The dawn of vaccines for cancer prevention

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Abstract | An important role of the immune system is in the surveillance for abnormal or transformed cells, which is known as cancer immunosurveillance. Through this process, the first changes to normal tissue homeostasis caused by infectious or other inflammatory insults can be detected by the immune system through the recognition of antigenic molecules (including tumour antigens) expressed by abnormal cells. However, as they develop, tumour cells can acquire antigenic and other changes that allow them to escape elimination by the immune system. To bias this process towards elimination, immunosurveillance can be improved by the administration of vaccines based on tumour antigens. Therapeutic cancer vaccines have been extensively tested in patients with advanced cancer but have had little clinical success, which has been attributed to the immunosuppressive tumour microenvironment. Thus, the administration of preventive vaccines at pre-malignant stages of the disease holds promise, as they function before tumour-associated immune suppression is established. Accordingly, immunological and clinical studies are yielding impressive results.

Checkpoint inhibitors
Antibodies or other drugs that inhibit the function of specific molecules (such as cytotoxic T lymphocyte antigen 4 (CTLA4), programmed cell death protein 1 (PD1) and PD1 ligand 1 (PDL1)) expressed on the surface of immune cells or cancer cells that serve as breaks or that keep immune responses in check at particular time points (checkpoints) in immune cell activation. Blocking the function of these molecules releases the breaks and can lead to tumour destruction.

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Treatment without prevention is simply unsustainable.
Bill Gates

In October 2015, as part of a Grand Challenges initiative, Cancer Research UK (CRUK) published a call for proposals to develop vaccines for the prevention of nonviral cancers (see Further information). At the same time, the US National Cancer Institute (NCI) convened a Cancer Prevention Think-Tank with research experts in the areas of immunoprevention, precision prevention and early detection, and surveillance and screening. In February 2016, the American Association for Cancer Research (AACR) held a Cancer Prevention Summit with immunoprevention prominently represented on the agenda (see Further information). Several reports related to these meetings were published, setting the course for increased efforts in cancer prevention[1–3]. Among the priority areas identified were molecular and immunological studies of pre-malignant states, the generation of a precancer genome atlas[4] for exploring the concept of precision prevention and the identification of new targets for prevention, including for immunoprevention. Also in early 2016, the Blue Ribbon Panel (see Further information) was appointed by the NCI to highlight priority areas in cancer research and prevention and to provide funding recommendations to the Cancer Moonshot programme. Recommendations from the Cancer Immunology Working Group to the Blue Ribbon Panel included support for basic, translational, computational and clinical research in immunotherapy and immunoprevention of all cancers[5]. The fiscal year 2019 NCI budget proposal for the first time includes vaccines for cancer prevention as a priority area (see Further information).

This push towards cancer prevention and the inclusion of immunoprevention by some of the most eminent cancer organizations is a welcome change. Cancer prevention research has been an active field of investigation for many years[6,7] and has yielded several chemopreventive agents that have been approved by the US Food and Drug Administration (FDA). Nevertheless, cancer prevention research has always taken a back seat to the much larger effort in cancer therapy for the many millions of patients currently living with cancer. Unfortunately, even the most successful cancer therapies, such as the newest immunotherapy approaches with checkpoint inhibitors[8] and adoptive transfer of engineered T cells[9], are making a relatively small impact on the large numbers of patients with cancer and are having the greatest impact on patients in developed countries.

The rationale to increase research on cancer prevention is supported by not only the need to decrease human suffering subsequent to cancer diagnosis but also economic necessity. In 2010 in the United States, there were 12.8 million patients with cancer, and that number is projected to increase to 18.1 million in 2020.

The associated treatment costs are projected to increase from US$124.57 billion in 2010 to $157.77 billion in 2020. With a projected annual increase of 2% in the cost of medical care, the real cost in 2020 may be closer to $173 billion[10]. There is also a discrepancy in the human and economic burden of cancer between developed and developing countries, as people in developing countries suffer and die in greater numbers without the benefit of effective but expensive cancer therapies and preventive measures, such as clinical surveillance and early detection. The desire to make cancer care a universal human right[11,12] supports an increased effort in developing more cost-effective cancer prevention approaches.

One such disease prevention approach is vaccination. It is clear that vaccines against cancer-causing viruses, such as human papillomavirus (HPV) and hepatitis B virus (HBV), are very effective in preventing the initial infection and therefore in markedly reducing the risk of cancers caused by these viruses. However, for the majority of cancers, infectious aetiology is either unknown or nonexistent, so other targets must be evaluated as candidate antigens for preventive vaccines. Because most tumour antigens are derived from self-molecules, generating a strong immune response against them has been considered to be breaking tolerance to self and to carry the risk of autoimmunity. For this reason, most cancer vaccine efforts have focused on developing vaccines to treat advanced cancer, for which the risks inherent in the target antigen choice have been more acceptable. The results have been disappointing in the therapeutic setting and have greatly under-represented the full potential of these vaccines. Nevertheless, we have gained great insight from trying to understand the failures of various cancer vaccine approaches.

In this Review, I discuss the probably enormous but still untested potential of vaccines for cancer prevention instead of cancer therapy and the path to their development. I review how lessons learnt from work on therapeutic cancer vaccines provide a strong basis for developing preventive vaccines, describe the past successes and current efforts in developing vaccines for the prevention of cancers with an infectious origin, propose that pre-malignant lesions should be the first targets for preventive vaccines and review a small but increasing number of clinical efforts to test vaccines for cancer prevention. Examples will be limited to studies in humans.

Therapeutic cancer vaccines

If people are constantly falling off a cliff, you could place ambulances under the cliff or build a fence on the top of the cliff. We are placing all too many ambulances under the cliff. Denis Burkitt

Identifying antigens. In the late 1970s and early 1980s, some researchers considered cancer to be a strictly genetic disease, whereas others considered it to be primarily due to a failure of immunosurveillance. It proved to be both, and this was reflected in the first attempts at active specific immunotherapy of cancer. These initial approaches involved identifying and targeting cancer antigens that resulted from mutations in the newly discovered cancer-causing genes (known as oncogenes; such as those of the RAS family), tumour suppressor genes (such as *TP53*) and other common mutations (such as gene fusions exemplified by BCR–ABL1). Vaccines based on these mutations showed immunogenicity and antitumour efficacy in mouse models and were promptly moved to clinical testing (TABLE 1).

Another set of antigens that were expected to elicit strong antitumour responses are the products of oncogenic viruses such as HPV, HBV and Epstein–Barr virus (EBV). Low frequencies of T cells against such antigens could be detected in patients with cancer[13,14]. Various vaccines were generated to elicit or boost these responses. These vaccines were immunogenic and protective in mouse models, but when they were tested in patients with advanced cervical cancer (HPV vaccines)[15], hepatocellular carcinoma (HCC; HBV vaccines)[13] and oropharyngeal carcinomas and Hodgkin disease (EBV vaccines)[14], they showed little or no clinical efficacy.

