nature reviews drug discovery

https://doi.org/10.1038/s41573-024-01081-5

Review article

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Vaccines for cancer prevention: exploring opportunities and navigating challenges

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Abstract

Improved understanding of cancer immunology has gradually brought increasing attention towards cancer-preventive vaccines as an important tool in the fight against cancer. The aim of this approach is to reduce cancer occurrence by inducing a specific immune response targeting tumours at an early stage before they can fully develop. The great advantage of preventive cancer vaccines lies in the potential to harness a less-compromised immune system in vaccine recipients before their immune responses become affected by the advanced status of the disease itself or by aggressive treatments such as chemotherapy. Successful implementation of immunoprevention against oncogenic viruses such as hepatitis B and papillomavirus has led to a dramatic decrease in virally induced cancers. Extending this approach to other cancers holds great promise but remains a major challenge. Here, we provide a comprehensive review of preclinical evidence supporting this approach, encouraging results from pioneering clinical studies as well as a discussion on the key aspects and open questions to address in order to design potent prophylactic cancer vaccines in the near future.

Sections

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Introduction

New medical avenues are needed to decrease the incidence of cancer and its deleterious economic impact, estimated to increase by 34% in 15 years, reaching US$ 246 billion by 2030 in the USA alone[1]. In this context, preventive vaccination constitutes a great opportunity to address both aspects. The old saying says: "Prevention is better than a cure", and the fact that the immune system in healthy individuals is less compromised by the disease than in patients constitutes a great advantage for immunoprevention approaches over therapeutic ones.

Immunoprevention strategies have already been successful in controlling the spread of several diseases, including smallpox, yellow fever[2] and, more recently, COVID-19 (ref. 3). In cancer, vaccines have been mostly used in therapeutic settings, after the disease has occurred, with very positive safety profiles but only limited clinical benefits[4]. However, exceptionally, they have proven successful in the preventative setting upon targeting oncogenic viruses such as human papillomavirus (HPV) and hepatitis B virus (HBV)[5]. Nevertheless, thanks to the major progress achieved in the past decades in better understanding the close interplay between the immune system and cancer, and to the lessons learnt from therapeutic cancer vaccination campaigns, cancer-preventive vaccines are gaining increasing attention and hold great potential against cancer morbidity. Importantly, cancer immunoprevention is amongst the main pillars of the 2022 renewal of the Cancer Moonshot Program by the Biden administration; the Cancer Moonshot Program was initially started in 2016 by the Obama administration and has already brought tremendous progress in cancer research developments[6]. The ambitious goals of this new phase are to reduce cancer mortality by at least 50% in the next 25 years and, amongst others, to develop a pan-anticancer vaccine able to prevent multiple cancer types[7]. Although we are far from this, such objectives seem realistically achievable in the future and require a multistep approach building up on our current evidence. The concept of cancer immunoediting recapitulates the interactions between tumour cells and the immune system from its early onset to late-stage disease and metastasis and is divided into three phases: elimination, equilibrium and escape[8]. In the elimination phase, also known as immunosurveillance, tumour recognition and clearance are usually driven by antigen-presenting cells, which, upon engulfing tumour material, process tumour antigens and present them to cognate $CD4^+$ and $CD8^+$ T cells, subsequently activating a cytotoxic response against tumour targets[9]. If this process is successful, the lesion is cleared, and the individual remains free of cancer. In other instances, tumour cells undergoing the rapid mutational process and constant immune selection pressure characteristic of tumour progression can develop antigens that are no longer recognized by the immune system. This editing process characterizes the equilibrium phase. The escape phase begins when tumour cells achieve resistance to immune attack by developing several mechanisms that further enable them to escape immune recognition and subsequently thrive in an uncontrolled manner. These mechanisms include (1) the downregulation of components of the antigen processing and presentation machinery (such as major histocompatibility complex I (MHC-I) molecules and surface co-stimulatory factors) essential for T cell recognition; (2) the expression of immunosuppressive molecular cues that further impair T cell responses such as CTLA4 and PD1; and (3) the production of tumour-release factors that can recruit immunoregulatory cells such as regulatory T cells, myeloid-derived suppressor cells and tumour-associated macrophages[10]. Together, these tumour-orchestrated processes eventually lead to the inability of the immune system to efficiently clear tumour cells, further supporting immune escape and cancer development (Fig. 1).

Cancer vaccines have primarily been used as adjuvant therapy in maintenance settings or in combination with other treatment regimens in metastatic cancer settings. In the adjuvant setting, they aim to eliminate any remaining cancer cells after standard treatment, with the objective of preventing recurrence. In the metastatic setting, they are used during the escape phase, in which a strong immunosuppressive tumour microenvironment (TME) has already been established, justifying their use with combinatorial regimens. Despite the sheer number of studies and different types of formulations, clinical outcomes have so far been modest and did not exceed 20% of clinical response[4,11]. It is consensus that such lack of efficacy is linked to the inability to overcome the overwhelming immunosuppressive TME and to mount an efficient immune response. Instead, phenotypic characterization of pre-cancerous lesions versus late-stage or metastatic cancer status confirmed that disease progression is linked to increasing suppressed immunity and impaired immune surveillance mechanisms[12–15]. This, together with other compiled evidence here reviewed, supports the vision for a paradigm shift in cancer vaccine applications that is necessary to release their full immunogenic potential. We claim that applying cancer vaccines at early disease onset (such as during the equilibrium phase) constitutes a great opportunity to intercept cancer before extensive immune suppression is established, boosting tumour recognition and tipping the back balance towards the elimination phase. Such a conceptual shift, paired with the current tremendous progress in cancer diagnostics and early detection, has the potential to have a dramatic impact on cancer management and morbidity. Indeed, given that cancers during this phase are often asymptomatic, detecting them poses a considerable challenge. Early cancer identification may be aided by the implementation of comprehensive screening programmes for populations at high risk such as those with genetic predispositions or particular environmental exposures. Imaging methods and biomarker assays that can identify low disease burden or molecular alterations associated with cancer initiation may present viable paths for identifying individuals in the equilibrium phase. Integrating these approaches into routine clinical practice could enhance our ability to prevent or intercept cancer at its earliest stages, constituting a method of prevention in which cancer vaccines can play an important part. Cancer prevention is categorized into three types: primary, secondary and tertiary. Primary prevention aims to prevent the onset of cancer by reducing exposure to risk factors through lifestyle changes, vaccinations and environmental safety measures. Secondary prevention, or medical interception, entails early detection and treatment of pre-cancerous conditions or early-stage cancers to prevent progression. Tertiary prevention, also considered as medical interception, focuses on managing and reducing the impact of advanced symptomatic disease, preventing recurrence, and improving quality of life and survivorship.

In this Review, we will provide an overview of prophylactic approaches in these three different settings and the encouraging results collected so far. We also discuss the important challenges that lie ahead in order to design more powerful formulations and extend current applications to other disease indications.

Primary prevention

This type of prevention entails the reduction of incidence of pre-malignant lesions and hence the onset of cancer. By vaccinating individuals before

