be extremely relevant especially for those rare cancers in humans, whose incidence is instead higher in the canine population.

Immunotherapeutic strategies tested in veterinary trials have spanned from autologous and allogeneic vaccines to DNA- and peptide-based immunization approaches (Bryan and Maitz, 2024; Tarone et al., 2019). Some examples of vaccination strategies in the veterinary field with significant translational potential for human clinics include, but are not limited to, the following. Several melanoma-associated antigens, such as the disialogangliosides GD2 and GD3 (Albertini et al., 2024; Milner et al., 2006), tyrosinase (Bergman et al., 2003; Grosenbaugh et al., 2011), gp100 (Alexander et al., 2006), and CSPG4 (Riccardo et al., 2014, 2022; Rolih et al., 2017) are shared by both human and canine melanomas. ONCEPT (Merial), the first and only FDA-approved DNA vaccine for anti-tumor therapy, is a DNA plasmid encoding the human tyrosinase and is intended for treating dogs with locally controlled melanomas. Studies have suggested that ONCEPT increases survival times in treated dogs compared to unvaccinated controls, with no reported adverse events. Despite some criticism regarding its effectiveness, ONCEPT's approval marked a new era in melanoma treatment for dogs, rising hope for the broader application of anti-cancer DNA vaccines (Bergman et al., 2006; Ottnod et al., 2013; Pellin, 2022; Verganti et al., 2017).

Another notable approach targets the HER2 antigen using a

recombinant *Listeria monocytogenes* (Lm)-based vaccine (Mason et al., 2016; Stroud et al., 2016). Tested in a phase I veterinary clinical trial, this vaccine significantly reduced metastasis and prolonged survival in dogs with osteosarcoma, leading to a conditional license from the United States Department of Agriculture (USDA) in 2017 for the adjuvant treatment of dogs with osteosarcoma. Encouraged by these results, a Phase Ib clinical trial of the vaccine (ADXS31-164) is now underway in human adult patients with HER2-expressing tumors (NCT02386501). This vaccine has since been licensed for development in the pediatric osteosarcoma setting by OS Therapies, in collaboration with the NCI Children's Oncology Group.

Other translationally relevant vaccination strategies include peptide-based vaccines targeting HER2 in HER2-overexpressing canine tumors (Doyle et al., 2021), DNA vaccines against p62 for mammary cancer (Gabai et al., 2014), TERT for B-cell lymphoma (Impellizeri et al., 2018), and CSPG4 for treating melanoma (Camerino et al., 2022; Giacobino et al., 2021; Piras et al., 2017; Riccardo et al., 2014, 2022) and osteosarcoma (Tarone et al., 2023). Collectively, these efforts underscore the significant contributions of comparative oncology in advancing anti-cancer vaccine development, with mutual benefits for both human and canine patients, reinforcing the "One Health, One Medicine" concept (King, 2021; Krol and Motyl, 2014; LeBlanc et al., 2016a).

6. Conclusions

The development of cancer vaccines has made notable progress, particularly in the primary prevention of virus-related cancers by targeting the underlying viral infections. Vaccines such as those for HPV and HBV have demonstrated remarkable success in reducing the incidence of cervical and liver cancers, respectively, by preventing the viral infections that cause these malignancies. This underscores the immense potential of preventive vaccination strategies in lowering cancer incidence on a global scale.

However, despite these achievements, cancer preventive vaccines still face significant challenges. A primary obstacle is the identification of proper tumor antigens to be targeted and the reliable identification of individuals with genetic predispositions or premalignant lesions who are at high risk of developing invasive cancers expressing those antigens. Targeting this population is crucial for successful preventive interventions. Another critical factor is the ability to induce long-lasting immune memory against tumor-associated antigens, ensuring durable protection against future cancer development. Furthermore, gaining a deeper understanding of the immune environment within these early-stage lesions is crucial for designing vaccines that can effectively halt tumor progression.

A range of vaccine platforms, including virus-, VLP-, bacterial, DNA-, mRNA-, and peptide-based vaccines, have been explored for cancer prevention and treatment. VLP-based vaccines have shown great promise, particularly in HPV prevention, offering a model of how immune responses can be harnessed against cancer-related antigens. In preclinical settings, various models - such as syngeneic, xenograft, and GEMMs - have been instrumental in understanding how these vaccines can trigger immune responses and prevent tumor formation. Moreover, comparative oncology models, especially in canines, are increasingly recognized for their potential to provide clinically relevant data and bridge the gap between preclinical studies and human trials.

Despite the promising advancements, expanding the success of vaccines beyond virus-related cancers requires addressing these challenges head-on. Future research must focus on improving the identification of at-risk individuals, enhancing the understanding of immune responses in early lesions, and refining vaccine strategies to induce robust and durable immunity (Stanton et al., 2024). This ongoing work holds the promise of significantly reducing the global burden of cancer through effective prevention strategies.

CRediT authorship contribution statement

Francesca Ruzzi: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Federica Riccardo:** Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing. **Laura Conti:** Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing. **Lidia Tarone:** Visualization, Writing – review & editing. **Maria Sofia Semprini:** Visualization, Writing – review & editing. **Elisabetta Bolli:** Visualization, Writing – review & editing. **Giuseppina Barutello:** Writing – review & editing. **Elena Quaglino:** Funding acquisition, Writing – review & editing. **Pier-Luigi Lollini:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Federica Cavallo:** Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

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Conflict of interest

The authors declare that there are no commercial or financial relationships that could be construed as a potential conflict of interest.

References

Abd-Aziz, N., Poh, C.L., 2022. Development of peptide-based vaccines for cancer. JAMA Oncol. 2022, 9749363.

Albertini, M.R., Zuleger, C.L., Ranheim, E.A., Shiyanbola, O., Sondel, P.M., Morris, Z.S., Eickhoff, J., Newton, M.A., Ong, I.M., Schwartz, R.W., Hayim, R., Kurzman, I.D., Turek, M., Vail, D.M., 2024. Administration of intratumoral GD2-directed interleukin-2 immunocytokine and local radiation therapy to activate immune rejection of spontaneous canine melanoma. Melanoma Res. 34 (4), 307–318.

Alexander, A.N., Huelsmeyer, M.K., Mitzey, A., Dubielzig, R.R., Kurzman, I.D., Macewen, E.G., Vail, D.M., 2006. Development of an allogeneic whole-cell tumor vaccine expressing xenogeneic gp100 and its implementation in a phase II clinical trial in canine patients with malignant melanoma. Cancer Immunol. Immunother. 55 (4), 433–442.

Andtbacka, R.H., Kaufman, H.L., Collichio, F., Amatruda, T., Senzer, N., Chesney, J., Delman, K.A., Spitler, L.E., Puzanov, I., Agarwala, S.S., Milhem, M., Cranmer, L., Curti, B., Lewis, K., Ross, M., Guthrie, T., Linette, G.P., Daniels, G.A., Harrington, K., Middleton, M.R., Miller Jr., W.H., Zager, J.S., Ye, Y., Yao, B., Li, A., Doleman, S., VanderWalde, A., Gansert, J., Coffin, R.S., 2015. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J. Clin. Oncol. 33 (25), 2780–2788.

Arab, A., Nikpoor, A.R., Asadi, P., Iraei, R., Yazdian-Robati, R., Sheikh, A., Kesharwani, P., 2022. Virus-like nanoparticles (VLPs) based technology in the development of breast cancer vaccines. Process Biochem. 123, 44–51.

Aurisicchio, L., Ciliberto, G., 2012. Genetic cancer vaccines: current status and perspectives. Expet Opin. Biol. Ther. 12 (8), 1043–1058.

Bareham, B., Georgakopoulos, N., Matas-Cespedes, A., Curran, M., Saeb-Parsy, K., 2021. Modeling human tumor-immune environments in vivo for the preclinical assessment of immunotherapies. Cancer Immunol. Immunother. 70 (10), 2737–2750.

Bartlett, D.L., Liu, Z., Sathaiah, M., Ravindranathan, R., Guo, Z., He, Y., Guo, Z.S., 2013. Oncolytic viruses as therapeutic cancer vaccines. Mol. Cancer 12 (1), 103.

Baryakova, T.H., Pogostin, B.H., Langer, R., McHugh, K.J., 2023. Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems. Nat. Rev. Drug Discov. 22 (5), 387–409.