By far the largest number of tumour antigens detected by T cells and antibodies from patients with cancer are derived from nonmutated cellular proteins that are differentially expressed between normal and tumour cells. Many of these tumour-associated antigens (TAAs) had been previously characterized as targets of tumour-specific monoclonal antibodies that were generated in mice against human tumours. Some of the well-known examples are carcinoembryonic antigen (CEA; also known as CEACAM5) and other oncofetal antigens, melanocytic antigens, the mucin family of molecules and various tumour-specific carbohydrates. Molecular and biochemical characterization of many TAAs revealed the basis of their tumour-specific expression and triggered the field of therapeutic cancer vaccines[16–19].

The vaccine effort. The period from 1990 to 2010 was characterized by a gold rush of effort to discover more TAAs and combine them with various adjuvants and delivery systems to achieve the greatest possible immunogenicity and hoped-for clinical effectiveness[17,20]. New developments and new knowledge in immunology and molecular biology were promptly incorporated into vaccine designs[16,21] (FIG. 1). The first clinical trials either tested peptide-based vaccines using TAAs such as the epithelial tumour antigen mucin 1 (MUC1)[22], melanoma-associated antigen 3 (MAGEA3)[23] and the breast cancer antigen human epidermal growth factor receptor 2 (HER2; also known as ERBB2 and NEU)[24], or tested vaccines composed of whole tumour cells or cell lysates that contained some of the known TAAs as well as potentially many others not yet identified[25]. When the importance of dendritic cells (DCs)[26] as professional antigen-presenting cells was established, *in vitro*-generated and fully activated DCs became a delivery vehicle for TAAs, and hundreds of DC-based vaccine trials were carried out in different cancer types[27]. There were also vaccines developed based on viral[28] or bacterial vectors[29] or virus-like particles[30] that were engineered to express TAAs in

Engineered T cells
T cells that have been modified *ex vivo* through gene transfer to assume new functions. For example, T cells can be transduced either with chimeric antigen receptors or with T cell receptors, which endows them with different antigen specificity from that of their endogenous T cell receptors.

Table 1 | **Important tumour antigens for vaccines**

Antigen category	Antigens	Tumour targets for therapeutic vaccines	Tested in therapeutic vaccines?	Suitable for preventive vaccines?	Setting for preventive vaccines
Cancer–testis: expressed in normal testis and no other healthy tissue	CT83, MAGEA1–4, NY-ESO-1, PRAME and SSX2	Bladder, breast, lung, melanoma, myeloma and ovarian	Yes	Yes	• Genetic risk (for example, *BRCA1* and *BRCA2* mutations) • Pre-malignant precursor lesions (for example, DCIS, MGUS, colonic polyps and bronchial neoplasia)
Differentiation-specific or lineage-specific: expressed by normal and tumour cells of the same organ or tissue type	CD19, GP100, MART1, PSA, PSMA and tyrosinase	B cell lymphoma, melanoma and prostate	Yes	No	None
Overexpressed: expressed at markedly higher levels on tumours compared with normal tissue and preferentially targeted on tumours by the immune system	CEA, cyclin B1, EGFR, EPHA2, HER2, mesothelin, MUC1, survivin and telomerase	Bladder, breast, cervical, colon, glioblastoma, hereditary nonpolyposis colon cancer, lung, myeloma, oesophageal, ovarian, pancreas and prostate	Yes	Yes	• Genetic risk (for example, *BRCA1* and *BRCA2* mutations) • Pre-malignant precursor lesions (for example, DCIS, MGUS, colonic polyps, bronchial neoplasia, Barrett oesophagus, pancreatic intraepithelial neoplasias, IPMNs and cervical intraepithelial neoplasias)
Post-translationally modified: products of tumour-specific changes in glycosylation and other modifications	Glycopeptides (for example, MUC1T and MUC1Tn), phosphopeptides (for example, LSP1 and NCOA1) and citrullinated peptides	All tumours	Yes	Yes	Pre-malignant precursor lesions (for example, DCIS, MGUS, colonic polyps, bronchial neoplasia, Barrett oesophagus, pancreatic intraepithelial neoplasias, IPMNs and cervical intraepithelial neoplasias)
Mutated oncogenes: products of common somatic mutations or gene translocations	BCR–ABL1, EGFR variant III, HRAS and KRAS	Acute lymphoblastic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia, glioblastoma, lung and pancreas	Yes	Yes	Pre-malignant precursor lesions (for example, pancreatic intraepithelial neoplasias and IPMNs)
Mutated neoantigens: peptides encompassing random somatic mutations in individual tumours	Unique to each tumour	All tumours	No	No	None

BCR–ABL1, fusion between breakpoint cluster region protein and ABL1; CEA, carcinoembryonic antigen; CT83, cancer–testis antigen 83; DCIS, ductal carcinomas *in situ*; EGFR, epidermal growth factor receptor; EPHA2, ephrin type A receptor 2; HER2, human epidermal growth factor receptor 2; IPMNs, intraductal papillary mucinous neoplasms; LSP1, lymphocyte-specific protein 1; MAGEA, melanoma-associated antigen; MART1, melanoma antigen recognized by T cells 1; MGUS, monoclonal gammopathy of undetermined significance; MUC1, mucin 1; NCOA1, nuclear receptor coactivator 1; PRAME, melanoma antigen preferentially expressed in tumours; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

addition to 'naked' DNA-based[31] or RNA-based vaccines[32]. Increasing knowledge of the importance of activating antigen-presenting cells through Toll-like receptors (TLRs) led to the development of many TLR ligands that were added to the vaccines as adjuvants to properly activate the immune system. However, despite applying the latest and best immunological knowledge to the design and testing of therapeutic cancer vaccines, the overall impact of vaccines on disease-free survival, overall survival and cancer recurrence has been minimal[21].

Several meta-analyses have been carried out on the therapeutic cancer vaccine effort over the past two decades to extract some commonalities characterizing the successes and failures that could inform future directions for vaccine efforts. One study evaluated 451 trials (phases II and III only) carried out in more than 25 different cancer types from 1999 to 2015 (REF. 33). Of those evaluated, 185 trials tested a vaccine in combination with chemotherapy, radiation, surgery, antibody therapy, hormone therapy or other therapy, and the other 266 trials applied the vaccine alone. Vaccine-only trials were more common in the first decade covered by the meta-analysis, with the combination trials dominating the second decade. Although the number of patients in phase III trials was relatively large compared with those in phase II trials, the number of phase III trials compared with phase II was very small. This indicates that the data from the numerous phase II trials were not strong enough to support further development. As a result, only one therapeutic vaccine, Sipuleucel-T, has been approved to date by the FDA for the treatment of prostate cancer on the basis of a 4.1-month increase in median survival[34]. Another retrospective cross-sectional and longitudinal study analysed 995 trials carried out between 1991 and 2013 (REF. 35). In this study, it was noted that the peak number of trials was in 2008 and has declined since. Of the 995 trials, only 40 (4%)