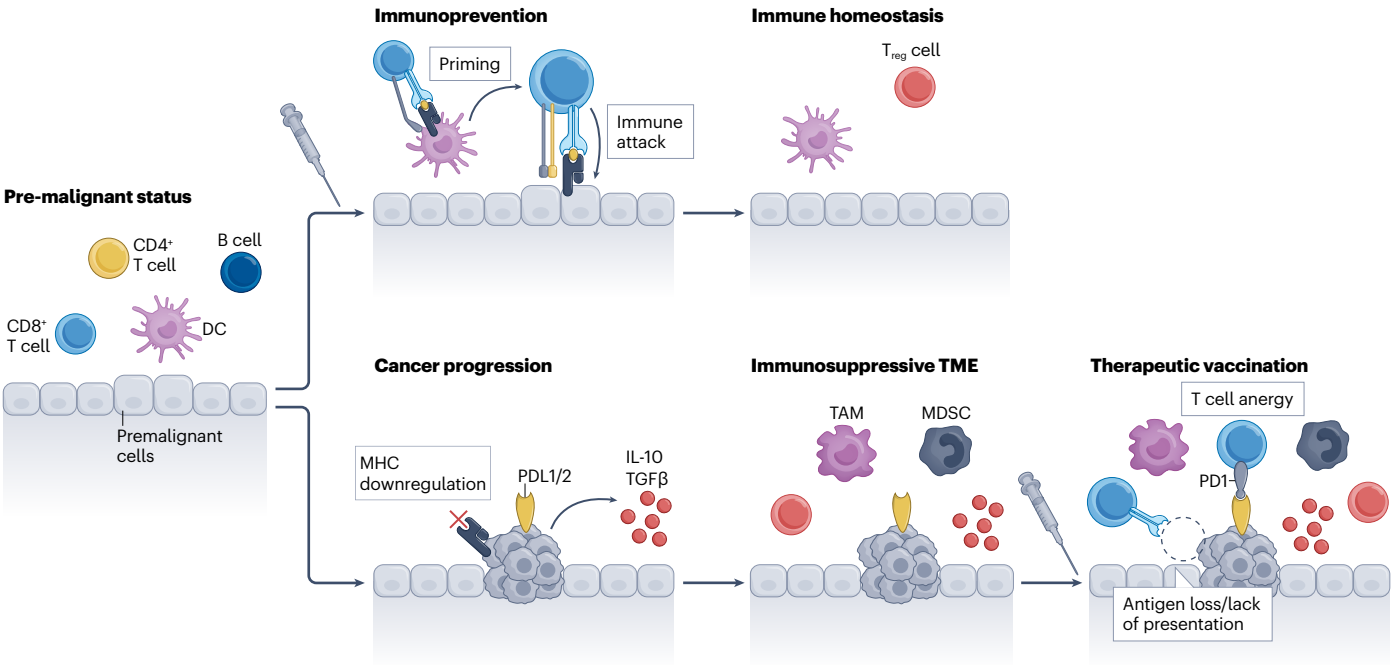

Fig. 1 | Immunoprevention approaches at early disease onset induce long-lasting protection against cancer. Pre-malignant cells arise during the carcinogenic process in the presence of a still immunocompetent microenvironment. Adaptive immune cells are recruited at the site and eliminate abnormal cells. However, in certain instances, this response is inadequate and leads to further disease progression. Immunoprevention approaches (top) can induce or further support immune recognition by the adaptive immune system, promoting clearance of pre-malignant lesions and eventually re-establishing immunosurveillance and homeostasis. If left untreated (bottom), disease progression leads to the establishment of an immunosuppressive tumour microenvironment (TME) characterized by major histocompatibility complex (MHC) downregulation, immune-checkpoint expression and release of immunosuppressive cues, and infiltration of immune cells with regulatory functions, overall leading to impairment in antigen presentation and immunosurveillance. Thus, therapeutic vaccination in this context is less efficient in inducing immune recognition and clearance of advanced tumour lesions. DC, dendritic cell; IL-10, interleukin-10; MDSC, myeloid-derived suppressor cell; TAM, tumour-associated macrophage; TGFβ, transforming growth factor-β; T_{reg}, regulatory T.

they are exposed to known cancer-causing agents, primary prevention efforts can significantly reduce the incidence of certain types of cancer.

Healthy individuals

Virally induced cancers. The best results in terms of cancer immunoprevention so far have been achieved in primary prevention, specifically against virally induced cancers. HBV infection is a recognized risk factor for the development of hepatocellular carcinoma. Since the first preventive vaccine against HBV became available in 1981, public vaccination campaigns have led to a dramatic drop of up to 70% in hepatocellular carcinoma cases in the general population[16–18]. Similarly, the introduction of mass vaccination in the healthy population against HPV, a recognized cause of ~5% of all cancers worldwide[19], was able to induce efficient and long-lasting protection with a reported 93% reduction in the prevalence of HPV infections 4 years after vaccination and a protection of >90% against HPV-related pre-cancerous lesions (with injection prior to HPV exposure)[18].

Interestingly, therapeutic vaccines administered to individuals with HPV infection instead (in tertiary prevention settings) demonstrated much lower clinical efficacy. A recent metadata analysis demonstrated that HPV therapeutic vaccination was able to induce an overall significant reduction of 22.1% in cervical intraepithelial neoplasia (a pre-malignant condition caused by HPV infection) incidence, compared to placebo, and a pooled efficacy of only 23.6% for complete resolution[20]. Once more, these results support the vision that cancer vaccines should be used early on, before or at disease onset, to release their true immune potential and advocate for the extension of this approach to cancers of non-viral origin.

Despite large efforts, preventive vaccine formulations against other cancer risk agents, such as Epstein–Barr virus (EBV), hepatitis C virus (HCV) or *Helicobacter pylori*, have so far failed in clinical trials or, in the case of Merkel virus, have not been investigated at all, to our knowledge[21–23], with research focusing mostly on therapeutic management after the infection[24]. Several aspects, often disease specific, have contributed to these failures.

In the case of EBV — a risk factor for several cancers, including Hodgkin, T cell and natural killer cell lymphomas, and gastric cancer, among others[23] — the main reason is linked to poor antigen selection. Despite the crucial discovery in 2000 that EBV lacking the gp350 virus protein was still able to infect host cells, thus suggesting that this target was dispensable for viral entry[25], a plethora of subsequent preclinical and clinical studies still focused on gp350-based vaccines, with expected limited outcomes[25]. Based on these observations, recent studies are now relying on a multivalent approach targeting up to four different viral proteins, including gH and gp42, which are essential for viral entry (for example, NCT05164094)[23].

Other crucial aspects that have not yet been fully addressed include high genetic heterogeneity in HCV[26], efficient immune escape

mechanisms for the *H. pylori* bacterial agent[27], and a lack of research and funding in the case of Merkel virus owing to low disease occurrence and thus limited financial reward for pharmaceutical companies. Despite this, epidemiological studies[28,29] and models[30–32] estimated that future introduction of effective preventive measures against these pathogens will substantially decrease infection, cancer-related incidence and health-care costs, advocating for further investigations aimed at addressing the abovementioned challenges; these are carefully reviewed below.

Proto-oncogenes. The key to the success obtained so far in preventive vaccination strategies against HPV-associated and HBV-associated cancers, compared with cancers of non-viral origin, lies mainly in the ability to target virus-specific antigens that are universal, easy to identify and essential for aetiology, hence limiting the occurrence of antigen-loss variants and subsequent immune escape. Viral antigens are also different from host self-antigens and are therefore not prone to central and peripheral tolerance mechanisms. One of the current challenges in the field is the identification of analogous potent non-viral cancer antigens, extending this approach to other cancer types.

Among the different classes of antigens currently available for vaccination purposes[33], proto-oncogenes constitute a very promising class for cancer primary prevention in healthy individuals[34]. Proto-oncogenes encode intracellular regulatory proteins (such as protein kinases), growth factors and growth factor receptors that are involved in cell growth and differentiation. Genetic modifications of proto-oncogenes, such as point mutation, chromosomal translocation, gene amplification or deletions, can lead to aberrant activation or enhanced expression of the encoded protein, causing alterations in cell growth and differentiation and, ultimately, neoplasia. Once genetically altered, a proto-oncogene becomes an oncogene, actively involved in cancer aetiology.

Given their crucial role in the carcinogenesis process, proto-oncogenes generally appear early on at disease onset and can be expressed in a high percentage of some tumour types and sometimes in more than one type of cancer, circumventing the need for personalized identification in each patient, and making them ideal targets for large vaccination campaigns. To date, more than 40 proto-oncogenes have been identified and classified[35], with some already partially investigated as cancer therapeutic targets. Notably, mutations in *RAS* and *RAF* oncogenes have already been targeted in advanced tumours with discreet success (such as *BRAF*-targeted therapies in melanoma)[36] and showed immunogenic properties in advanced-stage disease status[34]. Therapeutic vaccine studies targeting oncogene mutants have predominantly focused on patients with pancreatic or colorectal cancer (CRC) and showed statistically significant, albeit only moderate, survival improvements in immune-responsive patients compared to non-responsive patients[37,38]. These vaccine studies were either cell based, in which antigen-presenting cells were pulsed with the peptide of interest, or peptide based, consisting of lyophilized peptides admixed with the adjuvant DETOX[38] (Box 1).

In prophylactic settings, a recent pioneering study using an inducible model of lung cancer showed that a multi-peptide vaccine targeting multiple epitopes of mutant and wild-type KRAS was efficient

Box 1 | Different types of adjuvants and their effect on vaccination

Adjuvants are vaccine components that enhance the magnitude, breadth and durability of the immune response; however, they also have the potential to induce serious toxicities and autoimmunity. Therefore, they should be carefully selected, especially in the context of preventive vaccines administered to overall healthy individuals. Currently, five different adjuvants have been included in licensed vaccines and are thus considered relatively safe[151,194]. Although licensed vaccines mostly aim to activate plasma cells to produce antibody-mediated protection, anticancer vaccines usually seek to activate T cell-mediated immunity against mutated or aberrantly expressed self-proteins displayed on the cell surface on major histocompatibility complex (MHC) complexes. For this reason, licensed adjuvants are generally believed to be suboptimal in the context of cancer vaccination. The discovery in the late 1990s of Toll-like receptors (TLRs), receptors present on the cell surface of dendritic cells and capable of activating antigen-presenting cell functions upon the recognition of pathogen-associated molecular patterns and damage-associated molecular patterns, has revolutionized the adjuvant field and led to the discovery of important novel mediators of innate and adaptive immune responses[195]. Since then, TLR agonists have been largely implemented in vaccine formulations, showing increased vaccine efficacy in therapeutic cancer settings[196,197] and, in one case, in preventive settings: the TLR7 agonist imiquimod has been approved since 2004 for the treatment of actinic keratosis[198], a pre-malignant condition precursor of skin squamous cell carcinoma, and demonstrated efficacy not only in the clinical management of actinic keratosis but also in the immunoprevention of squamous cell carcinoma[199]. Such an example, so far unique, evidently supports the implementation of adjuvants in immunoprevention; however, important challenges still lie ahead for the selection of powerful adjuvants and their clinical translation. First of all, although several adjuvants have shown the ability to induce potent $CD8^+$ T cell responses leading to tumour growth inhibition in mice, in humans, that was only the case in live viral vaccines, whereas the rest reported a substantially lower efficacy[151,200]. Further mechanistic insights, especially in human settings, are therefore direly needed to better guide the translation from animal models to human hosts and potentially promote refined and more potent clinical approaches. Secondly, toxicity issues not only at the systemic but also at the cellular level constitute critical elements with potential impacts on safety and overall feasibility, and should therefore be carefully assessed and tackled. As an example, recent studies showed that sustained STING activation leads to T cell apoptosis owing to the high expression of STING in this cellular type, an effect not seen on macrophages or dendritic cells[201]. Therefore, active doses should be investigated and targeted delivery systems carefully considered to ensure both optimal adjuvant activity and the absence of toxicity or induced functional impairments. Thirdly, screening studies comparing the efficacies of various adjuvants and formulations in tumour control and investigating tumour type specificities are still largely lacking.