Batista-Duharte, A., Hassouneh, F., Alvarez-Heredia, P., Pera, A., Solana, R., 2022. Immune checkpoint inhibitors for vaccine improvements: current status and new approaches. Pharmaceutics 14 (8).
Beatty, P., Ranganathan, S., Finn, O.J., 2012. Prevention of colitis-associated colon cancer using a vaccine to target abnormal expression of the MUC1 tumor antigen. OncoImmunology 1 (3), 263–270.
Beatty, P.L., Narayanan, S., Gariepy, J., Ranganathan, S., Finn, O.J., 2010. Vaccine against MUC1 antigen expressed in inflammatory bowel disease and cancer lessens colonic inflammation and prevents progression to colitis-associated colon cancer. Cancer Prev. Res. 3 (4), 438–446.
Bergman, P.J., Camps-Palau, M.A., McKnight, J.A., Leibman, N.F., Craft, D.M., Leung, C., Liao, J., Riviere, I., Sadelain, M., Hohenhaus, A.E., Gregor, P., Houghton, A.N., Perales, M.A., Wolchok, J.D., 2006. Development of a xenogeneic DNA vaccine program for canine malignant melanoma at the Animal Medical Center. Vaccine 24 (21), 4582–4585.
Bergman, P.J., McKnight, J., Novosad, A., Charney, S., Farrelly, J., Craft, D., Wulderk, M., Jeffers, Y., Sadelain, M., Hohenhaus, A.E., Segal, N., Gregor, P., Engelhorn, M., Riviere, I., Houghton, A.N., Wolchok, J.D., 2003. Long-term survival of dogs with advanced malignant melanoma after DNA vaccination with xenogeneic human tyrosinase: a phase I trial. Clin. Cancer Res. 9 (4), 1284–1290.
Biswas, K., Mohammed, A., Sharan, S.K., Shoemaker, R.H., 2023a. Genetically engineered mouse models for hereditary cancer syndromes. Cancer Sci. 114 (5), 1800–1815.
Biswas, N., Chakrabarti, S., Padul, V., Jones, L.D., Ashili, S., 2023b. Designing neoantigen cancer vaccines, trials, and outcomes. Front. Immunol. 14, 1105420.
Blackburn, E.H., 2011. Cancer interception. Cancer Prev. Res. 4 (6), 787–792.
Bolivar, A.M., Duzagac, F., Deng, N., Reyes-Uribe, L., Chang, K., Wu, W., Bowen, C.M., Taggart, M.W., Thirumurthi, S., Lynch, P.M., You, Y.N., Rodriguez-Pascual, J., Lipkin, S.M., Kopetz, S., Scheet, P., Lizee, G.A., Reuben, A., Sinha, K.M., Vilar, E., 2024. Genomic landscape of Lynch syndrome colorectal neoplasia identifies shared mutated neoantigens for immunoprevention. Gastroenterology 166 (5), 787–801 e711.
Bolivar, A.M., Duzagac, F., Sinha, K.M., Vilar, E., 2023. Advances in vaccine development for cancer prevention and treatment in Lynch Syndrome. Mol. Aspect. Med. 93, 101204.
Bolli, E., O'Rourke, J.P., Conti, L., Lanzardo, S., Rolih, V., Christen, J.M., Barutello, G., Forni, M., Pericle, F., Cavallo, F., 2018. A Virus-Like-Particle immunotherapy targeting Epitope-Specific anti-xCT expressed on cancer stem cell inhibits the progression of metastatic cancer in vivo. OncoImmunology 7 (3), e1408746.
Bonte, P.E., Arribas, Y.A., Merlotti, A., Carrascal, M., Zhang, J.V., Zueva, E., Binder, Z.A., Alanio, C., Goudot, C., Amigorena, S., 2022. Single-cell RNA-seq-based proteogenomics identifies glioblastoma-specific transposable elements encoding HLA-I-presented peptides. Cell Rep. 39 (10), 110916.
Bosenberg, M., Liu, E.T., Yu, C.I., Palucka, K., 2023. Mouse models for immuno-oncology. Trends Cancer 9 (7), 578–590.
Bryan, J.N., Maitz, C.A., 2024. Translational history and hope of immunotherapy of canine tumors. Clin. Cancer Res. 30 (19), 4272–4285.
Buonaguro, L., Tagliamonte, M., 2023. Peptide-based vaccine for cancer therapies. Front. Immunol. 14, 1210044.
Burton, J.H., Johnston, S.A., Vail, D.M., Eickhoff, J.C., Sykes, K.F., Brown, J.R., Shen, L., Gervassi, A., Page, R.L., Willcox, J.L., Al-Nadaf, S., Willis, A.L., Biggs, D., Ralston, J., Mok, I., Kurzman, I.D., Huelsmeyer, M.K., Hayim, R., Smith, B.M., Thamm, D.H., 2024. Design of a randomized, placebo-controlled study evaluating efficacy and safety of a cancer preventative vaccine in dogs. Vet. Immunol. Immunopathol. 267, 110691.
Cafri, G., Gartner, J.J., Zaks, T., Hopson, K., Levin, N., Paria, B.C., Parkhurst, M.R., Yossef, R., Lowery, F.J., Jafferji, M.S., Prickett, T.D., Goff, S.L., McGowan, C.T., Seitter, S., Shindorf, M.L., Parikh, A., Chatani, P.D., Robbins, P.F., Rosenberg, S.A., 2020. mRNA vaccine-induced neoantigen-specific T cell immunity in patients with gastrointestinal cancer. J. Clin. Invest. 130 (11), 5976–5988.
Caldeira, J.C., Perrine, M., Pericle, F., Cavallo, F., 2020. Virus-like particles as an immunogenic platform for cancer vaccines. Viruses 12 (5).
Calogero, R.A., Quaglino, E., Saviozzi, S., Forni, G., Cavallo, F., 2008. Oncoantigens as anti-tumor vaccination targets: the chance of a lucky strike? Cancer Immunol. Immunother. 57 (11), 1685–1694.
Camerino, M., Giacobino, D., Manassero, L., Iussich, S., Riccardo, F., Cavallo, F., Tarone, L., Olimpo, M., Lardone, E., Martano, M., Del Magno, S., Buracco, P., Morello, E., 2022. Prognostic impact of bone invasion in canine oral malignant melanoma treated by surgery and anti-CSPG4 vaccination: a retrospective study on 68 cases (2010-2020). Vet. Comp. Oncol. 20 (1), 189–197.
Caproni, E., Corbellari, R., Tomasi, M., Isaac, S.J., Tamburini, S., Zanella, I., Grigolato, M., Gagliardi, A., Benedet, M., Baraldi, C., Croia, L., Di Lascio, G., Berti, A., Valensin, S., Bellini, E., Parri, M., Grandi, A., Grandi, G., 2023. Anti-tumor efficacy of in situ vaccination using bacterial outer membrane vesicles. Cancers 15 (13).
Cardillo, F., Bonfim, M., da Silva Vasconcelos Sousa, P., Mengel, J., Ribeiro Castello-Branco, L.R., Pinho, R.T., 2021. Bacillus calmette-guerin immunotherapy for cancer. Vaccines (Basel) 9 (5).
Cavallo, F., De Giovanni, C., Nanni, P., Forni, G., Lollini, P.L., 2011. 2011: the immune hallmarks of cancer. Cancer Immunol. Immunother. 60 (3), 319–326.
Chakraborty, C., Majumder, A., Bhattacharya, M., Chatterjee, S., Lee, S.-S., 2024. The landscape of neoantigens and its clinical applications: from immunobiology to cancer vaccines. Curr. Res. Biotechnol.
Cheever, M.A., Higano, C.S., 2011. PROVENGE (Sipuleucel-T) in prostate cancer: the first FDA-approved therapeutic cancer vaccine. Clin. Cancer Res. 17 (11), 3520–3526.
Chen, Z., Yong, T., Wei, Z., Zhang, X., Li, X., Qin, J., Li, J., Hu, J., Yang, X., Gan, L., 2024. Engineered probiotic-based personalized cancer vaccine potentiates antitumor immunity through initiating trained immunity. Adv. Sci. 11 (3), e2305081.
Cheng, K., Zhao, R., Li, Y., Qi, Y., Wang, Y., Zhang, Y., Qin, H., Qin, Y., Chen, L., Li, C., Liang, J., Li, Y., Xu, J., Han, X., Anderson, G.J., Shi, J., Ren, L., Zhao, X., Nie, G., 2021. Bioengineered bacteria-derived outer membrane vesicles as a versatile antigen display platform for tumor vaccination via Plug-and-Display technology. Nat. Commun. 12 (1), 2041.
Chiang, C.L., Benencia, F., Coukos, G., 2010. Whole tumor antigen vaccines. Semin. Immunol. 22 (3), 132–143.
Choi, Y., Lee, S., Kim, K., Kim, S.H., Chung, Y.J., Lee, C., 2018. Studying cancer immunotherapy using patient-derived xenografts (PDXs) in humanized mice. Exp. Mol. Med. 50 (8), 1–9.
Chow, L., Soontararak, S., Wheat, W., Ammons, D., Dow, S., 2022. Canine polarized macrophages express distinct functional and transcriptomic profiles. Front. Vet. Sci. 9, 988981.
Chow, L., Wheat, W., Ramirez, D., Impastato, R., Dow, S., 2024. Direct comparison of canine and human immune responses using transcriptomic and functional analyses. Sci. Rep. 14 (1), 2207.
Chu, X., Tian, W., Ning, J., Xiao, G., Zhou, Y., Wang, Z., Zhai, Z., Tanzhu, G., Yang, J., Zhou, R., 2024. Cancer stem cells: advances in knowledge and implications for cancer therapy. Signal Transduct. Targeted Ther. 9 (1), 170.
Chulpanova, D.S., Kitaeva, K.V., Rutland, C.S., Rizvanov, A.A., Solovyeva, V.V., 2020. Mouse tumor models for advanced cancer immunotherapy. Int. J. Mol. Sci. 21 (11).
Chuprin, J., Buettner, H., Seedhom, M.O., Greiner, D.L., Keck, J.G., Ishikawa, F., Shultz, L.D., Brehm, M.A., 2023. Humanized mouse models for immuno-oncology research. Nat. Rev. Clin. Oncol. 20 (3), 192–206.
Coley, W.B., 1898. The treatment of inoperable sarcoma with the 'mixed toxins of erysipelas and bacillus prodigiosus: immediate and final results in one hundred and forty cases. J. Am. Med. Assoc. XXXI (9), 456–465.
Conforti, A., Peruzzi, D., Giannetti, P., Biondo, A., Ciliberto, G., La Monica, N., Aurisicchio, L., 2009. A novel mouse model for evaluation and prediction of HLA-A2-restricted CEA cancer vaccine responses. J. Immunother. 32 (7), 744–754.
Cuzick, J., 2015. Gardasil 9 joins the fight against cervix cancer. Expert Rev. Vaccines 14 (8), 1047–1049.
Cuzick, J., Sestak, I., Forbes, J.F., Dowsett, M., Knox, J., Cawthorn, S., Saunders, C., Roche, N., Mansel, R.E., von Minckwitz, G., Bonanni, B., Palva, T., Howell, A., investigators, I.-I., 2014. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet 383 (9922), 1041–1048.
Cuzzubbo, S., Mangsbo, S., Nagarajan, D., Habra, K., Pockley, A.G., McArdle, S.E.B., 2020. Cancer vaccines: adjuvant potency, importance of age, lifestyle, and treatments. Front. Immunol. 11, 615240.
De Flora, S., Quaglia, A., Bennicelli, C., Vercelli, M., 2005. The epidemiological revolution of the 20th century. Faseb. J. 19 (8), 892–897.
De Giovanni, C., Nicoletti, G., Landuzzi, L., Romani, F., Croci, S., Palladini, A., Murgo, A., Antognoli, A., Ianzano, M.L., Stivani, V., Grosso, V., Iezzi, M., Stramucci, L., Barbieri, E., Lemoli, R.M., Nanni, P., Lollini, P.L., 2012. Human responses against HER-2-positive cancer cells in human immune system-engrafted mice. Br. J. Cancer 107 (8), 1302–1309.
De Giovanni, C., Nicoletti, G., Quaglino, E., Landuzzi, L., Palladini, A., Ianzano, M.L., Dall'Ora, M., Grosso, V., Ranieri, D., Laranga, R., Croci, S., Amici, A., Penichet, M.L., Iezzi, M., Cavallo, F., Nanni, P., Lollini, P.L., 2014. Vaccines against human HER2 prevent mammary carcinoma in mice transgenic for human HER2. Breast Cancer Res. 16 (1), R10.
Derre, L., Cesson, V., Lucca, I., Cerantola, Y., Valerio, M., Fritschi, U., Vlamopoulos, Y., Burruni, R., Legris, A.S., Dartiguenave, F., Gharbi, D., Martin, V., Vaucher, L., Speiser, D.E., Romero, P., Jichlinski, P., Nardelli-Haefliger, D., 2017. Intravesical Bacillus calmette guerin combined with a cancer vaccine increases local T-cell responses in non-muscle-invasive bladder cancer patients. Clin. Cancer Res. 23 (3), 717–725.
Devaud, C., Westwood, J.A., John, L.B., Flynn, J.K., Paquet-Fifield, S., Duong, C.P., Yong, C.S., Pegram, H.J., Stacker, S.A., Achen, M.G., Stewart, T.J., Snyder, L.A., Teng, M.W., Smyth, M.J., Darcy, P.K., Kershaw, M.H., 2014. Tissues in different anatomical sites can sculpt and vary the tumor microenvironment to affect responses to therapy. Mol. Ther. 22 (1), 18–27.
Di Lorenzo, A., Bolli, E., Ruiu, R., Ferrauto, G., Di Gregorio, E., Avalle, L., Savino, A., Poggio, P., Merighi, I.F., Riccardo, F., Brancaccio, M., Quaglino, E., Cavallo, F., Conti, L., 2022. Toll-like receptor 2 promotes breast cancer progression and resistance to chemotherapy. OncoImmunology 11 (1), 2086752.
Dillman, R.O., Cornforth, A.N., Nistor, G.I., McClay, E.F., Amatruda, T.T., Depriest, C., 2018. Randomized phase II trial of autologous dendritic cell vaccines versus autologous tumor cell vaccines in metastatic melanoma: 5-year follow up and additional analyses. J Immunother Cancer 6 (1), 19.
Disis, M.L.N., Guthrie, K.A., Liu, Y., Coveler, A.L., Higgins, D.M., Childs, J.S., Dang, Y., Salazar, L.G., 2023. Safety and outcomes of a plasmid DNA vaccine encoding the ERBB2 intracellular domain in patients with advanced-stage ERBB2-positive breast cancer: a phase 1 nonrandomized clinical trial. JAMA Oncol. 9 (1), 71–78.
Domchek, S.M., Vonderheide, R.H., 2024. Advancing cancer interception. Cancer Discov. 14 (4), 600–604.
Donofrio, G., Tebaldi, G., Lanzardo, S., Ruiu, R., Bolli, E., Ballatore, A., Rolih, V., Macchi, F., Conti, L., Cavallo, F., 2018. Bovine herpesvirus 4-based vector delivering the full length xCT DNA efficiently protects mice from mammary cancer metastases by targeting cancer stem cells. OncoImmunology 7 (12), e1494108.
Doyle, H.A., Gee, R.J., Masters, T.D., Gee, C.R., Booth, C.J., Peterson-Roth, E., Koski, R. A., Helfand, S.C., Price, L., Bascombe, D., Jackson, D., Ho, R., Post, G.R., Mamula, M.