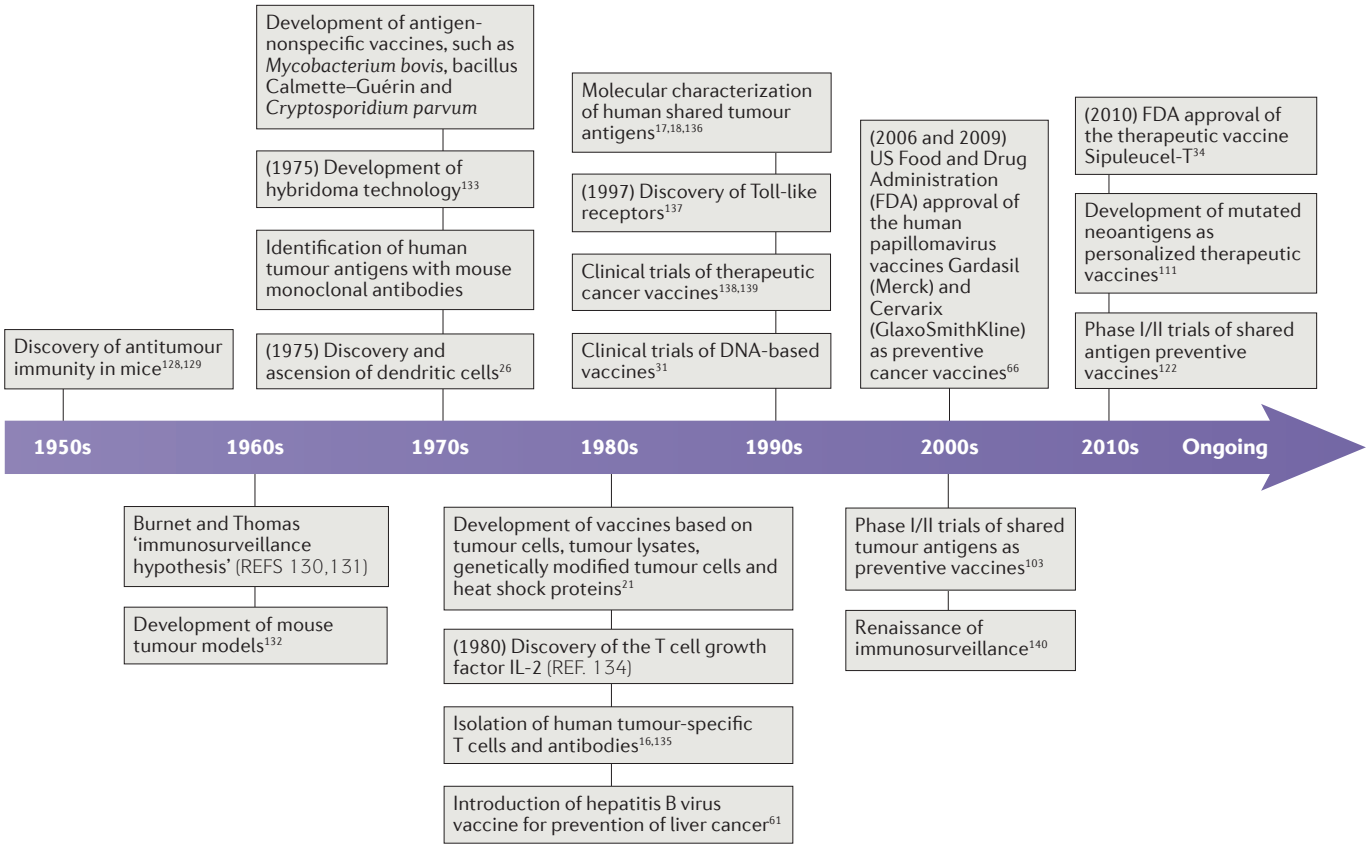

Figure 1 | **Timeline of cancer vaccine development.** Milestones in the development of cancer vaccines are indicated by the decade from which they were first reported.

were phase III trials, which tested 15 different vaccines and 8 different adjuvants. This again indicated that the other 96% of trials did not show positive data to support progression to phase III trials.

The trials reviewed in these two studies did not have long-term follow-up data; thus, the efficacy of the vaccines may have been underestimated. A recent report reviewed the 12-year survival of patients with nonresectable metastatic melanoma who received a vaccine composed of monocyte-derived DCs matured with tumour necrosis factor (TNF), IL-1β, IL-6 and prostaglandin E2 loaded with four MHC class I-binding and six MHC class II-binding melanoma-derived peptides, which was injected intradermally over a period of 2 years[36]. An impressive 19% of these patients are still alive, which compares well with the results of treatment of melanoma using checkpoint blockade against cytotoxic T lymphocyte antigen 4 (CTLA4)[37].

Most therapeutic vaccine trials included in the retrospective analyses were carried out in an adjuvant setting (using a wide variety of adjuvants) and were mostly composed of single antigens (which were mutated, nonmutated or viral antigens). The authors suggest that the weak or absent therapeutic efficacy was due to suboptimal vaccine design and that more complex vaccines using a wider range of tumour antigens and antigen combinations and viral vectors for their delivery would have given a different outcome. They also credit the vaccine failure to the paucity of good adjuvants. However, there is another way to interpret the data. The fact that a wide variety of antigens, adjuvants and delivery systems all gave the same lacklustre results suggests that the common denominator of vaccine failure was not the antigen, the adjuvant or the delivery vector but rather the advanced disease suppressing the patient's response to the vaccine.

Impact of the tumour microenvironment. In the first decade of therapeutic vaccine development and testing, not much was known about systemic and intratumoural immunosuppression. A few early reports of the compromised function of T cells and natural killer (NK) cells in patients with cancer[38–40] were not immediately appreciated. Many different mechanisms of immune suppression in cancer have since been identified, including the expansion of myeloid-derived suppressor cells (MDSCs)[41], tumour-associated macrophages and other myeloid cells[42] and regulatory T cells[43] in addition to the perturbation of cytokine networks[44], changes in host metabolism[45] and the production of amino acid-degrading enzymes and indoleamine 2,3-dioxygenase 1 (IDO1)[46,47] (FIG. 2). In addition, a recent report reveals an unexpected suppressive activity of oxygen and potassium in the tumour microenviroment[42].

Myeloid-derived suppressor cells
(MDSCs). A group of immature myeloid cells (including precursors of macrophages, granulocytes and dendritic cells) that are produced in response to various tumour-derived cytokines. These cells have been shown to induce tumour-associated antigen-specific $CD8^+$ T cell tolerance and to suppress other immune effector cells.

Tumour-associated macrophages
Cells that are an important component of the tumour microenvironment. They differentiate from circulating blood monocytes that have infiltrated tumours. They can have positive or negative effects on tumorigenesis (that is, tumour promotion or immunosurveillance, respectively).