in reducing tumour burden by >80%, while >20% of treated animals never developed the disease[39]. A subsequent study showed that its combination with the specific acetyl-CoA acetyltransferase 1 (ACAT1) inhibitor, avasimibe, which works by enhancing the effector function of tumour-specific $CD8^+$ cytotoxic T cells, was synergistic in increasing antitumour efficacy and delaying tumour development in a mouse model of lung tumorigenesis[40]. Importantly, the peptide sequences in these studies present a 100% identity with their human counterparts, supporting the direct clinical translation of this approach in the near future for immunoprevention of lung cancer, especially in populations at risk (such as smokers). Furthermore, targeting mutant KRAS with a pooled peptide vaccine is currently being clinically investigated for the prevention of pancreatic cancer in individuals at risk based on family history or germline mutation testing but who have not yet developed the disease (NCT05013216). Such examples in distinct cancer indications suggest that future vaccines against KRAS or other widely shared mutated neoantigens, if well designed, may well be applied to prevent several types of cancers before their manifestation.

Individuals at risk

Several pioneering studies have been recently launched to test the ability of cancer vaccines to prevent non-viral cancers in populations at high risk of developing cancer, either owing to life habits, such as heavy smokers, or genetic predisposition such as patients with *BRCA1* mutations at risk of developing triple-negative breast cancer or patients with Lynch syndrome at risk of developing CRC (Table 1).

Lynch syndrome. Lynch syndrome is a specific genetic condition in which mutations in the DNA mismatch repair (MMR) genes (*MSH2*, *MSH6* and *PMS1* on chromosome 2, *MLH1* on chromosome 3, *MSH3* on chromosome 5, and *PMS2* on chromosome 7) cause the accumulation of frameshift mutations leading to neoantigen expression and, frequently, development of CRC or endometrial cancer[41]. These neoantigens have predictable sequences and have therefore been implemented in multivalent preventive vaccines first tested in mouse models[42], and subsequently in phase I clinical trials, which are currently ongoing. In a recent study, Gebert et al. have identified four shared antigens derived from frameshift mutations through genome-wide sequencing, followed by in silico prediction and in vivo immunogenicity testing[42]. These candidates, able to induce T cell responses in naive healthy mice, were subsequently tested in the *VCMsh2* mouse model, which presents a deficiency in the MMR system and spontaneously develops intestinal cancer, thus recapitulating the Lynch syndrome disease condition. Results demonstrated that vaccination with these four peptides significantly increased antigen-specific adaptive immunity, reduced tumour burden and prolonged animal survival[42]. Based on this evidence, the group led by Vilar-Sanchez is now currently running an ambitious phase Ib–II trial aimed at testing the efficacy of a vaccine encompassing 209 neoantigens based on predicted and shared frameshift mutations (NCT05078866) in patients with Lynch syndrome. Another ongoing clinical trial is testing a preventive vaccine targeting 31 neoantigens from eight common dog cancers identified through frameshift peptide arrays[43]; the readout is based on the cancer incidence in a 5-year follow-up between the treatment and placebo groups[44].

Such a revolutionary approach constitutes one of the first prophylaxis attempts targeting neoantigen uniquely associated with malignant cells, which are normally patient specific and occur in the course of the disease. Thus, based on their outcomes, these pioneering studies will play a crucial part in shaping the future of cancer prevention and potentially pave the way for similar strategies targeting other related cancer syndromes.

Presence of tumour-associated antigens. Tumour-associated antigens (TAAs) constitute a class of antigens overexpressed in cancer cells but normally also present in healthy tissue. Owing to this somatic expression, TAAs are prone to central and peripheral tolerance leading to the depletion of TAA-specific T cells; for this reason, they are usually considered less immunogenic. However, some of them have crucial roles in tumorigenesis and cancer progression and are thus constitutively expressed across cancers, making them ideal candidates for mass vaccination approaches, especially in tumours characterized by a low mutational burden[4]. Among these is Wilms tumour gene 1 (WT1), which is often overexpressed in acute myeloid leukaemia and various solid tumours, including Wilms tumour, ovarian cancer and lung cancer. It has crucial roles in cell proliferation, differentiation and apoptosis through its involvement in various signalling pathways such as the Wnt–β-catenin pathway. Prostate-specific membrane antigen is predominantly overexpressed in prostate cancer and is implicated in tumour growth, invasion and metastasis, with its enzymatic activity facilitating nutrient uptake in cancer cells. Human telomerase reverse transcriptase is commonly mutated and upregulated in the majority of cancers, including CRC, breast and lung cancer, promoting immortalization through telomere maintenance and involvement in pathways regulating cell cycle progression and apoptosis[45,46]. These antigens have recently been the focus of a phase I trial (NCT04367675) aimed at treating healthy individuals bearing *BRCA1* or *BRCA2* mutations as they are at high risk of developing cancers such as triple-negative breast cancer[47]. Through a longitudinal analysis, the aim of this study is to demonstrate that inducing cancer antigen-specific immune responses in overall healthy individuals could lower the risk of developing the disease in the future. In particular, the vaccine treatment consists of the intramuscular administration of DNA encoding for the selected TAAs and interleukin-12 (IL-12) as adjuvant. This study is estimated to enrol 44 participants by the end of 2025. Interestingly, the same vaccine formulation has recently been tested in patients with newly diagnosed glioblastoma in combination with the PD1 checkpoint inhibitor cemiplimab. Although this does not represent immunoprevention, it does provide a good safety and immunogenicity profile, which can be encouraging for future immunoprevention approaches[48].

Healthy individuals bearing *BRCA1* and *BRCA2* mutations are the focus of another ongoing phase I clinical trial (NCT04674306) testing, in this case, the safety and preventative potential of α-lactalbumin. This protein belongs to a particular subclass of TAAs, the so-called retired antigens. These antigens are tissue-specific self-proteins whose expression disappears in adults as a result of the natural ageing process; however, they maintain expression in malignant cells. Thus, they could be potentially targeted in the mature population with no or limited risks of autoimmunity[49]. In particular, α-lactalbumin is normally expressed only during pregnancy and lactation but is expressed in triple-negative breast cancer [50]. Preclinical studies showed that immunoreactivity against α-lactalbumin provides substantial protection and therapy against growth of autochthonous tumours in transgenic mouse models of breast cancer and against 4T1 transplantable breast tumours in BALB/c mice[51]. These proof-of-principle analyses also evidenced how vaccination-induced responses occurred without any detectable inflammation in normal non-lactating breast tissue owing to the absence of expression of the vaccine antigen.