J., 2021. Vaccine-induced ErbB (EGFR/HER2)-specific immunity in spontaneous canine cancer. Transl Oncol 14 (11), 101205.
Fan, T., Zhang, M., Yang, J., Zhu, Z., Cao, W., Dong, C., 2023. Therapeutic cancer vaccines: advancements, challenges, and prospects. Signal Transduct. Targeted Ther. 8 (1), 450.
Faries, M.B., Mozzillo, N., Kashani-Sabet, M., Thompson, J.F., Kelley, M.C., DeConti, R. C., Lee, J.E., Huth, J.F., Wagner, J., Dalgleish, A., Pertschuk, D., Nardo, C., Stern, S., Elashoff, R., Gammon, G., Morton, D.L., Group, M.-I.C.T., 2017. Long-term survival after complete surgical resection and adjuvant immunotherapy for distant melanoma metastases. Ann. Surg Oncol. 24 (13), 3991–4000.
Finn, O.J., 2003. Cancer vaccines: between the idea and the reality. Nat. Rev. Immunol. 3 (8), 630–641.
Finn, O.J., 2018. The dawn of vaccines for cancer prevention. Nat. Rev. Immunol. 18 (3), 183–194.
Finn, O.J., 2021. Abstract SY17-03: tumor-associated antigen MUC1 vaccine for colon cancer prevention. Cancer Res. 81 (13_Suppl. ment). SY17-03-SY17-03.
Finn, O.J., Beatty, P.L., 2016. Cancer immunoprevention. Curr. Opin. Immunol. 39, 52–58.
Finn, O.J., Ward, J., Krpata, T., Fatis, S., McKolanis, J., Xue, J., Beatty, P., Jacqueline, C., Kaufman, S., Akerley, C., Felt, A., Fursa, K., Holland, A., Ambulay, L.S., Foster, N., McMurray, R., Strand, C., Salazar, A.M., Bengtson, L., Szabo, E., Limburg, P., Wojtowicz, M., Midthun, D.E., Pennathur, A., 2023. Abstract PR002: a pilot study of a MUC1 vaccine in current and former smokers at high risk for lung cancer. Cancer Prev. Res. 16 (1_Suppl. ment), PR002. PR002.
Fioretti, D., Iurescia, S., Fazio, V.M., Rinaldi, M., 2010. DNA vaccines: developing new strategies against cancer. J. Biomed. Biotechnol. 2010, 174378.
Foy, J.P., Tortereau, A., Caulin, C., Le Texier, V., Lavergne, E., Thomas, E., Chabaud, S., Perol, D., Lachuer, J., Lang, W., Hong, W.K., Goudot, P., Lippman, S.M., Bertolus, C., Saintigny, P., 2016. The dynamics of gene expression changes in a mouse model of oral tumorigenesis may help refine prevention and treatment strategies in patients with oral cancer. Oncotarget 7 (24), 35932–35945.
Gabai, V., Venanzi, F.M., Bagashova, E., Rud, O., Mariotti, F., Vullo, C., Catone, G., Sherman, M.Y., Concetti, A., Chursov, A., Latanova, A., Shcherbinina, V., Shifrin, V., Shneider, A., 2014. Pilot study of p62 DNA vaccine in dogs with mammary tumors. Oncotarget 5 (24), 12803–12810.
Gautam, N., Ramamoorthi, G., Champion, N., Han, H.S., Czerniecki, B.J., 2024. Reviewing the significance of dendritic cell vaccines in interrupting breast cancer development. Mol. Aspect. Med. 95, 101239.
Gebert, J., Gelincik, O., Oezcan-Wahlbrink, M., Marshall, J.D., Hernandez-Sanchez, A., Urban, K., Long, M., Cortes, E., Tosti, E., Katzenmaier, E.M., Song, Y., Elsaadi, A., Deng, N., Vilar, E., Fuchs, V., Nelius, N., Yuan, Y.P., Ahadova, A., Sei, S., Shoemaker, R.H., Umar, A., Wei, L., Liu, S., Bork, P., Edelmann, W., von Knebel Doeberitz, M., Lipkin, S.M., Kloor, M., 2021. Recurrent frameshift neoantigen vaccine elicits protective immunity with reduced tumor burden and improved overall survival in a Lynch syndrome mouse model. Gastroenterology 161 (4), 1288–1302 e1213.
Ghiringhelli, F., Menard, C., Puig, P.E., Ladoire, S., Roux, S., Martin, F., Solary, E., Le Cesne, A., Zitvogel, L., Chauffert, B., 2007. Metronomic cyclophosphamide regimen selectively depletes CD4+CD25+ regulatory T cells and restores T and NK effector functions in end stage cancer patients. Cancer Immunol. Immunother. 56 (5), 641–648.
Giacobino, D., Camerino, M., Riccardo, F., Cavallo, F., Tarone, L., Martano, M., Dentini, A., Iussich, S., Lardone, E., Franci, P., Valazza, A., Manassero, L., Del Magno, S., De Maria, R., Morello, E., Buracco, P., 2021. Difference in outcome between curative intent vs marginal excision as a first treatment in dogs with oral malignant melanoma and the impact of adjuvant CSPG4-DNA electrovaccination: a retrospective study on 155 cases. Vet. Comp. Oncol. 19 (4), 651–660.
Gil, E.Y., Jo, U.H., Lee, H.J., Kang, J., Seo, J.H., Lee, E.S., Kim, Y.H., Kim, I., Phan-Lai, V., Disis, M.L., Park, K.H., 2014. Vaccination with ErbB-2 peptides prevents cancer stem cell expansion and suppresses the development of spontaneous tumors in MMTV-PyMT transgenic mice. Breast Cancer Res. Treat. 147 (1), 69–80.
Gingrich, A.A., Reiter, T.E., Judge, S.J., York, D., Yanagisawa, M., Razmara, A., Sturgill, I., Basmaci, U.N., Brady, R.V., Stoffel, K., Murphy, W.J., Rebhun, R.B., Brown, C.T., Canter, R.J., 2021. Comparative immunogenomics of canine natural killer cells as immunotherapy target. Front. Immunol. 12, 670309.
Golden, E.B., Pellicciotta, I., Demaria, S., Barcellos-Hoff, M.H., Formenti, S.C., 2012. The convergence of radiation and immunogenic cell death signaling pathways. Front. Oncol. 2, 88.
Green, J.E., Shibata, M.A., Yoshidome, K., Liu, M.L., Jorcyk, C., Anver, M.R., Wigginton, J., Wiltrout, R., Shibata, E., Kaczmarczyk, S., Wang, W., Liu, Z.Y., Calvo, A., Couldrey, C., 2000. The C3(1)/SV40 T-antigen transgenic mouse model of mammary cancer: ductal epithelial cell targeting with multistage progression to carcinoma. Oncogene 19 (8), 1020–1027.
Gridelli, C., Ciuleanu, T., Domine, M., Szczesna, A., Bover, I., Cobo, M., Kentepozidis, N., Zarogoulidis, K., Kalofonos, C., Kazarnowisz, A., Korozan, M., de Las Penas, R., Majem, M., Chella, A., Griesinger, F., Bournakis, E., Sadjadian, P., Kotsakis, A., Chinet, T., Syrigos, K.N., Correale, P., Gallou, C., Jamet, J.M., Vetsika, E.K., Kosmatopoulos, K., Georgoulias, V., Vx-001-201 trial, t, 2020. Clinical activity of a htert (vx-001) cancer vaccine as post-chemotherapy maintenance immunotherapy in patients with stage IV non-small cell lung cancer: final results of a randomised phase 2 clinical trial. Br. J. Cancer 122 (10), 1461–1466.
Grosenbaugh, D.A., Leard, A.T., Bergman, P.J., Klein, M.K., Meleo, K., Susaneck, S., Hess, P.R., Jankowski, M.K., Jones, P.D., Leibman, N.F., Johnson, M.H., Kurzman, I. D., Wolchok, J.D., 2011. Safety and efficacy of a xenogeneic DNA vaccine encoding for human tyrosinase as adjunctive treatment for oral malignant melanoma in dogs following surgical excision of the primary tumor. Am. J. Vet. Res. 72 (12), 1631–1638.
Guasp, P., Reiche, C., Sethna, Z., Balachandran, V.P., 2024. RNA vaccines for cancer: principles to practice. Cancer Cell 42 (7), 1163–1184.
Guo, Z.S., Lu, B., Guo, Z., Giehl, E., Feist, M., Dai, E., Liu, W., Storkus, W.J., He, Y., Liu, Z., Bartlett, D.L., 2019. Vaccinia virus-mediated cancer immunotherapy: cancer vaccines and oncolytics. J Immunother Cancer 7 (1), 6.
Guo, Z.S., Thorne, S.H., Bartlett, D.L., 2008. Oncolytic virotherapy: molecular targets in tumor-selective replication and carrier cell-mediated delivery of oncolytic viruses. Biochim. Biophys. Acta 1785 (2), 217–231.
Hafron, J.M., Wilfehrt, H.M., Ferro, C., Harmon, M., Flanders, S.C., McKay, R.R., 2022. Real-world effectiveness of sipuleucel-T on overall survival in men with advanced prostate cancer treated with androgen receptor-targeting agents. Adv. Ther. 39 (6), 2515–2532.
Haldar, S.D., Huff, A., Diwan, E.A., Ferguson, A., Judkins, C., Lu, J., Wang, H., Sinan, H., Thoburn, C., Bever, K.M., Yarchoan, M., Thomas, A.M., Nauroth, J.M., Laheru, D.A., Goggins, M.G., Jaffee, E.M., Azad, N.S., Zaidi, N., 2024. Abstract CT022: mutant KRAS peptide-based vaccine in patients at high risk of developing pancreatic cancer: preliminary analysis from a phase I study. Cancer Res. 84 (7_Suppl. ment), CT022. CT022.
Haldar, S.D., Judkins, C., Ferguson, A., Diwan, E.A., Lim, S.J., Wang, H., Nauroth, J., Goggins, M., Laheru, D., Jaffee, E.M., Azad, N.S., Zaidi, N., 2023. A phase I study of a mutant KRAS-targeted long peptide vaccine in patients at high risk of developing pancreatic cancer. J. Clin. Oncol. 41 (4_Suppl. l), TPS758. TPS758.
Hall, M.T., Simms, K.T., Lew, J.B., Smith, M.A., Brotherton, J.M., Saville, M., Frazer, I.H., Canfell, K., 2019. The projected timeframe until cervical cancer elimination in Australia: a modelling study. Lancet Public Health 4 (1), e19–e27.
Harper, D.M., Franco, E.L., Wheeler, C., Ferris, D.G., Jenkins, D., Schuind, A., Zahaf, T., Innis, B., Naud, P., De Carvalho, N.S., Roteli-Martins, C.M., Teixeira, J., Blatter, M. M., Korn, A.P., Quint, W., Dubin, G., GlaxoSmithKline HPV Vaccine Study Group, 2004. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet 364 (9447), 1757–1765.
Hill, W., Caswell, D.R., Swanton, C., 2021. Capturing cancer evolution using genetically engineered mouse models (GEMMs). Trends Cell Biol. 31 (12), 1007–1018.
Hilton, T., Gunderson, A., Schmidt, M., Paustian, C., Bookhardt, S., McDonnell, G., Moudgil, T., Hu, H.-M., Bell, B., Fox, B., 2022. 5 Development of a vaccine to intercept oral cancer. J. mmunoTher. Cancer 10 (Suppl. 2), A6. A6.
Hsu, F.J., Benike, C., Fagnoni, F., Liles, T.M., Czerwinski, D., Taidi, B., Engleman, E.G., Levy, R., 1996. Vaccination of patients with B-cell lymphoma using autologous antigen-pulsed dendritic cells. Nat. Med. 2 (1), 52–58.
Hu, L., Zhang, Y., Kong, X., Wu, Z., Wang, H., 2024a. Impact of personalized peptide neoantigen vaccines on immunologic responses in patients with pancreatic cancer. J. Clin. Oncol. 42 (16_Suppl. l), e16351.
Hu, Z., Guo, X., Li, Z., Meng, Z., Huang, S., 2024b. The neoantigens derived from transposable elements - a hidden treasure for cancer immunotherapy. Biochim. Biophys. Acta Rev. Canc 1879 (5), 189126.
Huff, A.L., Haldar, S.D., Davis-Marcisak, E., Heumann, T., Longway, G., Hernandez, A., Konig, M.F., Mog, B., Danilova, L., Kagohara, L., Nauroth, J.M., Thomas, A.M., Fertig, E.J., Ho, W.J., Jaffee, E.M., Azad, N., Zaidi, N., 2023. Abstract LB197: a pooled mutant KRAS peptide vaccine activates polyfunctional T cell responses in patients with resected pancreatic cancer. Cancer Res. 83 (8_Suppl. ment), LB197. LB197.
Impellizeri, J.A., Gavazza, A., Greissworth, E., Crispo, A., Montella, M., Ciliberto, G., Lubas, G., Aurisicchio, L., 2018. Tel-eVax: a genetic vaccine targeting telomerase for treatment of canine lymphoma. J. Transl. Med. 16 (1), 349.
Jacob, J.B., Quaglino, E., Radkevich-Brown, O., Jones, R.F., Piechocki, M.P., Reyes, J.D., Weise, A., Amici, A., Wei, W.Z., 2010. Combining human and rat sequences in her-2 DNA vaccines blunts immune tolerance and drives antitumor immunity. Cancer Res. 70 (1), 119–128.
Jegerlehner, A., Wiesel, M., Dietmeier, K., Zabel, F., Gatto, D., Saudan, P., Bachmann, M. F., 2010. Carrier induced epitopic suppression of antibody responses induced by virus-like particles is a dynamic phenomenon caused by carrier-specific antibodies. Vaccine 28 (33), 5503–5512.
Jin, J., Yoshimura, K., Sewastjanow-Silva, M., Song, S., Ajani, J.A., 2023. Challenges and prospects of patient-derived xenografts for cancer research. Cancers 15 (17).
Kacen, A., Javitt, A., Kramer, M.P., Morgenstern, D., Tsaban, T., Shmueli, M.D., Teo, G. C., da Veiga Leprevost, F., Barnea, E., Yu, F., Admon, A., Eisenbach, L., Samuels, Y., Schueler-Furman, O., Levin, Y., Nesvizhskii, A.I., Merbl, Y., 2023. Post-translational modifications reshape the antigenic landscape of the MHC I immunopeptidome in tumors. Nat. Biotechnol. 41 (2), 239–251.
Kaczmarek, M., Poznanska, J., Fechner, F., Michalska, N., Paszkowska, S., Napierala, A., Mackiewicz, A., 2023. Cancer vaccine therapeutics: limitations and effectiveness-A literature review. Cells 12 (17).
Kantoff, P.W., Higano, C.S., Shore, N.D., Berger, E.R., Small, E.J., Penson, D.F., Redfern, C.H., Ferrari, A.C., Dreicer, R., Sims, R.B., Xu, Y., Frohlich, M.W., Schellhammer, P.F., Investigators, I.S., 2010. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N. Engl. J. Med. 363 (5), 411–422.
Keenan, B., Jaffee, E.M., 2013. Immunotherapy in preneoplastic disease: targeting early procarcinogenic inflammatory changes that lead to immune suppression and tumor tolerance. Ann. N. Y. Acad. Sci. 1284, 12–16.
Keenan, B.P., Saenger, Y., Kafrouni, M.I., Leubner, A., Lauer, P., Maitra, A., Rucki, A.A., Gunderson, A.J., Coussens, L.M., Brockstedt, D.G., Dubensky Jr., T.W., Hassan, R., Armstrong, T.D., Jaffee, E.M., 2014. A Listeria vaccine and depletion of T-regulatory cells activate immunity against early stage pancreatic intraepithelial neoplasms and prolong survival of mice. Gastroenterology 146 (7), 1784–1794 e1786.