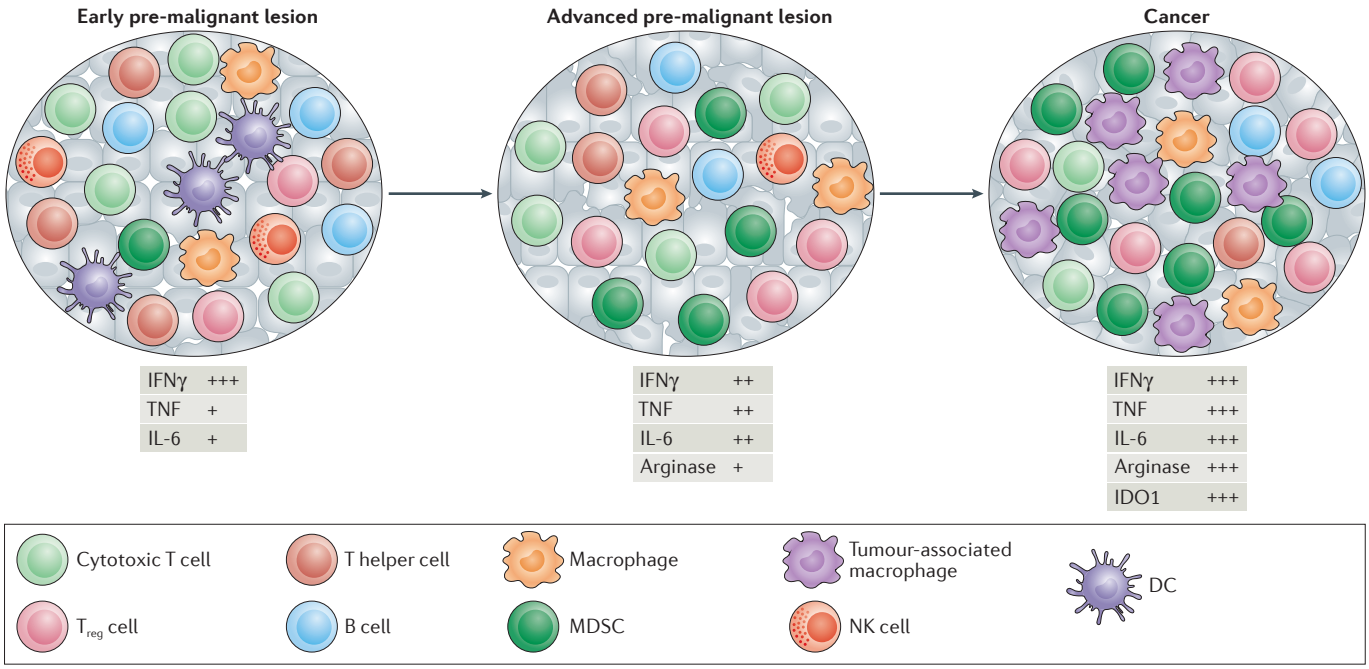

Figure 2 | **Progressive stages of cancer development are accompanied by changes in the local immune microenvironment.** Early pre-malignant lesions are infiltrated by both adaptive immune cells (T cells and B cells) and innate immune cells (natural killer (NK) cells and macrophages) that have an activated phenotype and produce effector cytokines (such as interferon-γ (IFNγ)), suggesting an ongoing antitumour response. Immunosuppressive regulatory T (T_{reg}) cells and myeloid-derived suppressor cells (MDSCs) are rare. Advanced pre-malignant lesions contain fewer T and B cells and many more T_{reg} cells and MDSCs and produce higher levels of pro-inflammatory cytokines (such as tumour necrosis factor (TNF) and IL-6), suggesting the transition from antitumour to pro-tumour immune responses. The cancer immune microenvironment is characterized by a predominance of immunosuppressive T_{reg} cells and MDSCs, as well as by the conversion of macrophages into immunosuppressive tumour-associated macrophages (TAMs). DC, dendritic cell; IDO1, indoleamine 2,3-dioxygenase 1.

In attempts to overcome immunosuppression, pharmaceutical companies are developing specific reagents, such as IDO1 inhibitors[48], and various ways to inhibit MDSCs either by blocking their growth factor receptors[49] or by reprogramming their metabolism[50]. There is accumulating evidence that standard treatments such as chemotherapy and radiation, if used appropriately, might also reverse immunosuppression[51,52].

These efforts to inhibit the suppressors and modulate the tumour microenvironment in favour of antitumour immunity underlie the so far unprecedented successes of checkpoint blockade immunotherapy achieved through targeting negative regulators of effector T cell function, such as CTLA4, programmed cell death protein 1 (PD1) and PD1 ligand 1 (PDL1)[53]. Inhibition of additional inhibitors is considered to be a good way to increase the success of this particular therapy as well as other forms of immunotherapy, including therapeutic vaccines. The extent to which this will be successful is likely to vary greatly. There is strong evidence that T cells can be profoundly affected by the long-term stay in the tumour microenvironment and exhibit an exhausted phenotype that may not be fully reversible[54]. These exhausted T cells do not respond well to checkpoint inhibitors, and if they do respond, the effect is transient[55]. They are also unlikely to greatly increase in number in response to a vaccine. Combination therapies in mouse models are showing encouraging results in which vaccines, checkpoint blockade and inhibition of one of the other immunosuppressive mechanisms are not effective when used alone, but a combination of two or three of these therapies results in an antitumour effect[56].

Combination approaches. High volumes of new data from immunotherapy trials with checkpoint inhibitors have suggested that including cancer vaccines as part of combination immunotherapy will increase the efficacy of checkpoint inhibitors as well as overall therapeutic efficacy[57–59]. This has brought a renewed enthusiasm for the therapeutic cancer vaccines field.

Many cancer vaccines have already been tested in clinical trials and so could be immediately used in combination with checkpoint inhibitors or other immunomodulators of the tumour microenvironment. However, there is a perception that many elements of therapeutic vaccines should be revisited: the choice and prioritization of tumour antigens to include new mutated neoantigens; antigen-delivery methods to include new oncolytic and other viral vectors, nanoparticles and *in vivo* DC targeting; vaccine formulations that will target exhausted memory T cells and trial designs to take into account immunological fitness of the patients. Some of this work is planned as an organized international collaboration between academic and industry scientists

Exhausted phenotype
The condition of functionally impaired antigen-specific T cells, typified by increased surface expression of programmed cell death protein 1 (PD1), which occurs in the context of persistent high antigen load. The defects in effector T cell function include a progressive decrease in their ability to produce cytokines, loss of proliferative capacity and decreased cytotoxicity, and these defects can result in apoptotic cell death.

known as The Human Vaccine Project[60]. Although new knowledge needs to be incorporated into (not so) old vaccines, there is no need to start with a blank slate. Several vaccines based on shared TAAs that are clearly immunogenic and not subject to self-tolerance, such as the cancer–testis antigen NY-ESO-1 (also known as CTAG1A), telomerase reverse transcriptase (TERT), MUC1 and HER2, or based on viral antigens, such as HPV E6 and E7 proteins, could be immediately tested in combination trials.