Table 1 | Clinical trials in cancer immunoprevention

Pre-malignant condition	Vaccine type	Type of study	Remarks	Refs.
Advanced colon adenoma	MUC1 peptide–poly(I:C)	Phase I	Highly immunogenic and long-lasting immune memory in 44% of participants	56
Advanced adenoma	MUC1 peptide–poly(I:C)	Phase II	Immunogenicity observed only in vaccinated patients	57
Heavy smoking	MUC1 peptide–poly(I:C)	Phase I	Preventive vaccine administered to current and former smokers at high risk of lung cancer	NCT03300817
BRCA1/2 mutations	hTERT, WT1 and PSMA DNA	Phase I	Vaccine administered to patients with cancer and healthy individuals harbouring *BRCA1* or *BRCA2* mutations	NCT04367675
BRCA1/*PALB2* mutations	α-Lactalbumin	Phase I	Vaccine administered to patients with cancer and healthy individuals harbouring *BRCA1* or *PALB2* mutations	NCT04674306
$HER2^+$ DCIS	DCs loaded with HER2 peptides	Phase I	HER2-specific immune responses	106
$HER2^+$ DCIS	DCs loaded with HER2 peptides	Phase I	Antigen-specific responses observed up to 52 months after immunization	107
$HER2^+$ DCIS	DCs loaded with HER2 peptides	Phase I	Complete regression in 5/27 patients; vaccination was more effective in ER^- DCIS	108
$HER2^+$ DCIS	DCs loaded with HER2 peptides	Phase I	55% of patients showed clinical responses; complete regression was more common for ER^- DCIS	109
$HER2^+$ DCIS; early invasive BC	DCs loaded with HER2 peptides	Phase I	Higher complete responses in patients with DCIS versus those with BC; no significant impact on different routes tested	65
$HER2^+$ DCIS	DCs loaded with HER2 peptides	Phase I	Ongoing; testing intranodal and/or intralesional injection	NCT02061332
$HER2^+$ DCIS	Multi-epitope HER2 peptide vaccine H2NVAC, GM-CSF	Phase Ib	Ongoing	NCT04144023
Individuals at high risk of pancreatic cancer	KRAS peptide vaccine, poly-ICLC	Phase I	Ongoing	NCT05013216
SMM	Lenalidomide+dexamethasone versus observation	Phase III	39% of patients developed MM in the treatment group compared to 82% in the observational group	74,75
SMM	Lenalidomide versus observation	Phase III	Significant delay progression to MM in the treated group	73
SMM	Lenalidomide+dexamethasone+/−daratumumab	Phase III	Ongoing	NCT03937635
SMM	Multivalent peptide vaccine+/−lenalidomide	Phase I	Clinical responses in 12/24 treated patients	110
SMM	Multivalent peptide vaccine, lenalidomide+/−citarinostat	Phase I	Ongoing	NCT02886065
SMM	Neoantigen personalized vaccine	Phase I	Ongoing	NCT03631043
Monoclonal gammopathy; SMM	DCs pulsed with DKK1 peptide	Phase I	Ongoing	NCT03591614
Lynch syndrome or CRC with MSI	DCs loaded with CEA and FS-predicted neoantigen peptides	Phase I–II	Ongoing	NCT01885702
Lynch syndrome	209 FS-predicted neoantigen peptides	Phase Ib–II	Ongoing	NCT05078866

BC, breast cancer; CEA, carcinoembryonic antigen; CRC, colorectal cancer; DC, dendritic cell; DCIS, ductal carcinoma in situ; ER, oestrogen receptor; FS, frameshift; GM-CSF, granulocyte–macrophage colony-stimulating factor; HER2, human epidermal growth factor receptor 2; hTERT, human telomerase reverse transcriptase; MIN, multiple intestinal neoplasia; MM, multiple myeloma; MSI, microsatellite instability; MUC1, mucin 1; poly(I:C), polyinosinic–polycytidylic acid; poly-ICLC, poly(I:C) mixed with carboxymethylcellulose and polylysine; PSMA, prostate-specific membrane antigen; SMM, smouldering multiple myeloma; WLT1, Wilms tumour gene 1.

Such results paved the way for the abovementioned clinical trial, which will assess the prevention potential of α-lactalbumin against triple-negative breast cancer in healthy individuals harbouring deleterious *BRCA1* or *PALB2* mutations. As these mutations are germline, they do not produce tumour-specific actionable antigens; however, populations harbouring these defects are at a higher risk of developing cancer and are thus candidates for preventative vaccines using the aforementioned TAAs. Moreover, thanks to the recent developments in immunogenomics, one can envision identifying yet another novel class of tumour-specific antigens in this population at high risk.

Secondary prevention

Secondary prevention targets individuals who may already have pre-cancerous lesions or early-stage cancer. By current routine exams and screening tests to detect disease in its earliest stages (such as mammograms to detect breast cancer), the potential use of vaccines can be considered for cancer interception. In addition, in the future, vaccines for secondary prevention may provide a valid therapeutic option to prevent disease recurrence not only after surgery but also for those instances in which surgical removal is not feasible and the only current solution is frequent screening or low-efficiency chemoprevention (for example, oral leukoplakia, asbestosis and monoclonal gammopathies)[52].

CRC and pancreatic cancer: MUC1

Pioneering work by the group led by Finn and other groups led to the discovery that TAAs are present in pre-malignant lesions and could be efficiently targeted to induce a protective immune response and hamper disease progression[53]. One example of this is the mucin 1 (MUC1) antigen, a protein normally present in healthy epithelium but aberrantly expressed and glycosylated in several tumours and pre-malignant conditions such as high-risk colonic polyps and high-grade pancreatic intraepithelial neoplasms, which may eventually progress to CRC and pancreatic adenocarcinoma, respectively[53]. This observation, together with the observation that MUC1 overexpression is associated with an increased risk for malignant transformation[54], led to early-phase clinical studies assessing safety and feasibility of MUC1 vaccination for immunoprevention in patients presenting pre-malignant lesions. The first human clinical trial in secondary prevention settings showed that treatment of individuals with a history of advanced-stage adenoma with a MUC1 peptide vaccine led to high levels of anti-MUC1 IgG and long-lasting immune memory in half of the individuals with a lack of toxicity[55,56]. A subsequent phase II clinical trial recently confirmed that MUC1-specific immune responses were efficiently induced and only observed in vaccinated patients diagnosed with advanced-stage adenoma[57]. Although there was no significant difference in adenocarcinoma recurrence between the placebo and the treated arm, a 38% absolute reduction versus 66% was recorded between the same two groups, close to significance ($P = 0.08$)[57]. The authors speculated that the lack of statistical significance was linked to the different timing of vaccine administration (<1 year from adenoma surgical removal, compared to up to 9 years after surgery in the previous phase I study[57]).

Importantly, MUC1-based vaccines have also been long used in patients with advanced-stage cancer in adjuvant settings with very poor or limited clinical benefits and suboptimal induction of MUC1-specific immunity[58,59]. Once again, this lack of efficacy has been linked to the immunosuppressive TME characterizing advanced disease status and to the negative impact of chemotherapy on the immune system functioning[60]. Nonetheless, MUC1 continues to be considered a promising and high-priority antigen to target owing to its widespread expression across different indications and its key role in cancer progression[61] (Table 2).

Breast cancer: HER2

Other recent examples of secondary prevention include targeting human epidermal growth factor receptor 2 (HER2), which is overexpressed in breast cancer cells and is a marker of poor prognosis[62,63] but is also highly expressed in 50% of pre-invasive breast cancer lesions (ductal carcinoma in situ (DCIS))[64] (Table 2). $HER2^+$ DCIS is associated with a higher tendency towards disease progression than $HER2^-$ DCIS[64]. For this reason, vaccination against HER2 has been tested in patients with DCIS to investigate its safety, immunogenicity, and ability to reduce the risk of developing breast cancer in several completed and currently ongoing clinical studies (Table 1). Overall, results revealed that vaccination with dendritic cells loaded with HER2 peptides induced HER2-specific immune responses and clinical benefits up to complete regression in 25–50% of treated patients (Table 1). Importantly, in one recent study, higher complete responses were observed in early disease status (DCIS) than in invasive breast cancer[65], another proof-of-principle example showing that TAAs can be efficiently targeted for cancer immunoprevention and should be further pursued.

Other indications

Isocitrate dehydrogenase (IDH)-mutant low-grade gliomas are slow-growing tumours of the central nervous system that predominantly manifest in young adults with an extremely high risk (>50%) of malignant transformation to high-grade gliomas (HGG)[66]. Despite the therapeutic advances in several other oncological areas, they are still considered incurable. Vaccines, especially ones targeting HGG-associated antigens, may offer a safe and effective option for possible prophylaxis of high-grade transformation. Several seminal studies conducted by Okada and colleagues have covered this deadly disease and would warrant further developments of preventive vaccines against transformation from low-grade gliomas to HGG[67–71].

Smouldering multiple myeloma (SMM) is an asymptomatic clonal proliferation of plasma cells that can eventually progress to multiple myeloma. Owing to its asymptomatic status and the lack of available treatments, this condition has been relegated to simple medical observation and close surveillance for more than 40 years. Recently, the advent of novel prophylactic treatments to avoid or slow down disease progression and the development of models for risk stratification have changed the medical scenario for this pre-malignant condition[72]. In particular, two recent phase III studies have demonstrated the protective effects of early intervention with lenalidomide in the group of patients with SMM with the highest risk of developing multiple myeloma, according to distinct risk models of disease progression[73–75]. Although these two studies used different risk stratification methods, they both demonstrated that early intervention significantly improved survival and reduced progression risk by over 90% compared to the observational arm. However, uncertainties about the best dose, treatment duration and potential side effects, including sporadic fatalities, have sparked debate over which patients should be treated and how to best identify them[72,76,77]. Current risk models rely on medical parameters such as bone marrow plasma cell composition and M-protein concentration. Risk stratification based on genetic cues, such as cytogenetic abnormalities, gene mutations and/or disease biology, currently in development should shed light on the heterogenicity of SMM and better guide medical decisions in the future. Furthermore, several ongoing clinical studies, such as NCT03937635 and NCT02886065, are currently investigating protective efficacy of lenalidomide in combination with other drug regimens in patients with SMM, including preventative vaccines that have the advantage of being safer with less side effects. These studies are either targeting known TAAs that are present in multiple myeloma or neoantigens derived from bone marrow biopsy and blood samples from patients with SMM (Table 1).