Kenter, G.G., Welters, M.J., Valentijn, A.R., Lowik, M.J., Berends-van der Meer, D.M., Vloon, A.P., Essahsah, F., Fathers, L.M., Offringa, R., Drijfhout, J.W., Wafelman, A. R., Oostendorp, J., Fleuren, G.J., van der Burg, S.H., Melief, C.J., 2009. Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. N. Engl. J. Med. 361 (19), 1838–1847.

Kersten, K., de Visser, K.E., van Miltenburg, M.H., Jonkers, J., 2017. Genetically engineered mouse models in oncology research and cancer medicine. EMBO Mol. Med. 9 (2), 137–153.

Kimura, T., McKolanis, J.R., Dzubinski, L.A., Islam, K., Potter, D.M., Salazar, A.M., Schoen, R.E., Finn, O.J., 2013. MUC1 vaccine for individuals with advanced adenoma of the colon: a cancer immunoprevention feasibility study. Cancer Prev. Res. 6 (1), 18–26.

King, T.A., 2021. The One Medicine concept: its emergence from history as a systematic approach to re-integrate human and veterinary medicine. Emerg Top Life Sci 5 (5), 643–654.

Kong, Y., Rose, C.M., Cass, A.A., Williams, A.G., Darwish, M., Lianoglou, S., Haverty, P. M., Tong, A.J., Blanchette, C., Albert, M.L., Mellman, I., Bourgon, R., Greally, J., Jhunjhunwala, S., Chen-Harris, H., 2019. Transposable element expression in tumors is associated with immune infiltration and increased antigenicity. Nat. Commun. 10 (1), 5228.

Krol, M., Motyl, T., 2014. Exploiting cancer genomics in pet animals to gain advantage for personalized medicine decisions. J. Appl. Genet. 55 (3), 337–341.

Labani-Motlagh, A., Ashja-Mahdavi, M., Loskog, A., 2020. The tumor microenvironment: a milieu hindering and obstructing antitumor immune responses. Front. Immunol. 11, 940.

Lakshminarayanan, V., Supekar, N.T., Wei, J., McCurry, D.B., Dueck, A.C., Kosiorek, H. E., Trivedi, P.P., Bradley, J.M., Madsen, C.S., Pathangey, L.B., Hoelzinger, D.B., Wolfert, M.A., Boons, G.J., Cohen, P.A., Gendler, S.J., 2016. MUC1 vaccines, comprised of glycosylated or non-glycosylated peptides or tumor-derived MUC1, can circumvent immunoediting to control tumor growth in MUC1 transgenic mice. PLoS One 11 (1), e0145920.

Landuzzi, L., Palladini, A., Ceccarelli, C., Asioli, S., Nicoletti, G., Giusti, V., Ruzzi, F., Ianzano, M.L., Scalambra, L., Laranga, R., Balboni, T., Arigoni, M., Olivero, M., Calogero, R.A., De Giovanni, C., Dall'Ora, M., Di Oto, E., Santini, D., Foschini, M.P., Cucchi, M.C., Zanotti, S., Taffurelli, M., Nanni, P., Lollini, P.L., 2021. Early stability and late random tumor progression of a HER2-positive primary breast cancer patient-derived xenograft. Sci. Rep. 11 (1), 1563.

Lanzardo, S., Conti, L., Rooke, R., Ruiu, R., Accart, N., Bolli, E., Arigoni, M., Macagno, M., Barrera, G., Pizzimenti, S., Aurisicchio, L., Calogero, R.A., Cavallo, F., 2016. Immunotargeting of antigen xCT attenuates stem-like cell behavior and metastatic progression in breast cancer. Cancer Res. 76 (1), 62–72.

Le Magnen, C., Dutta, A., Abate-Shen, C., 2016. Optimizing mouse models for precision cancer prevention. Nat. Rev. Cancer 16 (3), 187–196.