One variable not addressed by this plan is the cost of these new improved vaccines. The only FDA-approved vaccine, Sipuleucel-T, costs $90,000 per treatment course. The current plan is to make vaccines more complex, vectored and perhaps even personalized. Even as a monotherapy, these complex vaccines are likely to be costly, and if used in combination therapy, as required for metastatic disease, they will add to the already enormous cost of the other agents. One way to reduce the cost of cancer vaccines and improve their effectiveness is to continue to develop them as monotherapies for individuals without cancer but who are at risk of cancer to boost spontaneous immunosurveillance and to prevent cancer development.

Preventive cancer vaccines

Diseases can rarely be eliminated through early diagnosis or good treatment, but prevention can eliminate disease. Denis Burkitt

Vaccines for prevention of viral cancers. Chronic infection with HBV leads to chronic liver diseases and is a proven cause of HCC. Transmission of infection is both vertical, from mother to baby at birth, and horizontal, from person to person throughout life. Children infected with HBV before the age of 5 have a 25–50% chance of developing chronic liver disease that can lead to HCC, whereas infections later in life carry only a 1–5% chance. An HBV immunization programme was started in Taiwan in 1982 initially targeting infants of infected mothers, then all infants and finally it was given universally. It is one of the great success stories of a preventive vaccine for controlling viral infection as a means of reducing cancer incidence. The latest study looking at the long-term effects of Taiwan's infant HBV immunization programme in preventing liver cancer showed a significant ($P < 0.0001$) reduction in HCC incidence in vaccinated compared with nonvaccinated birth cohorts[61]. This study showed for the first time that a preventive cancer vaccine given in infancy provides protection in adulthood. A similar success story comes from a programme in Thailand that implemented universal HBV immunization between 1988 and 1992 (REF. 62).

Similar immunization strategies, repeated in other countries where HBV is endemic, as well as globally, will in time eliminate chronic liver diseases and HCC if mandatory vaccination remains enforced. A recent modelling study shows that a target of a 90% reduction in new cases and a 65% reduction in mortality can be reached by scaling up the coverage of infant immunization to 90%[63]. This would prevent an estimated 7.3 million deaths between now and 2030, 1.5 million of which would probably be due to HCC[63].

A more recent successful prevention story is that of HPV vaccines for the prevention of cervical and HPV-positive oral cancers. Like HBV, HPV can establish a chronic infection in approximately 20% of infected individuals, putting them at risk of these two cancers. An HPV vaccine was introduced in 2006 that was recommended for females aged 11–26, and since 2011 this vaccine has also been recommended for males aged 11–21. A decade later, and after testing in multiple clinical trials[64], HPV prevalence among females aged 14–19 had decreased by 64% and had decreased by 34% in females who were 20–24 years old[65]. Two currently approved vaccines, Gardasil (Merck) and Cervarix (GlaxoSmithKline), provide effective protection against chronic infection with HPV type 16 or type 18, and, importantly, they also protect against cervical intraepithelial neoplasia, adenocarcinoma *in situ* and cervical cancer[66]. Given already established trends, a substantial decrease in incidence and mortality from cervical cancer is projected by 2050 (REF. 67).

Vaccine-elicited immune responses against E6 and E7 antigens from HPV types 16 and 18 are also remarkable in that they could clear pre-malignant cervical and vulvar lesions[68,69]. Women with HPV-16-positive grade 3 vulvar lesions were vaccinated with long peptides from E6 and E7 oncoproteins admixed with incomplete Freund's adjuvant. Of the 20 vaccinated patients, 12 had a clinical response with relief of symptoms and 5 had a complete response. At 24 months after vaccination, 15 of 19 vaccinated patients had a clinical response and 9 of 19 had a complete response with clearance of HPV-16. Importantly, the clinical response directly correlated with the vaccine-elicited T cell responses. Another trial using a vaccine composed of 13 E6-derived and E7-derived peptides and the adjuvant Montanide reported similar results[70]. In total, 43 patients received either the vaccine alone or the vaccine together with the TLR7 agonist imiquimod applied to the injection site. At 12 months, 52% of patients had a clinical response, 8 of whom had complete viral clearance.

In another trial, a completely different vaccine formulation composed of two plasmids encoding HPV-16 E6 and E7 proteins or HPV-18 E6 and E7 proteins was administered by electroporation to women with HPV-16-positive or HPV-18-positive cervical intraepithelial neoplasia (CIN) lesions of grade 2 or 3. Overall, 49.5% of vaccinated women experienced pathological regression of lesions compared with 30.6% of women in the placebo group[71]. Finally, the most stringent test of the ability of an HPV vaccine to prevent cancer was the Papilloma Trial Against Cancer in Young Adults (PATRICIA), which was carried out with the HPV-16 and HPV-18 vaccine Cervarix[72]. It included women with CIN grade 3 lesions and cervical adenocarcinoma *in situ*. The vaccine efficacy against both CIN grade 3 and adenocarcinoma *in situ* was 100%.

The remarkable results for HPV vaccines and viral antigens that had not shown previous clinical efficacy in invasive disease[73–75] suggested that vaccines based on nonviral antigens that failed in the therapeutic setting were also likely to succeed in the prevention setting.

Vaccines for prevention of nonviral cancers. The idea of developing vaccines for the prevention of nonviral cancers is not new[76–81]. Work by chemoprevention researchers and pharmaceutical companies over the past 30 years to develop drug compounds for cancer prevention and large phase III trials led to FDA approvals of chemopreventive agents such as tamoxifen, and a question that was frequently raised was why these trials could not be a blueprint for preventive vaccine trials. Ironically, despite a steady and marked accumulation of publications on tumour antigens between the 1950s and the 1990s, there was a general belief that there were no suitable antigens for preventive vaccines for nonviral cancers. It was assumed that immune responses against nonviral antigens, specifically TAAs derived from self-molecules, would cross-react with the respective self-molecules on healthy tissues and cause damaging autoimmunity. Unfortunately, the minority of TAAs that warranted such caution, such as some melanoma antigens that caused vitiligo, received the majority of the attention[82]. In the meantime, many TAAs expressed on liquid and solid tumours (including melanoma) were being safely incorporated into therapeutic vaccines that caused no autoimmunity either in preclinical models, where safety could be adequately tested, or in clinical trials, where therapeutic effects were not accompanied by any substantial toxic effects. Furthermore, the cancer-reactive antibodies and T cells found in patients with cancer that led to the discovery of many TAAs were increasingly being reported as memory responses in healthy individuals[83–88], and their presence at diagnosis was associated with better prognosis[89,90]. These immune responses could be induced either by tumours eliminated before becoming clinical disease or more likely by abnormal expression of self-molecules during nonmalignant events such as viral and bacterial infections or acute or chronic inflammation (FIG. 3). In a case–control study in ovarian cancer, immune responses against the TAA MUC1, which is abnormally expressed by epithelial cells in conditions such as breast mastitis, pelvic surgery and mumps or in individuals who are currently smoking was revealed as a potential protective mechanism[91,92]. Epidemiological evidence has accumulated to show that such events are associated with a marked reduction in lifetime risk of many different cancers[93].