The case of multiple myeloma prevention through SMM treatment well depicts the conundrum faced in the treatment of a pre-malignant condition that is often mild or asymptomatic: treating

Table 2 | Tumour antigens for preventive vaccines against human non-viral cancers

Antigen category	Antigen	Pre-malignant condition	Potential preventive target	Remarks
TAA	MUC1	Intraductal papillary mucinous neoplasm; villous adenoma; colon polyp carcinoma	CRC, pancreatic cancer	Vaccination against pre-malignant lesions achieved high levels of anti-MUC1 IgG, long-lasting immune memory in half the participants and lack of toxicity[55]
TAA	HER2	DCIS; pre-malignant gastric cancer	Breast cancer	Vaccination in patients with DCIS induced long-lasting immune responses and disease regression in a subset of patients[55,106–109]
TAA	CEA	Colon polyp carcinoma	CRC, adenoma	CEA vaccination reported safe and immunogenic activity against pre-cancerous lesions in transgenic mice[159] and against CRC in adjuvant settings[160]
TAA	Cyclin B1	Pre-neoplastic lung disease	Lung cancer	Immunosurveillance role reported in pre-malignant lesions in heavy smokers[161]
TAA	CDH3, KRT23, MMP7	Adenoma	CRC	Overexpressed in both pre-malignant and malignant lesions, also immunogenic[162]
TAA	ENO1	Pre-malignant pancreatic intraepithelial lesions	Pancreatic cancer	Preventive DNA vaccine induced antitumour humoral and cellular responses and increased survival in mice[163]
TAA	XBP1, CD138, CS1	Smouldering multiple myeloma	Multiple myeloma	Multivalent peptide vaccine induced clinical responses in half of the treated patient population[110]
TAA	hTERT	NA	90% human tumours[163]	Preventive DNA vaccine inhibited tumour formation and progression in mice[164]
TAA	CDC25B, COX2	NA	CRC	Preventive peptide vaccine inhibited tumour formation in mice[165]
Cancer-testis antigens	MAGEA, NY-ESO-1, GAGE, SAGE1, CT47A	Oesophageal squamous neoplasm	Oesophageal squamous cell carcinoma	Expression of these antigens normally expressed only in germ cells, reported in human pre-cancerous lesions[166]
Neoantigen	*RAS* mutants	NA	30% human tumours[167]	*RAS* mutants are drivers of oncogenic process and immunogenic in both cancer mouse models[168] and patients[169]
Neoantigen	*RAF* mutants	NA	10–15% human cancers[34]	Target therapy against *BRAF* V600E oncogene extensively tested so far against advanced tumours with positive outcomes[36]
Neoantigen	>200 FS-predicted neoantigens	Lynch syndrome	CRC	Putative neoantigens caused by predicted FS mutations[170,171]
Retired antigen	α-Lactalbumin	NA	Triple-negative breast cancer	Tumorigenesis inhibition in breast cancer mouse model[51]
Retired antigen	AMHR2	NA	Epithelial ovary carcinoma	Tumorigenesis inhibition in ovarian cancer mouse model[172]

AMHR2, anti-Müllerian hormone receptor II; CEA, carcinoembryonic antigen; COX2, cyclooxygenase 2; CRC, colorectal carcinoma, DCIS, ductal carcinoma in situ; FS, frameshift; HER2, human epidermal growth factor receptor 2; hTERT, human telomerase reverse transcriptase; MAGEA, melanoma-associated antigen A; MUC1, mucin 1; NA, non-applicable; TAAs, tumour-associated antigens.

too early leads to adverse events or important toxic effects and treating too late leads to the risk of irreversible disease progression. In this sense, carefully designed clinical studies and longitudinal observations are obviously key in identifying optimal timing, therapy and patient stratification for preventative measures (see also Future perspectives below).

Tertiary prevention

This category encompasses all therapeutic cancer vaccines that have been largely used as adjuvant therapy in a minimal residual disease setting after surgery and standard of care treatments, and therefore in patients already diagnosed with late-stage cancer.

So far, dendritic cell-based and peptide-based vaccines[78] remain the most common approaches for cancer therapeutic vaccination. However, recent novel antigen delivery platforms, such as antigens encoded in viral vector DNA or mRNA encapsulated in nanoparticles, are currently under investigation with promising results[79–83].

Within the TAA class, peptides from the melanoma-associated antigen (MAGE) family are the most common targets[84–86], whereas other antigens tested in adjuvant settings also include MUC1, WT1 antigens[87] or autologous tumour lysate[88], amongst others. Additionally, a smaller portion of clinical trials recently focused also on neoantigens[79,89,90]. This imbalance is likely due to the long and cumbersome process involved and the complex machinery needed in the identification of patient-private neoantigens (see ref. 4 for a recent systematic review on dendritic cell therapeutic vaccines and targets). To date, sipuleucel-T, an autologous cellular vaccine designed for metastatic castration-resistant prostate cancer that consists of peripheral blood mononuclear cells incubated with a fusion protein composed of prostatic acid phosphatase and granulocyte–macrophage

colony-stimulating factor (GM-CSF), is the only dendritic cell-based therapy approved by the FDA for this patient population, with a median survival increase of only 4.1 months against castration-resistant prostate cancer[91].

Despite the sheer number of studies recently reviewed elsewhere[4,92], what we have globally learnt so far is that therapeutic cancer vaccination is safe overall and able to mount a cancer-specific immune response, prolonging progression-free survival in some cases; however, the therapeutic benefits in terms of both progression-free and overall survival remain limited (reviewed in refs. 93,94). In general, for all types of vaccines, a certain degree of improvement has been achieved in combination with other immune therapeutic regimens (such as with immune-checkpoint inhibitors, chemotherapy, radiotherapy and others)[95,96] but clinical efficacy is still largely suboptimal[97] with few vaccines making it to phase III trials and the trials completed not reporting any significant benefits[98,99]. Thus, therapeutic vaccination is increasingly filling therapeutic gaps where other treatments or immunotherapies are proving ineffective (such as in patients with glioblastoma that failed to respond to temozolomide[100] or to immune-checkpoint inhibitors[101–103]) or in concomitance with other therapeutic interventions in a prime-and-boost approach[95]. Indeed, these combinatorial approaches started to demonstrate a glimmer of hope when a personalized mRNA-4157 was recently given fast-track designation FDA approval when given in combination with pembrolizumab to patients with resected high-risk melanoma[104].

Nevertheless, most successful vaccine studies are conducted in a patient population who are in remission with no evidence of disease, compared with those in advanced settings in which tumours are already established. Moreover, a recent study in mouse models demonstrated that the same vaccine that could prevent the occurrence of tumours and efficiently inhibit micrometastases failed in mounting an immune response against established tumours[105]. This logic highlights, once again, the opportunity that lies in implementing vaccines earlier on in primary and secondary prevention settings to release their true potential and achieve higher benefits.

Please note that, although mouse models do provide insights into vaccine efficacy against tumour initiation or growth, they oversimplify human immune responses and tumour environments. Variations in timing, dosage and mouse immune competence limit translational relevance and study interpretation, yet the scientific community still relies on them as there is no better alternative.

Clinical trials of preventive vaccines

Although cancer vaccines have so far mostly focused on therapeutic adjuvant settings with limited clinical outcomes[4,92], a few proof-of-principle clinical studies have already been carried out in true preventive settings with more promising results. As previously mentioned, initial studies have focused on single antigens such as MUC1 and HER2 expressed in pre-malignant conditions of advanced adenomas and DCIS, respectively[55–57,65,106–109] (Table 1). Overall, these early-phase studies have confirmed the high safety profile of cancer vaccines and demonstrated the positive induction of antigen-specific immune responses and clinical benefits up to complete regression in 25–50% of treated patients, according to the study[55–57,65,106–109] (Table 1). Similarly, a multivalent peptide vaccine designed to treat SMM, alone ($n = 12$) or in combination with lenalidomide ($n = 12$), was well tolerated and induced either stable disease or clinical response in 7 and 5 patients, respectively[110]. Notably, such effects recorded in these pioneering studies promisingly outcompete the 10–20% average response rates demonstrated so far by therapeutic cancer vaccination[4,92]. Thus, such observations paved the way for the surge of a new wave of studies currently testing the safety and efficacy of preventive vaccines in several indications (Table 1). Importantly, among these, the studies in patients affected by Lynch syndrome (NCT01885702; NCT05078866) will be particularly crucial in demonstrating the feasibility and efficacy of vaccination with predicted neoantigens also in secondary prevention, a hypothesis so far unexplored. Similarly, the results from ongoing studies in individuals without cancer harbouring cancer risk factors such as heavy smoking (NCT03300817), *BRCA1* mutations (NCT04367675 and NCT04674306) or family history or germline mutations (NCT05013216) will potentially provide the first proof of principle of the use of vaccines for primary immunoprevention beyond cancers of viral origin.