LeBlanc, A.K., Mazcko, C., Brown, D.E., Koehler, J.W., Miller, A.D., Miller, C.R., Bentley, R.T., Packer, R.A., Breen, M., Boudreau, C.E., Levine, J.M., Simpson, R.M., Halsey, C., Kisseberth, W., Rossmeisl Jr., J.H., Dickinson, P.J., Fan, T.M., Corps, K., Aldape, K., Puduvalli, V., Pluhar, G.E., Gilbert, M.R., 2016a. Creation of an NCI comparative brain tumor consortium: informing the translation of new knowledge from canine to human brain tumor patients. Neuro Oncol. 18 (9), 1209–1218.

LeBlanc, A.K., Mazcko, C.N., Khanna, C., 2016b. Defining the value of a comparative approach to cancer drug development. Clin. Cancer Res. 22 (9), 2133–2138.

Lee, J., Woodruff, M.C., Kim, E.H., Nam, J.H., 2023a. Knife's edge: balancing immunogenicity and reactogenicity in mRNA vaccines. Exp. Mol. Med. 55 (7), 1305–1313.

Lee, K.W., Yam, J.W.P., Mao, X., 2023b. Dendritic cell vaccines: a shift from conventional approach to new generations. Cells 12 (17).

Leoni, G., D'Alise, A.M., Cotugno, G., Langone, F., Garzia, I., De Lucia, M., Fichera, I., Vitale, R., Bignone, V., Tucci, F.G., Mori, F., Leuzzi, A., Di Matteo, E., Troise, F., Abbate, A., Merone, R., Ruzza, V., Diodoro, M.G., Yadav, M., Gordon-Alonso, M., Vanhaver, C., Panigada, M., Soprana, E., Siccardi, A., Folgori, A., Colloca, S., van der Bruggen, P., Nicosia, A., Lahm, A., Catanese, M.T., Scarselli, E., 2020. A genetic vaccine encoding shared cancer neoantigens to treat tumors with microsatellite instability. Cancer Res. 80 (18), 3972–3982.

Lepore Signorile, M., Disciglio, V., Di Carlo, G., Pisani, A., Simone, C., Ingravallo, G., 2021. From genetics to histomolecular characterization: an insight into colorectal carcinogenesis in Lynch syndrome. Int. J. Mol. Sci. 22 (13).

Li, Z., Sun, C., Wang, F., Wang, X., Zhu, J., Luo, L., Ding, X., Zhang, Y., Ding, P., Wang, H., Pu, M., Li, Y., Wang, S., Qin, Q., Wei, Y., Sun, J., Wang, X., Luo, Y., Chen, D., Qiu, W., 2022. Molecular mechanisms governing circulating immune cell heterogeneity across different species revealed by single-cell sequencing. Clin. Transl. Med. 12 (1), e689.

Liau, L.M., Ashkan, K., Brem, S., Campian, J.L., Trusheim, J.E., Iwamoto, F.M., Tran, D. D., Ansstas, G., Cobbs, C.S., Heth, J.A., Salacz, M.E., D'Andre, S., Aiken, R.D., Moshel, Y.A., Nam, J.Y., Pillainayagam, C.P., Wagner, S.A., Walter, K.A., Chaudhary, R., Goldlust, S.A., Lee, I.Y., Bota, D.A., Elinzano, H., Grewal, J., Lillehei, K., Mikkelsen, T., Walbert, T., Abram, S., Brenner, A.J., Ewend, M.G., Khagi, S., Lovick, D.S., Portnow, J., Kim, L., Loudon, W.G., Martinez, N.L., Thompson, R.C., Avigan, D.E., Fink, K.L., Geoffroy, F.J., Giglio, P., Gligich, O., Krex, D., Lindhorst, S.M., Lutzky, J., Meisel, H.J., Nadji-Ohl, M., Sanchin, L., Sloan, A., Taylor, L.P., Wu, J.K., Dunbar, E.M., Etame, A.B., Kesari, S., Mathieu, D., Piccioni, D.E., Baskin, D.S., Lacroix, M., May, S.A., New, P.Z., Pluard, T.J., Toms, S. A., Tse, V., Peak, S., Villano, J.L., Battiste, J.D., Mulholland, P.J., Pearlman, M.L., Petrecca, K., Schulder, M., Prins, R.M., Boynton, A.L., Bosch, M.L., 2023. Association of autologous tumor lysate-loaded dendritic cell vaccination with extension of survival among patients with newly diagnosed and recurrent glioblastoma: a phase 3 prospective externally controlled cohort trial. JAMA Oncol. 9 (1), 112–121.

Lichty, B.D., Breitbach, C.J., Stojdl, D.F., Bell, J.C., 2014. Going viral with cancer immunotherapy. Nat. Rev. Cancer 14 (8), 559–567.

Lin, M.J., Svensson-Arvelund, J., Lubitz, G.S., Marabelle, A., Melero, I., Brown, B.D., Brody, J.D., 2022. Cancer vaccines: the next immunotherapy frontier. Nat Cancer 3 (8), 911–926.

Liu, D., Che, X., Wang, X., Ma, C., Wu, G., 2023. Tumor vaccines: unleashing the power of the immune system to fight cancer. Pharmaceuticals 16 (10).

Liu, W., Tang, H., Li, L., Wang, X., Yu, Z., Li, J., 2021. Peptide-based therapeutic cancer vaccine: current trends in clinical application. Cell Prolif. 54 (5), e13025.

Lollini, P.L., Cavallo, F., De Giovanni, C., Nanni, P., 2013. Preclinical vaccines against mammary carcinoma. Expert Rev. Vaccines 12 (12), 1449–1463.

Lollini, P.L., Cavallo, F., Nanni, P., Forni, G., 2006. Vaccines for tumour prevention. Nat. Rev. Cancer 6 (3), 204–216.

Lopes, A., Vandermeulen, G., Preat, V., 2019. Cancer DNA vaccines: current preclinical and clinical developments and future perspectives. J. Exp. Clin. Cancer Res. 38 (1), 146.

Lopes, A., Vanvarenberg, K., Preat, V., Vandermeulen, G., 2017. Codon-optimized P1A-encoding DNA vaccine: toward a therapeutic vaccination against P815 mastocytoma. Mol. Ther. Nucleic Acids 8, 404–415.

Ma, P., Beatty, P.L., McKolanis, J., Brand, R., Schoen, R.E., Finn, O.J., 2019. Circulating myeloid derived suppressor cells (MDSC) that accumulate in premalignancy share phenotypic and functional characteristics with MDSC in cancer. Front. Immunol. 10, 1401.

Maeng, H., Terabe, M., Berzofsky, J.A., 2018. Cancer vaccines: translation from mice to human clinical trials. Curr. Opin. Immunol. 51, 111–122.

Manoutcharian, K., Gevorkian, G., 2024. Are we getting closer to a successful neoantigen cancer vaccine? Mol. Aspect. Med. 96, 101254.

Marriott, M., Post, B., Chablani, L., 2023. A comparison of cancer vaccine adjuvants in clinical trials. Cancer Treat Res Commun 34, 100667.

Mason, N.J., Gnanandarajah, J.S., Engiles, J.B., Gray, F., Laughlin, D., Gaurnier-Hausser, A., Wallecha, A., Huebner, M., Paterson, Y., 2016. Immunotherapy with a HER2-targeting Listeria induces HER2-specific immunity and demonstrates potential therapeutic effects in a phase I trial in canine osteosarcoma. Clin. Cancer Res. 22 (17), 4380–4390.

McArdle, S., 2009. Cancer vaccines: uses of HLA transgenic mice compared to genetically modified mice. Front Biosci (Landmark Ed) 14 (12), 4640–4651.

Meng, J., Lv, Y., Bao, W., Meng, Z., Wang, S., Wu, Y., Li, S., Jiao, Z., Tian, Z., Ma, G., Wei, W., 2023. Generation of whole tumor cell vaccine for on-demand manipulation of immune responses against cancer under near-infrared laser irradiation. Nat. Commun. 14 (1), 4505.

Milhem, M., Zakharia, Y., Davar, D., Buchbinder, E., Medina, T., Daud, A., Ribas, A., Niu, J., Gibney, G., Margolin, K., Olszanski, A., Mehmi, I., Sato, T., Shaheen, M., Morris, A., Mauro, D., Campbell, K., Kelley, H., Bao, R., Weiner, G., Luke, J., Krieg, A., Wooldridge, J., Kirkwood, J., 2020. 304 Intratumoral injection of CMP-001, a toll-like receptor 9 (TLR9) agonist, in combination with pembrolizumab reversed programmed death receptor 1 (PD-1) blockade resistance in advanced melanoma. J. mmunoTher. Cancer 8 (Suppl. 3), A186–A187.

Milner, R.J., Salute, M., Crawford, C., Abbot, J.R., Farese, J., 2006. The immune response to disialoganglioside GD3 vaccination in normal dogs: a melanoma surface antigen vaccine. Vet. Immunol. Immunopathol. 114 (3–4), 273–284.

Mo, Y., Ma, J., Zhang, H., Shen, J., Chen, J., Hong, J., Xu, Y., Qian, C., 2022. Prophylactic and therapeutic HPV vaccines: current scenario and perspectives. Front. Cell. Infect. Microbiol. 12, 909223.

Mohsen, M.O., Bachmann, M.F., 2022. Virus-like particle vaccinology, from bench to bedside. Cell. Mol. Immunol. 19 (9), 993–1011.

Mohsen, M.O., Speiser, D.E., Knuth, A., Bachmann, M.F., 2020. Virus-like particles for vaccination against cancer. Wiley Interdiscip Rev Nanomed Nanobiotechnol 12 (1), e1579.

Mohsen, M.O., Speiser, D.E., Michaux, J., Pak, H., Stevenson, B.J., Vogel, M., Inchakalody, V.P., de Brot, S., Dermime, S., Coukos, G., Bassani-Sternberg, M., Bachmann, M.F., 2022. Bedside formulation of a personalized multi-neoantigen vaccine against mammary carcinoma. J Immunother Cancer 10 (1).

Morse, M.A., Gwin, W.R., Mitchell, D.A., 2021. Vaccine therapies for cancer: then and now. Targeted Oncol. 16 (2), 121–152.

Murwanti, R., Denda-Nagai, K., Sugiura, D., Mogushi, K., Gendler, S.J., Irimura, T., 2023. Prevention of inflammation-driven colon carcinogenesis in human MUC1 transgenic mice by vaccination with MUC1 DNA and dendritic cells. Cancers 15 (6).

Najafi, S., Mortezaee, K., 2023. Advances in dendritic cell vaccination therapy of cancer. Biomed. Pharmacother. 164, 114954.