Pre-malignant lesions as initial targets. An important advance in the field of cancer immunoprevention has been the development of increasingly sophisticated clinical imaging tools and other modalities that can diagnose early cancer and even pre-cancer changes. Pre-malignant lesions are beginning to have an important role in all modes of cancer prevention, including immunoprevention[94–97]. Current management of pre-malignant lesions is either surgical removal or frequent screening. However, many resected lesions recur after surgery, or those that are untreated can progress to cancer. A vaccine administered at this early stage could boost immunosurveillance to eliminate pre-malignant lesions, prevent their recurrence after surgery or prevent their progression to cancer. This setting has many advantages, including a shorter time of interaction of abnormal cells with the immune system, thus presumably avoiding immune exhaustion, and a less immunosuppressive local microenvironment that allows vaccine-elicited T cells to function at the site of the lesion.

The importance of boosting pre-existing immunosurveillance of pre-malignant lesions with a vaccine, even if the lesion is surgically removed, is illustrated by one of many studies showing that apparently normal tissue adjacent to a lesion is different from normal tissues from healthy controls[98]. For example, in the colonic mucosa adjacent to unifocal colon polyps, there were marked alterations in gene expression that predicted polyp recurrences[98]. A strong immune memory response elicited by vaccination would be expected to prevent these polyp recurrences. Many pre-malignant lesions have now been shown to be under immune surveillance, and multiple target antigens have been identified. In patients with monoclonal gammopathy of undetermined significance (MGUS), which is a precursor to multiple myeloma, the presence of pre-existing T cell immunity and antibody responses against the stem cell antigen transcription factor SOX2 independently correlates with a reduced risk of progression to multiple myeloma[99]. This suggests a benefit from boosting anti-SOX2 immunity in all patients with MGUS by using a preventive vaccine. Patients diagnosed with intraductal papillary mucinous neoplasms (IPMNs), which are precursors to pancreatic cancer, have circulating IgG antibodies against MUC1, which is overexpressed in a hypoglycosylated abnormal form in IPMNs as well as in pancreatic cancer. In addition, the dysplastic regions of the IPMN cysts are heavily infiltrated by $CD4^+$ and $CD8^+$ T cells[100], suggesting that both pre-existing humoral and cellular immunity can be boosted by a MUC1-based vaccine. Similarly, oral leukoplakias, which are pre-malignant precursors of oral squamous cell carcinomas, are heavily infiltrated with Langerhans cells and T cells, indicating active immunosurveillance of these lesions[101].

Using the pre-malignant setting to improve the effectiveness of cancer vaccines is a good compromise between preventing cancer in completely healthy individuals, for whom vaccines may be most effective but carry a certain degree of risk, and treating patients with advanced cancer, for whom vaccine effectiveness is profoundly diminished. A new focus on understanding the pre-malignant microenvironment has revealed that highly advanced lesions may already exert multiple types of immunosuppression[100,102–106] that could affect responses to preventive vaccines. This should motivate further studies in vaccine safety so that vaccines may eventually be given to young and healthy individuals who are at risk of nonviral cancers.

Tamoxifen
A drug used for the prevention of oestrogen receptor (ER)-positive breast cancer. Tamoxifen is a pro-drug that is metabolized in the liver into active metabolites that have a high affinity for the ER and can compete with endogenous oestrogen.

Monoclonal gammopathy of undetermined significance
(MGUS). A medical condition characterized by the presence of abnormal immunoglobulins and expanded clones of plasma cells that can progress to multiple myeloma, thus requiring periodic surveillance.