Future perspectives

Cancer-preventive vaccination holds great promise in the prevention of cancer but several challenges still lie ahead for the development of truly effective preventive vaccines for the general population.

The first challenge deals with the safety concerns of treating overall healthy or asymptomatic individuals according to the Hippocratic rule "*primum non nocere*" (first do no harm). There is a substantial difference between treating a healthy individual, even if associated with high-risk factors, and the compassionate intervention in patients with advanced-stage cancers, with different levels of tolerable toxicities. Detailed preclinical assessment and targeted population design, starting with patients at high risk, are crucial to ensuring minimal impact on development and public acceptance of cancer vaccines during initial testing[111,112].

Moreover, within the population at risk, tumour occurrence is infrequent and spontaneous regression is frequent. Therefore, well-designed trials must enrol an adequate number of participants with appropriate control groups to potentially achieve meaningful and comparable results. Crucially, these studies should define achievable end points to accelerate progress in the field. Various surrogate end points should be considered because no single end point is expected to entirely correlate with disease prevention. Examples include assessing changes in the immune environment due to therapies, observing polyfunctional T cell responses post-vaccination, and evaluating the elimination of pre-invasive disease in window-of-opportunity studies[113].

A second critical aspect in the design of powerful prophylactic vaccines lies in the choice of antigen. Targeted antigens should guarantee disease specificity to avoid off-target effects while simultaneously ensuring disease control. TAAs such as MUC1 and HER2 have demonstrated promising results in early clinical trials, whereas others still await clinical testing (Tables 1 and 3). Although these trials showed the feasibility and safety of this approach, a thorough omics analysis of antigen profiles in pre-malignant conditions is crucial. This aims to pinpoint key immunodominant epitopes and disease-controlling antigens for prioritized targeting. Such analyses can uncover potent new antigens and support multi-targeted strategies, mitigating tumour escape mechanisms like antigen loss or downregulation. Clinical trials in preventative settings have so far mostly targeted single antigens; whereas these were usually linked to disease aetiology, observed limited or partial responses may well be due to the abovementioned mechanisms of tumour escape that could be better avoided through the use of multivalent vaccines.

Initiatives like the PreCancer Atlas have amassed extensive data, creating 3D atlases of pre-cancerous lesions using genomic, transcriptomic, epigenomic and multiplex immunofluorescence analyses for various cancers, including CRC[114], familial adenomatous

Table 3 | Main genetically engineered mouse models for preclinical testing of preventive cancer vaccines

Type of tumours spontaneously developed	Cancer-inducing gene	Mouse model	Vaccine platform
Adenomatous polyps, CRC	APC (mutant/truncated)	$APC^{min-/+}$; APC^{1309}	DCs/tumour fusion cells[173], HER3 peptide[174]
Adenoma	CEA/APC mutant	CEA.Tg/MIN	CEA-Vaccinia virus[159,175], CEA adenovirus[176], engineered DCs expressing CEA, GM-CSF and IL-12 (ref. 177), mTERT DNA vaccine[164]
Prostate adenocarcinoma	SV40 Tag	TRAMP	$GM\text{-}CSF^{+}$ irradiated TRAMP cells[178], Tag-IV-pulsed DCs[179], *mTert* DNA vaccine[164], mPSCA-mSTEAP DNA vaccine[180]
Mammary carcinoma	*Erbb2*	BALB-neuT	IL-12 (ref. 181), HER2-expressing tumour cells[182], HER2-expressing DCs[183]
Mammary carcinoma	*Erbb2*	FVB-neu	IL-12 (ref. 181), HER2-expressing tumour cells[184], HER2 DNA vaccines[184,185]
Mammary carcinoma	Polyoma middle T antigen/MUC1	MMT	$Dendritic/MUC1^{+}$ tumour fusion cells[186]
Melanoma	*Cdk4* mutations	$Cdk4R24C^{+/+}$	*Trp2* adenovirus[187,188]
Tumours at various sites (for example, kidney, liver, spleen, thymus)	SV40 Tag	Cre–*loxP*	Sarcoma cells expressing IL-7, CD80 and SV40 Tag[189]
IBD, colitis-associated colon cancer	MUC1	$IL10^{-/-}$/MUC1	MUC1 peptide[190]
Hepatocellular carcinoma; cholangiocarcinoma	P19 deletion/*Kras* or *Nras* mutations	$P19^{Arf-/-}$/$KRAS^{G12V}$-Ova or $NRAS^{G12V}$-Ova	Live attenuated *Listeria* expressing Ova[191]
Basal cell carcinoma	*Ptch1* mutations	$Ptch1^{+/-}$	HHIP peptides[192]
Pancreatic insulinoma	SV40 Tag	RIP1/Tag4	SV40 Tag peptides[193]
Lynch syndrome, CRC	*Msh2* mutations	VCMsh2	Frameshift-predicted neoantigen peptides[42]

APC, adenomatous polyposis coli gene; CEA, carcinoembryonic antigen; CRC, colorectal cancer; DC, dendritic cell; GM-CSF, granulocyte–macrophage colony-stimulating factor; HER, human epidermal growth factor receptor; IBD, inflammatory bowel disease; IL, interleukin; mPSCA, murine prostate stem cell antigen; mSTEAP, murine 6-transmembrane epithelial antigen of prostate; mTERT, murine telomerase reverse transcriptase; MUC1, mucin 1; TRAMP, tumour-prone transgenic adenocarcinoma mouse prostate.

polyposis-related CRC[115], melanoma[116] and breast cancer[117,118]. These systematic maps of pre-malignant biology are openly accessible on web portals such as cBioPortal for Cancer Genomics or The Human Tumour Atlas Network. Current efforts are focused on: (1) expanding sample collection and longitudinal analysis across different pre-malignant conditions, linking them with clinical progression; (2) extending molecular profiling to healthy individuals with risk factors like hereditary predisposition and inflammatory conditions; and (3) conducting secondary analyses to identify molecular markers for early detection and therapeutic targets to prevent malignant transition. Advancements in these areas are pivotal for shaping future vaccination strategies aimed at cancer prevention.

In the same direction, future studies should also assess the feasibility of targeting proto-oncogenes — a class of antigens that, owing to their crucial role in carcinogenesis, usually appear at early disease onset and are less prone to antigen loss. Several proto-oncogenes have already been identified (such as *RAS* and *RAF* mutants) but have still not been tested in preventative settings, to our knowledge. Vaccine formulations targeting non-canonical antigens are currently being tested in therapeutic settings. Indeed, immunogenomics approaches to identify these non-canonical targets using next-generation sequencing and bioinformatics tools to detect and predict neoantigens (analysed for their potential to elicit immune responses through various algorithms and data bases) as well as techniques, such as single-cell sequencing and mass spectrometry, that validate the immunogenicity of these neoantigens have been the gold standard of current therapeutic vaccine studies[33,79,119]. In addition to this, molecular profiling of pre-cancerous lesions will shed light on the so-called cancer 'dark matter' and its role in pre-malignancy, constituting a potential additional target for cancer immunoprevention. The dark matter of the cancer genome is defined as the class of epitopes that arise from non-canonical, aberrantly translated peptides derived from upstream open reading frames, non-coding RNA, pseudogenes, out-of-frame transcripts[120] or neojunctions[121]. Although these peptides can also be found in somatic cells, distinct proteogenomics-based studies were able to identify tumour-specific epitopes of this type that were even shared across patient samples[122,123]; the magnitude, role and identity of the dark matter of the cancer genome in pre-malignancy remains to be fully elucidated.

Additional targets may arise from current research aimed at deconvoluting T cell responses in the cancer therapeutic field. Here, bottom-up approaches based on T cell recognition assays and aimed at identifying tumour-specific T cell receptors and their cognate antigens have recently emerged[124]. These efforts rely on high-throughput T cell-based screening campaigns in which target cells are first transduced with whole-genome target antigen libraries and then sampled against T cell populations[125]. Antigen-specific T cells are then subsequently enriched, isolated and characterized either through direct target cell killing[126,127] or thanks to the presence of a reporting gene[128,129]. Although these systems present the great advantage of being based on T cell functional recognition rather than on prediction algorithms or purely receptor binding, their current applications are mostly focused on guiding the design of personalized vaccines by profiling patient-specific candidate neoantigen libraries and identification of potential off-target effects. Therefore, their effect on cancer prophylaxis on the wider healthy or risk population may be limited; however, it may well be that these approaches could lead to the identification of novel shared neoantigens that have been missed through the more canonical whole-genome sequencing and in silico prediction approach.