Nanni, P., Landuzzi, L., Manara, M.C., Righi, A., Nicoletti, G., Cristalli, C., Pasello, M., Parra, A., Carrabotta, M., Ferracin, M., Palladini, A., Ianzano, M.L., Giusti, V., Ruzzi, F., Magnani, M., Donati, D.M., Picci, P., Lollini, P.L., Scotlandi, K., 2019. Bone sarcoma patient-derived xenografts are faithful and stable preclinical models for molecular and therapeutic investigations. Sci. Rep. 9 (1), 12174.

Nemunaitis, J., 1999. Oncolytic viruses. Invest. N. Drugs 17 (4), 375–386.

Oh, J.H., Cho, J.Y., 2023. Comparative oncology: overcoming human cancer through companion animal studies. Exp. Mol. Med. 55 (4), 725–734.

Olson, B., Li, Y., Lin, Y., Liu, E.T., Patnaik, A., 2018. Mouse models for cancer immunotherapy research. Cancer Discov. 8 (11), 1358–1365.

Ottnod, J.M., Smedley, R.C., Walshaw, R., Hauptman, J.G., Kiupel, M., Obradovich, J.E., 2013. A retrospective analysis of the efficacy of Oncept vaccine for the adjunct treatment of canine oral malignant melanoma. Vet. Comp. Oncol. 11 (3), 219–229.

Palladini, A., Landuzzi, L., Lollini, P.L., Nanni, P., 2018. Cancer immunoprevention: from mice to early clinical trials. BMC Immunol. 19 (1), 16.

Pandya, A., Shah, Y., Kothari, N., Postwala, H., Shah, A., Parekh, P., Chorawala, M.R., 2023. The future of cancer immunotherapy: DNA vaccines leading the way. Med. Oncol. 40 (7), 200.
Pant, S., Wainberg, Z.A., Weekes, C.D., Furqan, M., Kasi, P.M., Devoe, C.E., Leal, A.D., Chung, V., Basturk, O., VanWyk, H., Tavares, A.M., Seenappa, L.M., Perry, J.R., Kheoh, T., McNeil, L.K., Welkowsky, E., DeMuth, P.C., Haqq, C.M., O'Reilly, E.M., 2024. Lymph-node-targeted, mKRAS-specific amphiphile vaccine in pancreatic and colorectal cancer: the phase 1 AMPLIFY-201 trial. Nat. Med. 30 (2), 531–542.
Pardi, N., Hogan, M.J., Porter, F.W., Weissman, D., 2018. mRNA vaccines - a new era in vaccinology. Nat. Rev. Drug Discov. 17 (4), 261–279.
Parmiani, G., Castelli, C., Pilla, L., Santinami, M., Colombo, M.P., Rivoltini, L., 2007. Opposite immune functions of GM-CSF administered as vaccine adjuvant in cancer patients. Ann. Oncol. 18 (2), 226–232.
Paston, S.J., Brentville, V.A., Symonds, P., Durrant, L.G., 2021. Cancer vaccines, adjuvants, and delivery systems. Front. Immunol. 12, 627932.
Patel, J.M., Cui, Z., Wen, Z.F., Dinh, C.T., Hu, H.M., 2019. Peritumoral administration of DRibbles-pulsed antigen-presenting cells enhances the antitumor efficacy of anti-GITR and anti-PD-1 antibodies via an antigen presenting independent mechanism. J Immunother Cancer 7 (1), 311.
Pellin, M.A., 2022. The use of oncept melanoma vaccine in veterinary patients: a review of the literature. Vet Sci 9 (11).
Perez, C.R., De Palma, M., 2019. Engineering dendritic cell vaccines to improve cancer immunotherapy. Nat. Commun. 10 (1), 5408.
Perez-Banos, A., Gleisner, M.A., Flores, I., Pereda, C., Navarrete, M., Araya, J.P., Navarro, G., Quezada-Monras, C., Tittarelli, A., Salazar-Onfray, F., 2023. Whole tumour cell-based vaccines: tuning the instruments to orchestrate an optimal antitumour immune response. Br. J. Cancer 129 (4), 572–585.
Piechocki, M.P., Ho, Y.S., Pilon, S., Wei, W.Z., 2003. Human ErbB-2 (Her-2) transgenic mice: a model system for testing Her-2 based vaccines. J. Immunol. 171 (11), 5787–5794.
Piras, L.A., Riccardo, F., Iussich, S., Maniscalco, L., Gattino, F., Martano, M., Morello, E., Lorda Mayayo, S., Rolih, V., Garavaglia, F., De Maria, R., Lardone, E., Collivignarelli, F., Mignacca, D., Giacobino, D., Ferrone, S., Cavallo, F., Buracco, P., 2017. Prolongation of survival of dogs with oral malignant melanoma treated by en bloc surgical resection and adjuvant CSPG4-antigen electrovaccination. Vet. Comp. Oncol. 15 (3), 996–1013.
Pol, J., Kroemer, G., Galluzzi, L., 2016. First oncolytic virus approved for melanoma immunotherapy. OncoImmunology 5 (1), e1115641.
Prasad, V., 2016. Translation failure and medical reversal: two sides to the same coin. Eur. J. Cancer 52, 197–200.
Quaglino, E., Conti, L., Cavallo, F., 2020. Breast cancer stem cell antigens as targets for immunotherapy. Semin. Immunol. 47, 101386.
Quaglino, E., Iezzi, M., Mastini, C., Amici, A., Pericle, F., Di Carlo, E., Pupa, S.M., De Giovanni, C., Spadaro, M., Curcio, C., Lollini, P.L., Musiani, P., Forni, G., Cavallo, F., 2004. Electroporated DNA vaccine clears away multifocal mammary carcinomas in her-2/neu transgenic mice. Cancer Res. 64 (8), 2858–2864.
Quaglino, E., Mastini, C., Amici, A., Marchini, C., Iezzi, M., Lanzardo, S., De Giovanni, C., Montani, M., Lollini, P.L., Masucci, G., Forni, G., Cavallo, F., 2010. A better immune reaction to Erbb-2 tumors is elicited in mice by DNA vaccines encoding rat/human chimeric proteins. Cancer Res. 70 (7), 2604–2612.
Quaglino, E., Mastini, C., Forni, G., Cavallo, F., 2008. ErbB2 transgenic mice: a tool for investigation of the immune prevention and treatment of mammary carcinomas. Curr Protoc Immunol Chapter 20. Unit 20 29 21-20 29-10.
Quaglino, E., Riccardo, F., Macagno, M., Bandini, S., Cojoca, R., Ercole, E., Amici, A., Cavallo, F., 2011. Chimeric DNA vaccines against ErbB2+ carcinomas: from mice to humans. Cancers 3 (3), 3225–3241.
Rabu, C., Rangan, L., Florenceau, L., Fortun, A., Charpentier, M., Dupre, E., Paolini, L., Beauvillain, C., Dupel, E., Latouche, J.B., Adotevi, O., Labarriere, N., Lang, F., 2019. Cancer vaccines: designing artificial synthetic long peptides to improve presentation of class I and class II T cell epitopes by dendritic cells. OncoImmunology 8 (4), e1560919.
Reits, E.A., Hodge, J.W., Herberts, C.A., Groothuis, T.A., Chakraborty, M., Wansley, E.K., Camphausen, K., Luiten, R.M., de Ru, A.H., Neijssen, J., Griekspoor, A., Mesman, E., Verreck, F.A., Spits, H., Schlom, J., van Veelen, P., Neefjes, J.J., 2006. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. J. Exp. Med. 203 (5), 1259–1271.
Ren, D., Xiong, S., Ren, Y., Yang, X., Zhao, X., Jin, J., Xu, M., Liang, T., Guo, L., Weng, L., 2024. Advances in therapeutic cancer vaccines: harnessing immune adjuvants for enhanced efficacy and future perspectives. Comput. Struct. Biotechnol. J. 23, 1833–1843.
Riccardo, F., Iussich, S., Maniscalco, L., Lorda Mayayo, S., La Rosa, G., Arigoni, M., De Maria, R., Gattino, F., Lanzardo, S., Lardone, E., Martano, M., Morello, E., Prestigio, S., Fiore, A., Quaglino, E., Zabarino, S., Ferrone, S., Buracco, P., Cavallo, F., 2014. CSPG4-specific immunity and survival prolongation in dogs with oral malignant melanoma immunized with human CSPG4 DNA. Clin. Cancer Res. 20 (14), 3753–3762.
Riccardo, F., Tarone, L., Camerino, M., Giacobino, D., Iussich, S., Barutello, G., Arigoni, M., Conti, L., Bolli, E., Quaglino, E., Merighi, I.F., Morello, E., Dentini, A., Ferrone, S., Buracco, P., Cavallo, F., 2022. Antigen mimicry as an effective strategy to induce CSPG4-targeted immunity in dogs with oral melanoma: a veterinary trial. J Immunother Cancer 10 (5).
Rolih, V., Barutello, G., Iussich, S., De Maria, R., Quaglino, E., Buracco, P., Cavallo, F., Riccardo, F., 2017. CSPG4: a prototype oncoantigen for translational immunotherapy studies. J. Transl. Med. 15 (1), 151.
Rolih, V., Caldeira, J., Bolli, E., Salameh, A., Conti, L., Barutello, G., Riccardo, F., Magri, J., Lamolinara, A., Parra, K., Valenzuela, P., Francia, G., Iezzi, M., Pericle, F., Cavallo, F., 2020. Development of a VLP-based vaccine displaying an xCT extracellular domain for the treatment of metastatic breast cancer. Cancers 12 (6).
Ronzitti, G., Gross, D.A., Mingozzi, F., 2020. Human immune responses to adeno-associated virus (AAV) vectors. Front. Immunol. 11, 670.
Roy, D.G., Geoffroy, K., Marguerie, M., Khan, S.T., Martin, N.T., Kmiecik, J., Bobbala, D., Aitken, A.S., de Souza, C.T., Stephenson, K.B., Lichty, B.D., Auer, R.C., Stojdl, D.F., Bell, J.C., Bourgeois-Daigneault, M.C., 2021. Adjuvant oncolytic virotherapy for personalized anti-cancer vaccination. Nat. Commun. 12 (1), 2626.
Ruiu, R., Rolih, V., Bolli, E., Barutello, G., Riccardo, F., Quaglino, E., Merighi, I.F., Pericle, F., Donofrio, G., Cavallo, F., Conti, L., 2019. Fighting breast cancer stem cells through the immune-targeting of the xCT cystine-glutamate antiporter. Cancer Immunol. Immunother. 68 (1), 131–141.
Ruzzi, F., Palladini, A., Clemmensen, S., Strobaek, A., Buijs, N., Domeyer, T., Dorosz, J., Soroka, V., Grzadziela, D., Rasmussen, C.J., Nielsen, I.B., Soegaard, M., Semprini, M. S., Scalambra, L., Angelicola, S., Landuzzi, L., Lollini, P.L., Thorn, M., 2022. Prevention and therapy of metastatic HER-2(+) mammary carcinoma with a human candidate HER-2 virus-like particle vaccine. Biomedicines 10 (10).
Ruzzi, F., Semprini, M.S., Scalambra, L., Palladini, A., Angelicola, S., Cappello, C., Pittino, O.M., Nanni, P., Lollini, P.L., 2023. Virus-like particle (VLP) vaccines for cancer immunotherapy. Int. J. Mol. Sci. 24 (16).
Salio, M., Cella, M., Suter, M., Lanzavecchia, A., 1999. Inhibition of dendritic cell maturation by herpes simplex virus. Eur. J. Immunol. 29 (10), 3245–3253.
Saltos, A., Khalil, F., Smith, M., Li, J., Schell, M., Antonia, S.J., Gray, J.E., 2018. Clinical associations of mucin 1 in human lung cancer and precancerous lesions. Oncotarget 9 (86), 35666–35675.
Sander, A.F., Lollini, P.L., 2018. Virus-like antigen display for cancer vaccine development, what is the potential? Expert Rev. Vaccines 17 (4), 285–288.
Saxena, M., van der Burg, S.H., Melief, C.J.M., Bhardwaj, N., 2021. Therapeutic cancer vaccines. Nat. Rev. Cancer 21 (6), 360–378.
Sayour, E.J., Boczkowski, D., Mitchell, D.A., Nair, S.K., 2024. Cancer mRNA vaccines: clinical advances and future opportunities. Nat. Rev. Clin. Oncol. 21 (7), 489–500.
Schoen, R.E., Boardman, L.A., Cruz-Correa, M., Bansal, A., Kastenberg, D., Hur, C., Dzubinski, L., Kaufman, S.F., Rodriguez, L.M., Richmond, E., Umar, A., Szabo, E., Salazar, A., McKolanis, J., Beatty, P., Pai, R.K., Singhi, A.D., Jacqueline, C.M., Bao, R., Diergaarde, B., McMurray, R.P., Strand, C., Foster, N.R., Zahrieh, D.M., Limburg, P.J., Finn, O.J., 2023. Randomized, double-blind, placebo-controlled trial of MUC1 peptide vaccine for prevention of recurrent colorectal adenoma. Clin. Cancer Res. 29 (9), 1678–1688.
Sher, Y.P., Lin, S.I., Chen, I.H., Liu, H.Y., Lin, C.Y., Chiang, I.P., Roffler, S., Chen, H.W., Liu, S.J., 2016. A HLA-A2-restricted CTL epitope induces anti-tumor effects against human lung cancer in mouse xenograft model. Oncotarget 7 (1), 671–683.
Skolnik, J.M., Morrow, M.P., 2023. Vaccines for HPV-associated diseases. Mol. Aspect. Med. 94, 101224.
Soares, K.C., Rucki, A.A., Wu, A.A., Olino, K., Xiao, Q., Chai, Y., Wamwea, A., Bigelow, E., Lutz, E., Liu, L., Yao, S., Anders, R.A., Laheru, D., Wolfgang, C.L., Edil, B. H., Schulick, R.D., Jaffee, E.M., Zheng, L., 2015. PD-1/PD-L1 blockade together with vaccine therapy facilitates effector T-cell infiltration into pancreatic tumors. J. Immunother. 38 (1), 1–11.
Speiser, D.E., Schwarz, K., Baumgaertner, P., Manolova, V., Devevre, E., Sterry, W., Walden, P., Zippelius, A., Conzett, K.B., Senti, G., Voelter, V., Cerottini, J.P., Guggisberg, D., Willers, J., Geldhof, C., Romero, P., Kundig, T., Knuth, A., Dummer, R., Trefzer, U., Bachmann, M.F., 2010. Memory and effector CD8 T-cell responses after nanoparticle vaccination of melanoma patients. J. Immunother. 33 (8), 848–858.
Sprooten, J., Ceusters, J., Coosemans, A., Agostinis, P., De Vleeschouwer, S., Zitvogel, L., Kroemer, G., Galluzzi, L., Garg, A.D., 2019. Trial watch: dendritic cell vaccination for cancer immunotherapy. OncoImmunology 8 (11), e1638212.
Srinivasan, R., Wolchok, J.D., 2004. Tumor antigens for cancer immunotherapy: therapeutic potential of xenogeneic DNA vaccines. J. Transl. Med. 2 (1), 12.
Srivatsan, S., Patel, J.M., Bozeman, E.N., Imasuen, I.E., He, S., Daniels, D., Selvaraj, P., 2014. Allogeneic tumor cell vaccines: the promise and limitations in clinical trials. Hum. Vaccines Immunother. 10 (1), 52–63.
Stanton, S.E., Castle, P.E., Finn, O.J., Sei, S., Emens, L.A., 2024. Advances and challenges in cancer immunoprevention and immune interception. J Immunother Cancer 12 (3).
Stephens, A.J., Burgess-Brown, N.A., Jiang, S., 2021. Beyond just peptide antigens: the complex world of peptide-based cancer vaccines. Front. Immunol. 12, 696791.
Stevenson, V.B., Klahn, S., LeRoith, T., Huckle, W.R., 2022. Canine melanoma: a review of diagnostics and comparative mechanisms of disease and immunotolerance in the era of the immunotherapies. Front. Vet. Sci. 9, 1046636.
Stroud, C., Dmitriev, I., Kashentseva, E., Bryan, J.N., Curiel, D.T., Rindt, H., Reinero, C., Henry, C.J., Bergman, P.J., Mason, N.J., Gnanandarajah, J.S., Engiles, J.B., Gray, F., Laughlin, D., Gaurnier-Hausser, A., Wallecha, A., Huebner, M., Paterson, Y., O'Connor, D., Treml, L.S., Stannard, J.P., Cook, J.L., Jacobs, M., Wyckoff, G.J., Likins, L., Sabbagh, U., Skaff, A., Guloy, A.S., Hays, H.D., LeBlanc, A.K., Coates, J.R., Katz, M.L., Lyons, L.A., Johnson, G.C., Johnson, G.S., O'Brien, D.P., Duan, D., Calvet, J.P., Gandolfi, B., Baron, D.A., Weiss, M.L., Webster, D.A., Karanu, F.N., Robb, E.J., Harman, R.J., 2016. A One Health overview, facilitating advances in comparative medicine and translational research. Clin. Transl. Med. 5 (Suppl. 1), 26.
Swain, S.M., Shastry, M., Hamilton, E., 2023. Targeting HER2-positive breast cancer: advances and future directions. Nat. Rev. Drug Discov. 22 (2), 101–126.
Sylvester, R.J., van der, M.A., Lamm, D.L., 2002. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J. Urol. 168 (5), 1964–1970.