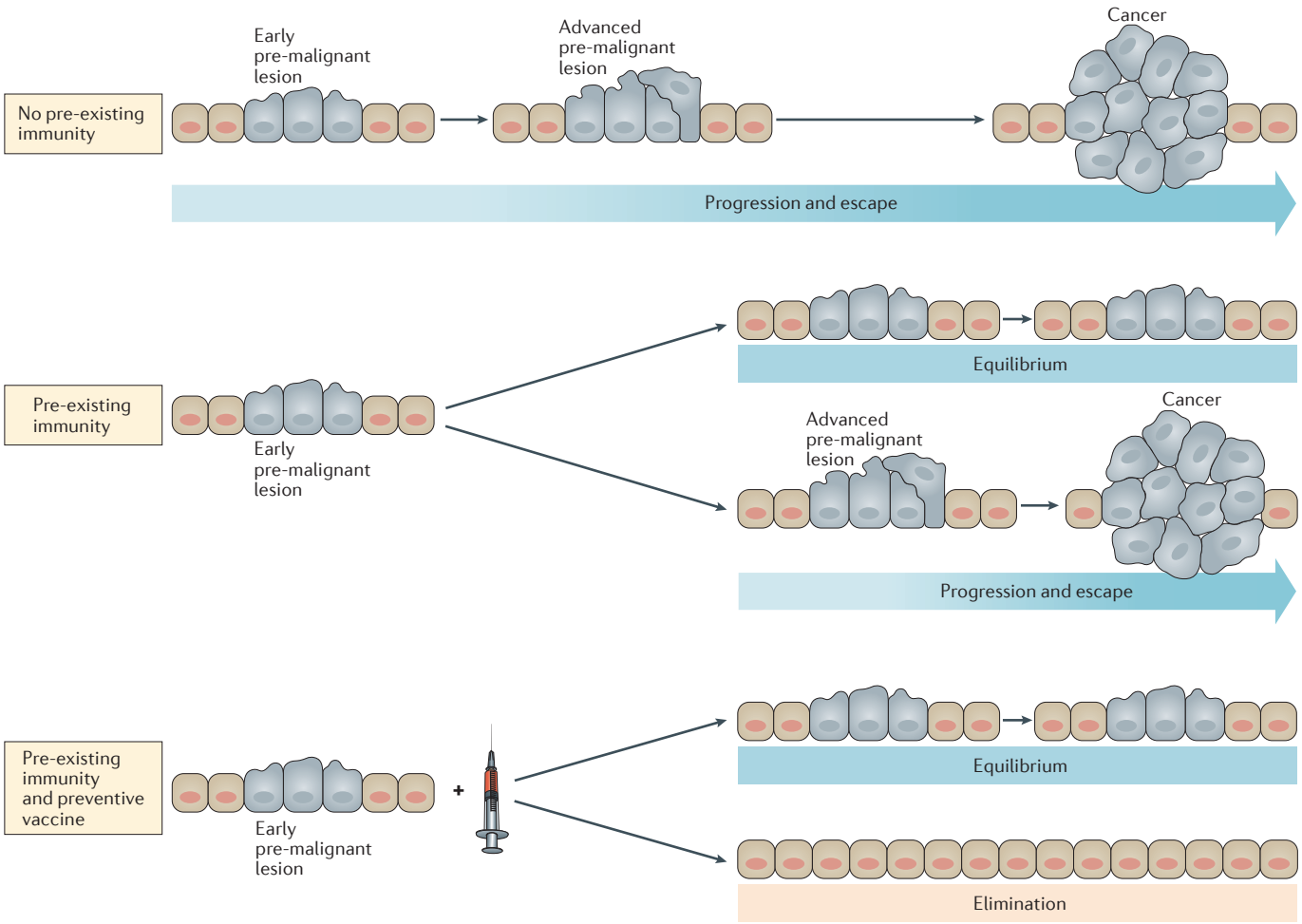

Figure 3 | **Boosting antitumour immunosurveillance with a vaccine determines disease outcome.** Cancers develop from an early pre-malignant lesion, to an advanced pre-malignant lesion and to a malignant cancer. Immunosurveillance of cancer can have three different outcomes: elimination, which is a full victory for the immune system; equilibrium, which is a tie between the immune system and cancer; or escape, which is a full victory for the cancer. At the time of diagnosis, in some patients, there is no evidence that the immune system has detected pre-malignant or malignant changes (no pre-existing immunity), which allows unopposed progression (escape). Other patients have some antitumour antibodies and T cells (pre-existing immunity) and, depending on their strength, the result can be either equilibrium or escape. If this pre-existing immunity is boosted and strengthened with a preventive vaccine, the expected result would be either equilibrium or elimination, with potentially lifelong protection from immune memory elicited by the vaccine.

Candidate antigens. To start testing preventive cancer vaccines, it is important to identify nonviral candidate antigens that are abnormally expressed by pre-malignant lesions and cancers and to investigate their immunogenicity[107]. In addition to SOX2 and MUC1, other TAAs that have been identified on tumours are expressed by pre-malignant lesions. The TAA cyclin B1, which is overexpressed in the cytoplasm of many different tumours including lung cancer, is also abnormally expressed in pre-neoplastic lung lesions in individuals who smoke heavily and who are at high risk of developing lung cancer. These lesions are subject to immune surveillance, as cyclin B1-specific IgG is present in people who smoke heavily[87]. Cancer–testis antigens, such as MAGEA antigens, NY-ESO-1, G antigen (GAGE), sarcoma antigen 1 (SAGE1), cancer–testis antigen 47A (CT47A), nuclear RNA export factor 2 (NXF2), MAGEC1 and MAGEC2, that are commonly expressed by oesophageal cancer are also expressed to the same degree in its precursor lesions[108]. One of the best-known breast cancer TAAs, HER2, is overexpressed in ductal carcinoma *in situ* (DCIS), is a precursor to invasive breast cancer and is a target of T cell surveillance. It was recently shown that T helper 1 cell responses directed against HER2 are lost during tumorigenesis[109]. These responses are greatly diminished even in stage 1 breast cancer compared with those seen in DCIS[109]. These observations set the stage for applying HER2 vaccines, which have had limited effectiveness in invasive breast cancer, to this early, pre-malignant stage as preventive vaccines.

In addition to investigating the expression of the known TAAs, other approaches are revealing new candidate antigens. A recent study identified 150 genes in existing microarray data sets that were upregulated more than twofold in colorectal cancer as well as in pre-malignant colonic adenomas compared with normal colon tissue.

Silencing of the most upregulated genes — *CDH3* (which encodes cadherin 3), *CLDN1* (which encodes claudin 1), *KRT23* (which encodes keratin 23) and *MMP7* (which encodes matrix metalloproteinase 7) — in colon cancer cell lines resulted in cell death. Most importantly, sera from patients with early stage colorectal cancer contained IgG antibodies specific for three of these proteins (cadherin 3, keratin 23 and matrix metalloproteinase 7), identifying these proteins as biologically relevant targets for preventive cancer vaccines[110]. The antigens mentioned above are shared, nonmutated TAAs (TABLE 1) and are excellent candidate antigens for preventive vaccines because they are proven targets of spontaneous immune surveillance. They are expressed by a large number of human cancers and would therefore be very broadly applicable. Furthermore, TAAs such as HER2 and MUC1 are essential for cancer progression and therefore cannot be lost by the tumour as a means to escape immune control.

Recent evidence suggests that mutated antigens are more immunogenic than nonmutated TAAs and will elicit higher affinity antibodies and higher numbers of T cells. Although this still needs to be conclusively shown, new personalized therapeutic vaccines are being designed based on sequencing of each patient's tumour to identify potential biologically and immunologically important mutated antigens[111]. Personalized preventive vaccines would then be possible in the setting of pre-malignant lesions that could be biopsied and sequenced, an approach that is currently highly impractical and resource-demanding. A more practical approach that could yield an off-the-shelf vaccine against mutated antigens would be to use predictable mutations, such as those in the RAS family of oncogenes or the cancer suppressor gene *TP53*. Mutated oncogenes initially held a lot of promise as highly cancer-specific, immunogenic and broadly applicable cancer vaccine antigens, but therapeutic vaccines based on mutated oncogenes did not perform any better than vaccines based on nonmutated shared antigens[112,113]. This result might be different in a preventive setting. Mutations in oncogenes and cancer suppressor genes occur very early in the process of tumorigenesis, and many pre-malignant lesions, such as those leading to pancreatic, breast, lung or colon cancers, already harbour *KRAS* or *TP53* mutations that could be targeted with off-the-shelf preventive mutated-antigen vaccines. A set of antigens that falls somewhere between the shared mutated and the unique mutated antigens is found in cancers associated with Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer), which are caused by germline mutations in DNA mismatch repair genes. These tumours induce potent immunosurveillance directed in part against frameshift mutations, some of which give rise to predictable immunogenic frameshift peptides. Carriers of Lynch syndrome mutations would be good candidates for preventive vaccination against frameshift-peptide antigens[114].

In 2009, a successful effort was made to prioritize the further development of hundreds of tumour antigens as candidates for therapeutic cancer vaccines[115]. Many of these antigens are also candidates for preventive vaccines, and new antigens and antigen categories have since been defined. A similar effort to prioritize antigens for preventive vaccines is warranted and could be especially useful in these early steps in the development of preventive vaccines.

In addition to the challenge of selecting the right antigens, there will be challenges in selecting or developing the right adjuvants and the right delivery systems. These issues have been under intense investigation and are the subjects of other reviews[116–121].