Conversely, antigen discovery efforts in pre-malignant conditions may also inform therapeutic intervention in patients who have already progressed to invasive cancer status. The identification of

immunogenic and driver mutations appearing early in the carcinogenic process may in fact still be applicable in therapeutic settings against late cancer stages (tertiary prevention). An example of this is the link between Lynch syndrome and deficient MMR (dMMR) cancers, which are both characterized by a deficiency in the MMR system (due to a hereditary germline condition or to acquired genetic alterations, respectively) that leads to accumulations of frameshift mutations subsequently translated into neoantigens. We have already discussed the possibility of predicting such frameshift epitopes in patients with Lynch syndrome, which led to currently ongoing clinical trials testing their safety and immunogenicity (Table 1). In addition, several studies have demonstrated that certain frameshift mutations are not only positively selected and shared across dMMR-positive cancers[130,131] but some can also be immunogenic, leading to tumour cell recognition and killing by antigen-specific T cells[132–134]. Given that such mutations confer growth and evolutionary advantage to cancer cells, it may be the case that some

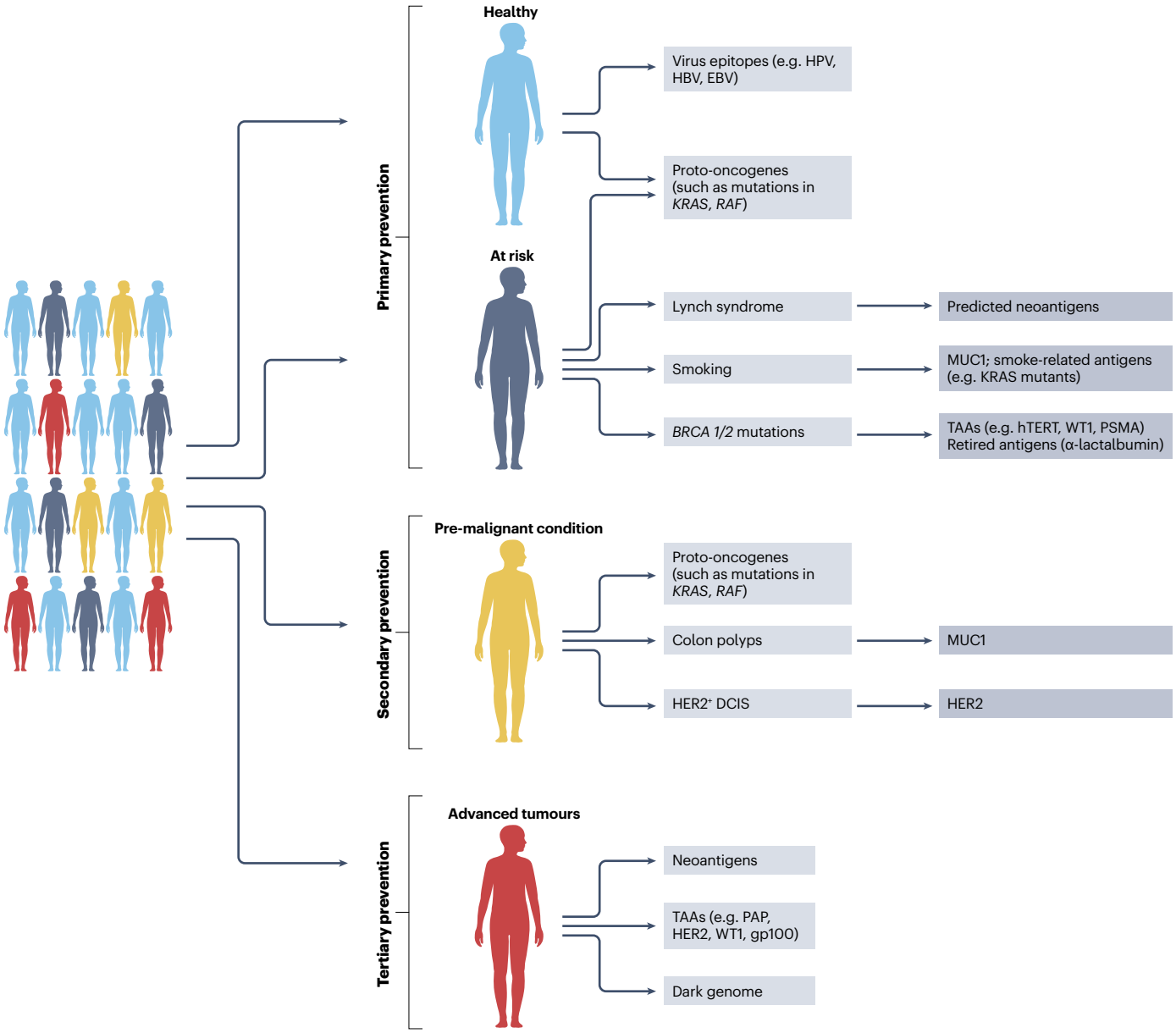

Fig. 2 | Population stratification and vaccination opportunities against cancer. Schematic representation of the antigen landscape for prophylactic and therapeutic vaccination strategies aimed at preventing cancer in three different settings according to population characteristics. In primary settings, in which the intervention occurs in healthy individuals or those at high risk; in secondary settings, in which individuals with a pre-malignant condition can be treated aiming to prevent progression to a more advanced disease status; or in tertiary settings, in which therapeutic vaccines can be used in patients with established cancer to prevent further disease progression or recurrence. DCIS, ductal carcinoma in situ; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HER2, human epidermal growth factor receptor 2; HPV, human papillomavirus; hTERT, human telomerase reverse transcriptase; MUC1, mucin 1; PAP, prostatic acid phosphatase; PSMA, prostate-specific membrane antigen; TAAs, tumour-associated antigens; WT1, Wilms tumour gene 1.

Box 2 | The importance of the dose regimen in vaccine protocol design

A crucial aspect concerning both vaccine efficacy and safety is the correct regimen dose. A high dose may be toxic or counterproductive, causing T cell exhaustion[202], but an insufficient one may be even detrimental, inducing antigen tolerance and subsequent immune escape mechanisms. The issue of the dosage is also an economic one. A lower, efficient dose may enable vaccine administration to a larger number of individuals and lower associated costs, giving easier access also to low-income or developing countries. The case of HPV vaccination is exemplary in this sense: although preventive vaccines were first approved with a three-dose regimen in 2006, subsequent analyses showed that one to two doses were sufficient to induce protective responses[203,204]; thus, a one-dose administration has now been recently recommended by regulatory authorities, since 2022 (ref. 204). Vaccine dose is thus a critical parameter to carefully consider in the final formulation of preventative vaccines currently in development.

of them are already present at early pre-malignant state and retained throughout cancer progression, making them a potential target also against metastatic cancer. Cancers that are dMMR constitute around 4% of total cancer cases; however, the frequency depends on cancer type and can increase up to 22% in the case of endometrial cancer[135]. Patients with dMMR cancers may therefore benefit in the future from antigen discovery efforts currently under way in pre-cancerous settings.

Although a pan-cancer vaccine remains an ideal remedy to be sought, it is most likely that future vaccine intervention will be tailored to specific individual characteristics and population stratification according to medical conditions or risk factors in a more focused and targeted fashion (Fig. 2). Here, the case of smokers versus non-smokers and lung cancer is exemplary. Although smoking is a well-known recognized risk factor for lung cancer, the latter may also occur amongst non-smokers. However, histological and genetic characteristics of lung cancer in smokers and never-smokers differ so much that it has been recently proposed to consider them as two separate diseases[136,137]. First of all, mutational burden is seven times higher in smokers, suggesting that most of these mutations are passenger mutations with no impact on cell transformation, whereas most mutations in patients with non-smoking lung cancer are most probably linked to carcinogenesis[138]. Secondly, mutational identities may largely differ with, for example, *EGFR* mutations more frequent in non-smokers and *KRAS* mutations occurring more often in smokers[139,140]. Interestingly, it is well known that the *EML4–ALK* gene fusion is mutually exclusive with *EGFR* and *KRAS* driver mutations, with a higher frequency in patients with non-smoking lung cancer[141–143]. Finally, methylation of genes, such as *AHRR* (encoding aryl hydrocarbon receptor repressor) and *F2RL3* (encoding proteinase-activated receptor 4), is also influenced by smoking habits, with hypomethylation mostly frequent in smokers and linked to a higher risk of cancer occurrence[144]. From such brief excursus, it is clear that risk stratification and antigen targeting should be carefully assessed and tailored to the population of interest, an aspect valid not only for lung cancer risk and smoking status but also for other cancer types and risk factors (Fig. 2). The same applies to patient HLA haplotypes, which should also be considered when designing vaccines. Indeed, specific HLA alleles can affect vaccine efficacy and safety. Recent studies have shown that certain HLA-I alleles enhance responses to cancer vaccines and predict outcomes for immunotherapies[145–147].