Tamburini, S., Zhang, Y., Gagliardi, A., Di Lascio, G., Caproni, E., Benedet, M., Tomasi, M., Corbellari, R., Zanella, I., Croia, L., Grandi, G., Muller, M., Grandi, A., 2023. Bacterial outer membrane vesicles as a platform for the development of a broadly protective human papillomavirus vaccine based on the minor capsid protein L2. Vaccines (Basel) 11 (10).

Tang, C.K., Pietersz, G.A., 2009. Intracellular detection and immune signaling pathways of DNA vaccines. Expert Rev. Vaccines 8 (9), 1161–1170.

Tarone, L., Barutello, G., Iussich, S., Giacobino, D., Quaglino, E., Buracco, P., Cavallo, F., Riccardo, F., 2019. Naturally occurring cancers in pet dogs as pre-clinical models for cancer immunotherapy. Cancer Immunol. Immunother. 68 (11), 1839–1853.

Tarone, L., Giacobino, D., Camerino, M., Ferrone, S., Buracco, P., Cavallo, F., Riccardo, F., 2022a. Canine melanoma immunology and immunotherapy: relevance of translational research. Front. Vet. Sci. 9, 803093.

Tarone, L., Giacobino, D., Camerino, M., Maniscalco, L., Iussich, S., Parisi, L., Giovannini, G., Dentini, A., Bolli, E., Quaglino, E., Merighi, I.F., Morello, E., Buracco, P., Riccardo, F., Cavallo, F., 2023. A chimeric human/dog-DNA vaccine against CSPG4 induces immunity with therapeutic potential in comparative preclinical models of osteosarcoma. Mol. Ther. 31 (8), 2342–2359.

Tarone, L., Mareschi, K., Tirtei, E., Giacobino, D., Camerino, M., Buracco, P., Morello, E., Cavallo, F., Riccardo, F., 2022b. Improving osteosarcoma treatment: comparative oncology in action. Life (Basel) 12 (12).

Tay, J., Levesque, J.P., Winkler, I.G., 2017. Cellular players of hematopoietic stem cell mobilization in the bone marrow niche. Int. J. Hematol. 105 (2), 129–140.

Temizoz, B., Kuroda, E., Ishii, K.J., 2016. Vaccine adjuvants as potential cancer immunotherapeutics. Int. Immunol. 28 (7), 329–338.

Thomas, S.J., Moreira Jr., E.D., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J.L., Perez Marc, G., Polack, F.P., Zerbini, C., Bailey, R., Swanson, K.A., Xu, X., Roychoudhury, S., Koury, K., Bouguermouh, S., Kalina, W.V., Cooper, D., Frenck Jr., R.W., Hammitt, L.L., Tureci, O., Nell, H., Schaefer, A., Unal, S., Yang, Q., Liberator, P., Tresnan, D.B., Mather, S., Dormitzer, P.R., Sahin, U., Gruber, W.C., Jansen, K.U., Group, C.C.T., 2021. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine through 6 months. N. Engl. J. Med. 385 (19), 1761–1773.

Tornesello, A.L., Tagliamonte, M., Buonaguro, F.M., Tornesello, M.L., Buonaguro, L., 2022. Virus-like particles as preventive and therapeutic cancer vaccines. Vaccines (Basel) 10 (2).

Turajlic, S., Litchfield, K., Xu, H., Rosenthal, R., McGranahan, N., Reading, J.L., Wong, Y. N.S., Rowan, A., Kanu, N., Al Bakir, M., Chambers, T., Salgado, R., Savas, P., Loi, S., Birkbak, N.J., Sansregret, L., Gore, M., Larkin, J., Quezada, S.A., Swanton, C., 2017. Insertion-and-deletion-derived tumour-specific neoantigens and the immunogenic phenotype: a pan-cancer analysis. Lancet Oncol. 18 (8), 1009–1021.

Twitty, C.G., Jensen, S.M., Hu, H.M., Fox, B.A., 2011. Tumor-derived autophagosome vaccine: induction of cross-protective immune responses against short-lived proteins through a p62-dependent mechanism. Clin. Cancer Res. 17 (20), 6467–6481.