Towards clinical application

These are very early days for the clinical testing of preventive cancer vaccines. Justifiably, the initial trials involve antigens that have been previously characterized in great detail for their immunogenicity and safety in both preclinical and clinical studies as components of therapeutic cancer vaccines. Also justifiably, the chosen setting is the advanced pre-malignant state that immediately precedes stage 1 cancer, such as DCIS. In a clinical trial testing the effect of a HER2-based vaccine in DCIS[122], 13 patients were vaccinated before surgery with four weekly injections of their own *in vitro*-matured and activated DCs loaded with HLA class I-binding and HLA class II-binding HER2-derived peptides. To increase immunogenicity, the vaccine was injected into the regional lymph nodes. All patients developed peptide-specific $CD4^+$ and $CD8^+$ effector T cells as well as complement-binding, tumour-lytic antibodies. At the time of surgery, 7 of 11 patients showed decreased DCIS size; the residual DCIS showed infiltration of T cells and B cells and a marked decrease in HER2 positivity. These encouraging results were replicated or bettered in a second trial in 27 patients with DCIS[123]. At surgery, 5 of 27 vaccinated patients had no evidence of DCIS and in the 22 patients with the disease, 50% had lost HER2 expression. The vaccine seemed to be more effective in patients who were negative for oestrogen receptor (ER), as it eradicated DCIS in 40% of these patients compared with 5.9% of patients who were positive for ER. There was also considerable immunoediting of the DCIS phenotype. If these obviously effective immune responses are confirmed to be long-lived, women with mutations in *BRCA1* or *BRCA2* should be the next candidate population for preventive HER2-based vaccines and other new vaccines.

The other well-known TAA that has gone into clinical testing as a preventive cancer vaccine is MUC1. Therapeutic MUC1-based vaccines have been tested in numerous trials around the world[124] and were the first vaccines based on a self-molecule to be tested[22]. A 100-amino-acid-long MUC1 peptide admixed with the TLR3 agonist polyinosinic–polycytidylic acid stabilized with polylysine and carboxymethylcellulose (poly-ICLC) was administered to individuals with a history of pre-malignant villous adenomas, which are immediate precursors of colon cancer[103]. The goal was to test vaccine safety and immunogenicity in healthy people without cancer but who were at risk of adenoma recurrence and colon cancer. The vaccine was given at weeks 0, 2 and 10, and a booster was given after 1 year. Of the 39 vaccinated individuals, 17 (43.6%) developed high levels of MUC1-specific IgG and long-lasting memory responses

Immunoediting
A process by which the immune system of a host may alter the gene expression of an emerging tumour such that the most immunogenic epitopes are removed or edited, thereby facilitating tumour escape from immune recognition.

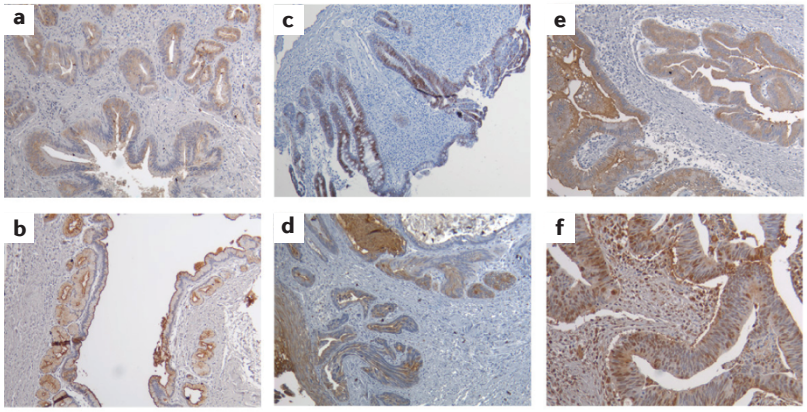

Figure 4 | **Mucin 1 as an example of candidate shared antigens for broadly applicable preventive vaccines.** Mucin 1 (MUC1) is abnormally expressed by multiple pre-malignant lesions and related cancers: Barrett oesophagus and oesophageal cancer (parts **a**,**b**); intraductal papillary mucinous neoplasms and pancreatic cancer (parts **c**,**d**); and Crohn disease and colitis-associated colon cancer (parts **e**,**f**). Tissues were stained with a mouse monoclonal antibody that recognizes the tumour-associated form of MUC1.

with no evidence of any toxic effects involving normal tissues. The absence of an immune response in 56.4% of individuals correlated with increased numbers of circulating MDSCs, indicating that this advanced pre-malignant stage is already establishing an immunosuppressive microenvironment that could promote progression to cancer. The complete safety of the elicited immunity in the vaccine responders suggests that vaccinating individuals diagnosed with earlier-stage polyps would be a better choice. Nevertheless, the safety and immunogenicity of this vaccine in the responders supported the design of an ongoing multicentre, placebo-controlled and blinded efficacy trial[125]. The MUC1-based vaccine was administered to 110 individuals who had advanced adenomas removed within 6 months to 1 year before vaccination. Of the total, 55 participants were given the MUC1 vaccine at weeks 0, 2 and 10 with a booster given at week 55. The other 55 participants were injected with a placebo. So far, there have been no adverse events beyond reactions at the injection site. The trial is still blinded and has just entered the observation phase. Villous adenomas are expected to recur within 1–3 years after surgical resection in 48% of the participants. This timing allows for clinical trials with a somewhat small number of individuals and a moderately short time to completion. In the case of the MUC1 vaccine efficacy trials, the study should reveal the protective effect of the vaccine within 3–5 years. Because MUC1 is expressed by many tumours and their pre-malignant lesions (FIG. 4), other preventive vaccine trials are currently being considered, including a trial in people who smoke and are therefore at risk of lung cancer that was due to start in November 2017 (REF. 126).

As this section illustrates, these are early days for preclinical and clinical studies of preventive cancer vaccines in several different settings, from fairly advanced lesions (for example, DCIS) to less advanced pre-malignant lesions (for example, colonic polyps and MGUS) or in individuals with genetic (such as Lynch syndrome), environmental or lifestyle (such as smoking) risks for cancer. Thorough evaluation in appropriate animal models of the immune responses induced in various preventive settings will be required. A preventive vaccine given early in life to an individual who is a carrier for a cancer mutation might elicit lifelong protection, whereas a vaccine given to an older individual who smokes or to a patient with advanced colonic polyps might require yearly boosters to maintain protective immunity. This research will be helped by already ongoing efforts to understand early biomarkers of vaccine effectiveness[127].

Concluding remarks

Cancer is the second leading cause of death worldwide, and cancer treatments continue to be a major burden on health-care costs. It is clear that the great heterogeneity of cancer cells and the highly organized tumour microenvironment that can resist many forms of therapy, including immunotherapy, will compromise even the most scientifically sophisticated current attempts at a cure. A profoundly different approach to the cancer problem is needed, and, ironically, it might be an old approach that has resolved major health plagues throughout history — disease prevention through vaccination. For the past three decades, cancer vaccines have been designed for the treatment of late-stage disease rather than for prevention. Now, with better insight into the importance of cancer immunosurveillance during cancer development and the benefits of maintaining strong immunity to slow tumour progression, researchers are starting to turn their attention to vaccines for cancer prevention. It is hoped that vaccines given to individuals with a known genetic risk of cancer or to those showing early stages of tumour development, such as pre-malignant lesions, could strengthen and/or prolong immune surveillance and ensure a cancer-free life.

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