Successful delivery mechanisms, optimal adjuvants and clinically relevant doses are also other areas worthy of particular attention to improve both vaccine safety and efficacy (please refer to Boxes 1, 2 and 3 for more information about adjuvants, doses and different platforms, respectively). A large plethora of modalities has been tested so far, but the scientific community has not yet reached a consensus as to what would be the ideal formulation. For example, the formulation design substantially influences the type of immune response elicited. In preventive contexts, both humoral (B cell-driven) and cellular (T cell-driven) responses are important, with the humoral response preferred for inducing long-lasting protection and with T cells providing immune memory and enhancing the recognition and elimination of nascent tumour cells[148,149]. Another possibility is that different formulations work differently according to the target indication or antigen type. Indeed, non-virally derived cancers may have different immunological requirements to be eliminated compared to virally driven ones. Particularly, the recent case of the fast development of an anti-COVID-19

Glossary

Asbestosis
Lung disease in individuals who have been exposed to and inhaled asbestos fibres over a long period of time, typically in the mining and construction industry. It involves thickening and scarring of lung tissues that can cause difficulty breathing and might progress into lung cancer.

Cancer immunoediting
The dynamic process by which the immune system suppresses and promotes cancer development. It has three phases: elimination, equilibrium and escape.

Leukoplakia
A mucosal white lesion of unknown aetiology that develops in the oral cavity and, less frequently, in other mucosa of the human body (for example, gastrointestinal tract, urinary tract). It has been associated with smoking habits and is a cancer risk factor.

Monoclonal gammopathies
A series of conditions in which abnormally high levels of a specific monoclonal antibody protein (M-protein) are found in the blood. It is a recognized risk factor for multiple myeloma.

M-protein concentration
Measurement of M-protein levels in blood in individuals affected by monoclonal gammopathies used to stratify patients for their risk of developing multiple myeloma. A cut-off of 15 g/l is generally considered to discriminate between populations at low risk (>15 g/l) and those at high risk (>15 g/l).

Peripheral tolerance
The process whereby the immune system becomes unresponsive to self-antigens in the peripheral tissues. Peripheral tolerance mechanisms ensure that self-reactive lymphocytes in peripheral tissues do not activate and trigger autoimmune reactions. Such mechanisms include T cell anergy, regulatory T cells and tolerogenic dendritic cell activity.

Triple-negative breast cancer
A subtype of breast cancer lacking overexpression of oestrogen receptor (ER), progesterone receptor (PR) and *ERBB2* amplification, limiting targeted therapy options. It tends to be more aggressive than other breast cancers, with higher rates of recurrence and metastasis, necessitating multimodal treatment. It predominantly affects younger women and has a poorer prognosis compared to other breast cancer subtypes.

Box 3 | Antigen formulation is an important component in successful vaccination design

In addition to the nature and number of antigens to target, their delivery method and formulation also play a crucial part in the design of a successful vaccination strategy. To address this point, different vaccine platforms are currently being pursued in an attempt to improve safety, ease and cost of manufacturing, persistency and, ultimately, efficacy.

Among these, peptide-based vaccines present great advantages, such as generally low cost of production, high stability, flexibility and good biocompatibility, and have thus been largely implemented in clinical trials. Despite encouraging preclinical results and a high safety profile, therapeutic efficacy has so far been very limited, partially due to suboptimal pharmacokinetics (such as short in vivo half-life) and overall low immunogenicity of peptides[78]. Although initial formulations focused only on short peptides (8–11 amino acids) that could be directly loaded on major histocompatibility complex I (MHC-I) molecules to trigger a $CD8^+$-dependent cytotoxic immune response, the introduction of synthetic longer peptides of 11–30 amino acids has brought some improvements[205]. This is believed to be mostly linked to the fact that synthetic longer peptides need to first undergo antigen processing by professional antigen-presenting cells in order to be presented, meaning that they can also be loaded on MHC-II molecules and thus stimulate a concomitant $CD4^+$ response. However, clinical benefits of this approach remain limited and other vaccine modalities are currently emerging.

Antigen delivery methods based on nucleic acids have recently met renewed interest and enthusiasm. As testified by the virtuous example of the COVID-19 vaccine, nucleic acid-based vaccines can, in fact, be easily and rapidly manufactured, present a good safety profile, and can trigger potent and durable immune responses. In addition to this, they also have intrinsic immunoadjuvant activity by stimulating innate immune pathways (such as STING and Toll-like receptors). DNA-based cancer vaccines have been more largely used in the past, and only a few have currently entered phase II clinical trials whereas mRNA-based vaccine trials are currently more numerous and in more advanced stages (see ref. 80 for a recent comprehensive review). mRNA vaccines do not require genome integration, circumventing the risk of genome mutagenesis and are thus considered safer. In addition to this, they have also demonstrated clinical efficacy in therapeutic settings in several trials with some reported cases of complete remission[79,81,206]. It is now generally believed that these features, together with the general shift in public acceptance after the example of COVID-19 mass vaccination, will undoubtedly lead to more widespread use of this modality in the near future. Alternatively, all these different antigen sources have also been used to stimulate autologous antigen-presenting cells ex vivo, which are then re-injected into patients in both prophylactic (Table 2) or therapeutic settings[4,11]. However, the cumbersome and costly process of cell manufacturing, the limited scalability of this approach and the modest clinical outcomes observed so far[4,11] will probably lead to the shift towards more versatile and agile platforms also in cancer prophylactic settings in the near future.

vaccine based on mRNA technology suggests that antigen-encoding mRNA is a promising, fast, low-cost and efficient method to induce antigen-specific immune responses, which can also be produced in good manufacturing practice grade for clinical applications. This approach is currently being tested in cancer therapeutic settings with some encouraging preliminary results[150] and should be thus further explored also in the context of cancer immunoprevention. Lessons learned from vaccines that have already successfully entered the clinic should assist in designing the optimal formulation. Adjuvants such as alum, MF59 or bacillus Calmette–Guérin, already included in licensed vaccine formulations, constitute some examples that researchers can look at for efficient approaches already validated and available to be implemented in cancer vaccine prophylaxis. In addition, although licensed adjuvants usually rely on natural products that are readily available, recent synthetic chemistry efforts led to the identification of potent small molecules better designed for adjuvant purposes and currently in various stages of preclinical and clinical evaluation that are worthy of attention[151] (Table 3). In any case, as mentioned, this aspect should be addressed in carefully designed comparative studies both in preclinical and clinical settings to identify optimal formulations.

Further to this, a technical issue deals with the difficulty of correctly assessing the efficacy of preventive approaches. The success of a therapeutic intervention can be easily determined through symptoms disappearing or mildewing, but how can we efficiently estimate and predict prevention efficacy in the long term? Some significant surrogate end points, such as the induction of de novo antigen-specific immune responses, have been proposed so far, especially focusing on the antibody-elicited responses, which normally confer long-term and memory protection[152]. However, a systematic careful examination and identification of surrogate biomarkers of efficacy is still needed in the field.

Finally, even in the presence of an effective vaccine formulation, practical issues linked to large-scale manufacturing, commercial challenges and public acceptance should be carefully addressed to guarantee the success of vaccination campaigns. The recent case of COVID-19 mass production and administration taught us several lessons. First of all, that public investment and engagement can play a key part in accelerating vaccine design. Such a strategy should be further extended to cancer-related pathogens, such as Merkel virus, whose low occurrence does not guarantee sufficiently profitable revenues to pharmaceutical companies but that, if correctly prevented, may significantly decrease associated skin cancer incidence and health care-related economic burden. Secondly, public acceptance of preventive vaccination in the absence of disease or strong symptoms is not trivial to achieve and should be fostered by carefully designed information campaigns. Here, several recent studies in the context of HPV vaccination demonstrated the positive effect of educational videos[153], announcement training[154] and appropriate counselling by health professionals[155] on vaccine acceptance by participating individuals. These educational interventions therefore have a crucial role and should be carefully assessed and implemented also in future cancer prophylaxis strategies.

Conclusions

So far, vaccines have been mostly implemented in therapeutic settings against advanced-stage tumours with high safety profiles yet

with limited clinical benefits. Despite this, evidence now suggests that the true immunological potential of vaccines lies instead in prevention settings prior to disease occurrence, as successful examples in other medical conditions testify. Multiple groups have independently demonstrated that vaccine-induced protection decreases as cancer progresses[156–158], while proof-of-principle studies here reviewed have already demonstrated the feasibility of the vaccine immunoprevention approach. Therefore, we are now at a turning point in which significant emphasis and attention have finally been brought to developing novel platforms for vaccine cancer immunoprevention. To progress from hope to a global impact in cancer management, we need now to capitalize on the lessons learnt from therapeutic cancer vaccination in the past decades and address key challenges in clinical trial design and in identifying ideal target populations, vaccine formulation, antigens and biomarkers of vaccine efficacy.

Published online: 02 December 2024

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Author contributions

L.E.K. conceptualized the article and contributed to writing major parts of the discussion and conclusions. M.G. contributed to researching data for the article and writing the initial draft. Both authors contributed to reviewing and/or editing the manuscript before submission.

Competing interests

The authors declare no competing interests to disclose.

Additional information

Peer review information *Nature Reviews Drug Discovery* thanks Hideho Okada, Neeha Zaidi and the other, anonymous, reviewer for their contribution to the peer review of this work.

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