Ulmer, J.B., Donnelly, J.J., Parker, S.E., Rhodes, G.H., Felgner, P.L., Dwarki, V.J., Gromkowski, S.H., Deck, R.R., DeWitt, C.M., Friedman, A., et al., 1993. Heterologous protection against influenza by injection of DNA encoding a viral protein. Science 259 (5102), 1745–1749.

van Dorst, M., Pyuza, J.J., Nkurunungi, G., Kullaya, V.I., Smits, H.H., Hogendoorn, P.C. W., Wammes, L.J., Everts, B., Elliott, A.M., Jochems, S.P., Yazdanbakhsh, M., 2024. Immunological factors linked to geographical variation in vaccine responses. Nat. Rev. Immunol. 24 (4), 250–263.

van Drunen Littel-van den Hurk, S., Hannaman, D., 2010. Electroporation for DNA immunization: clinical application. Expert Rev. Vaccines 9 (5), 503–517.

Vannini, A., Parenti, F., Forghieri, C., Barboni, C., Zaghini, A., Campadelli-Fiume, G., Gianni, T., 2023. Innovative retargeted oncolytic herpesvirus against nectin4-positive cancers. Front. Mol. Biosci. 10, 1149973.

Verganti, S., Berlato, D., Blackwood, L., Amores-Fuster, I., Polton, G.A., Elders, R., Doyle, R., Taylor, A., Murphy, S., 2017. Use of Oncept melanoma vaccine in 69 canine oral malignant melanomas in the UK. J. Small Anim. Pract. 58 (1), 10–16.

Vienot, A., Jacquin, M., Rebucci-Peixoto, M., Pureur, D., Ghiringhelli, F., Assenat, E., Hammel, P., Rosmorduc, O., Stouvenot, M., Allaire, M., Bouattour, M., Regnault, H., Fratte, S., Raymond, E., Soularue, E., Husson-Wetzel, S., Di Martino, V., Muller, A., Clairet, A.L., Fagnoni-Legat, C., Adotevi, O., Meurisse, A., Vernerey, D., Borg, C., 2023. Evaluation of the interest to combine a CD4 Th1-inducer cancer vaccine derived from telomerase and atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma: a randomized non-comparative phase II study (TERTIO - PRODIGE 82). BMC Cancer 23 (1), 710.

Vinayak, S., Cecil, D.L., Disis, M.L., 2024. Vaccines for breast cancer prevention: are we there yet? Mol. Aspect. Med. 98, 101292.

Wang, B., Pei, J., Xu, S., Liu, J., Yu, J., 2023. Recent advances in mRNA cancer vaccines: meeting challenges and embracing opportunities. Front. Immunol. 14, 1246682.

Wang, S., Guo, J., Bai, Y., Sun, C., Wu, Y., Liu, Z., Liu, X., Wang, Y., Wang, Z., Zhang, Y., Hao, H., 2022. Bacterial outer membrane vesicles as a candidate tumor vaccine platform. Front. Immunol. 13, 987419.

Wang, S.H., Cao, Z., Farazuddin, M., Chen, J., Janczak, K.W., Tang, S., Cannon, J., Baker Jr., J.R., 2024. A novel intranasal peptide vaccine inhibits non-small cell lung cancer with KRAS mutation. Cancer Gene Ther. 31 (3), 464–471.

Wang, T.Y., Liu, Q., Ren, Y., Alam, S.K., Wang, L., Zhu, Z., Hoeppner, L.H., Dehm, S.M., Cao, Q., Yang, R., 2021. A pan-cancer transcriptome analysis of exitron splicing identifies novel cancer driver genes and neoepitopes. Mol. Cell 81 (10), 2246–2260 e2212.

Weber, J.S., Carlino, M.S., Khattak, A., Meniawy, T., Ansstas, G., Taylor, M.H., Kim, K.B., McKean, M., Long, G.V., Sullivan, R.J., Faries, M., Tran, T.T., Cowey, C.L., Pecora, A., Shaheen, M., Segar, J., Medina, T., Atkinson, V., Gibney, G.T., Luke, J.J., Thomas, S., Buchbinder, E.I., Healy, J.A., Huang, M., Morrissey, M., Feldman, I., Sehgal, V., Robert-Tissot, C., Hou, P., Zhu, L., Brown, M., Aanur, P., Meehan, R.S., Zaks, T., 2024. Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942): a randomised, phase 2b study. Lancet 403 (10427), 632–644.

Wei, Z., Zhou, C., Zhang, Z., Guan, M., Zhang, C., Liu, Z., Liu, Q., 2019. The landscape of tumor fusion neoantigens: a pan-cancer analysis. iScience 21, 249–260.

Westwood, J.A., Darcy, P.K., Kershaw, M.H., 2014. The potential impact of mouse model selection in preclinical evaluation of cancer immunotherapy. OncoImmunology 3 (7), e946361.

Witt, K., Ligtenberg, M.A., Conti, L., Lanzardo, S., Ruiu, R., Wallmann, T., Tufvesson-Stiller, H., Chambers, B.J., Rolny, C., Lladser, A., Lundqvist, A., Cavallo, F., Kiessling, R., 2018. Cripto-1 plasmid DNA vaccination targets metastasis and cancer stem cells in murine mammary carcinoma. Cancer Immunol. Res. 6 (11), 1417–1425.

Xie, N., Shen, G., Gao, W., Huang, Z., Huang, C., Fu, L., 2023a. Neoantigens: promising targets for cancer therapy. Signal Transduct. Targeted Ther. 8 (1), 9.

Xie, Y.J., Liu, W.Q., Li, D., Hou, J.C., Coghi, P.S., Fan, X.X., 2023b. Overcoming suppressive tumor microenvironment by vaccines in solid tumor. Vaccines (Basel) 11 (2).

Yaghoubi, A., Khazaei, M., Jalili, S., Hasanian, S.M., Avan, A., Soleimanpour, S., Cho, W. C., 2020. Bacteria as a double-action sword in cancer. Biochim. Biophys. Acta Rev. Canc 1874 (1), 188388.

Yan, C., Nebhan, C.A., Saleh, N., Shattuck-Brandt, R., Chen, S.C., Ayers, G.D., Weiss, V., Richmond, A., Vilgelm, A.E., 2023. Generation of orthotopic patient-derived xenografts in humanized mice for evaluation of emerging targeted therapies and immunotherapy combinations for melanoma. Cancers 15 (14).

Yang, B., Jeang, J., Yang, A., Wu, T.C., Hung, C.F., 2014. DNA vaccine for cancer immunotherapy. Hum. Vaccines Immunother. 10 (11), 3153–3164.

Yankauckas, M.A., Morrow, J.E., Parker, S.E., Abai, A., Rhodes, G.H., Dwarki, V.J., Gromkowski, S.H., 1993. Long-term anti-nucleoprotein cellular and humoral immunity is induced by intramuscular injection of plasmid DNA containing NP gene. DNA Cell Biol. 12 (9), 771–776.

Yarchoan, M., Gane, E.J., Marron, T.U., Perales-Linares, R., Yan, J., Cooch, N., Shu, D.H., Fertig, E.J., Kagohara, L.T., Bartha, G., Northcott, J., Lyle, J., Rochestie, S., Peters, J., Connor, J.T., Jaffee, E.M., Csiki, I., Weiner, D.B., Perales-Puchalt, A., Sardesai, N.Y., 2024. Personalized neoantigen vaccine and pembrolizumab in advanced hepatocellular carcinoma: a phase 1/2 trial. Nat. Med. 30 (4), 1044–1053.

You, Z., Zhou, W., Weng, J., Feng, H., Liang, P., Li, Y., Shi, F., 2021. Application of HER2 peptide vaccines in patients with breast cancer: a systematic review and meta-analysis. Cancer Cell Int. 21 (1), 489.

Young, M.R.I., 2017. Redirecting the focus of cancer immunotherapy to premalignant conditions. Cancer Lett. 391, 83–88.

Yu, G., Li, Y., Cui, Z., Morris, N.P., Weinberg, A.D., Fox, B.A., Urba, W.J., Wang, L., Hu, H.M., 2016. Combinational immunotherapy with allo-DRibble vaccines and anti-OX40 Co-stimulation leads to generation of cross-reactive effector T cells and tumor regression. Sci. Rep. 6, 37558.

Yu, J., Sun, H., Cao, W., Song, Y., Jiang, Z., 2022. Research progress on dendritic cell vaccines in cancer immunotherapy. Exp. Hematol. Oncol. 11 (1), 3.

Yun, C.O., Hong, J., Yoon, A.R., 2022. Current clinical landscape of oncolytic viruses as novel cancer immunotherapeutic and recent preclinical advancements. Front. Immunol. 13, 953410.

Zaidi, N., Huff, A., Marcisak-Davis, E., Haldar, D., Heumann, T., Konig, M., Mog, B., Montagne, J., Longway, G., Andaloori, L., Lyman, M., Danilova, L., Nauroth, J., Kagohara, L., Fertig, E., Azad, N., Jaffee, E., 2022. Abstract IA013: intercepting pancreatic cancer development with mutant KRAS-targeted immunotherapy. Cancer Res. 82 (22_Suppl. ment), IA013. IA013.

Zanetti, M., 2017. A second chance for telomerase reverse transcriptase in anticancer immunotherapy. Nat. Rev. Clin. Oncol. 14 (2), 115–128.

Zhang, G., Tang, T., Chen, Y., Huang, X., Liang, T., 2023a. mRNA vaccines in disease prevention and treatment. Signal Transduct. Targeted Ther. 8 (1), 365.

Zhang, X., Cui, H., Zhang, W., Li, Z., Gao, J., 2023b. Engineered tumor cell-derived vaccines against cancer: the art of combating poison with poison. Bioact. Mater. 22, 491–517.

Zhao, T., Cai, Y., Jiang, Y., He, X., Wei, Y., Yu, Y., Tian, X., 2023. Vaccine adjuvants: mechanisms and platforms. Signal Transduct. Targeted Ther. 8 (1), 283.

Zhao, W., Zhao, G., Wang, B., 2018. Revisiting GM-CSF as an adjuvant for therapeutic vaccines. Cell. Mol. Immunol. 15 (2), 187–189.

Zheng, J.H., Nguyen, V.H., Jiang, S.N., Park, S.H., Tan, W., Hong, S.H., Shin, M.G., Chung, I.J., Hong, Y., Bom, H.S., Choy, H.E., Lee, S.E., Rhee, J.H., Min, J.J., 2017. Two-step enhanced cancer immunotherapy with engineered Salmonella typhimurium secreting heterologous flagellin. Sci. Transl. Med. 9 (376).

Zhou, J., Sun, X.Y., Stenzel, D.J., Frazer, I.H., 1991. Expression of vaccinia recombinant HPV 16 L1 and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles. Virology 185 (1), 251–257.

Zhou, M., Tang, Y., Xu, W., Hao, X., Li, Y., Huang, S., Xiang, D., Wu, J., 2023. Bacteria-based immunotherapy for cancer: a systematic review of preclinical studies. Front. Immunol. 14, 1140463.

zur Hausen, H., 2002. Papillomaviruses and cancer: from basic studies to clinical application. Nat. Rev. Cancer 2 (5), 342–350.