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Prophylactic Cancer Vaccination by Targeting Functional Non-Self

Vincent K. Tuohy^{1,2} and Ritika Jaini¹

¹Department of Immunology, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA

²Departments of Pathology and Molecular Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio USA

Abstract

Despite the monumental success of childhood prophylactic vaccination, there is no similar program designed to provide protection as we age against adult onset diseases like breast cancer. Instead, the predominant focus of current cancer vaccine strategy is to vaccinate after the tumors become established. This strategy has at best provided incremental improvement in overall survival. We propose the development of an adult vaccination program modeled on the childhood program that provides protection against diseases we confront as we enter our middle age. Since most cases of adult cancers are not associated with definitive etiopathogenic viruses, we propose extending our selection of vaccine targets to tissue specific self proteins that are overexpressed in developing tumors but are no longer expressed in normal tissues (*'retired or former self'*), are expressed in normal tissues under readily avoidable conditions (*'conditional self'*), or are incapable of targeting any clinically significant autoimmune complications (*'irrelevant self'*). By extending prophylactic vaccination to such *'functional non-self'*, prophylactic vaccination against adult onset diseases like breast cancer may occur safely in the absence of any autoimmune inflammatory complications and may potentially reduce disease incidence in a manner that mimics the impact of childhood vaccination on diseases like measles and polio.

Keywords

Cancer Vaccine; Autoimmune; Tumor Immunotherapy

The Childhood Vaccination Program

The childhood vaccination program arguably represents the most powerful and most successful medical intervention in history and has prevented untold levels of morbidity and mortality against diseases once considered scourges against humanity (1,2; Figure 1). In its current manifestation, vaccines against 16 different pathogens are available and recommended by the Centers for Disease Control and Prevention (3). These include viral vaccines against hepatitis A, hepatitis B, influenza, measles, mumps, rubella, polio, rotavirus, varicella, and human papillomavirus (HPV³) and bacterial vaccines against hemophilus influenzae B (Hib), meningococcus, pneumococcus, tetanus, diphtheria, and pertussis. Childhood vaccination has virtually eliminated the endemic transmission of polio,

Address for Correspondence: Dr. Vincent K. Tuohy, Department of Immunology, NB30, Lerner Research Institute, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195; Phone: 216-445-9684; Fax: 216-444-8372; tuohyv@ccf.org.

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measles, and rubella in the United States, and worldwide vaccination against smallpox has actually eradicated this once dreaded disease. Some vaccines including those against Hib and tetanus, are even more effective at providing immunity than natural infection with the wild-type pathogen (4,5). Although the Hib vaccine prevents only one form of meningitis, it has nearly eliminated what was once the most common cause of bacterial meningitis in infants and children in the United States. Since Hib vaccines were introduced, the incidence of invasive Hib disease in infants and children in the United States has decreased by 99% (4). Moreover, many of the other childhood vaccines have reduced morbidity and mortality similarly often exceeding 99% of pre-vaccine levels (6). Although often maligned, there is little doubt about the efficacy of childhood vaccination in creating dramatic reductions in disease incidence, morbidity, and mortality.

The Importance of Prophylaxis in the Childhood Vaccination Program

Optimization of childhood vaccination typically involves temporally spaced multiple immunizations that boost immunity, and many of the vaccines incorporate several variants or strains of each attenuated target pathogen or their derived components (3). However, at the heart of the remarkable success of the childhood vaccination program is one profound fundamental principle, namely, that effective vaccine induced immunity must be provided prophylactically, long before the child engages the wild-type pathogen. This prophylactic feature provides sufficient time for the child to develop a substantial immune response capable of inducing rapid and efficient neutralization and clearance following infection. There is little impact on viral clearance or alleviation of symptoms when vaccination occurs following infection (7). Rabies vaccination is a notable one of these few post-exposure prophylactic situations facilitated by the extended incubation period of the wild-type pathogen that allows time for an effective vaccine induced immunity to develop after infection (8). However, there is no substantial evidence showing efficacy when vaccination against pathogens occurs after the appearance of symptoms. Such evidence may appear to emerge with the recent development of multivalent vaccines incorporating several viral strains that may theoretically provide acute and longterm protection against the vaccine targeted pathogen strains not involved in the initial infection. However, it must be noted that such protection would indeed be prophylactic since the vaccine induced immunity would occur prior to exposure to the unencountered pathogenic strain. In any event, it is most important to recognize that the powerful disease protection provided by the childhood vaccination program is due primarily to the effective prophylactic nature of the immunity induced prior to exposure to wild-type pathogen and long before the appearance of clinical symptoms.

Therapeutic Cancer Vaccination against Tumor-Restricted Antigens

Despite the proven efficacy of prophylactic vaccination against childhood diseases, the development of cancer vaccines has had a predominant therapeutic focus for more than thirty years (9). Countless strategies have employed the fundamental approach of vaccinating after tumors have emerged and grown. This strategy is equivalent to the unsuccessful approach of vaccinating against pathogens after the appearance of symptoms and has resulted in a long history of frustration and disappointment despite some recent modest success (10).

³**Nonstandard abbreviations used:** autoimmune regulator transcription factor (AIRE); dendritic cells (DCs); epidermal growth factor receptor tyrosine kinase (HER2 or *neu*); glycoprotein100 (gp100); hemophilus influenzae B (Hib); hepatitis B virus (HBV); hepatitis C virus (HCV); human papillomavirus (HPV); human mammary tumor virus (HMTV); human T cell leukemia virus (HTLV-1); major histocompatibility complex (MHC); medullary thymic epithelial cells (mTECs); melanoma antigen recognized by T cells (MART-1); mouse mammary tumor virus (MMTV); polyomavirus middle T antigen (PyVT); prostate acid phosphatase (PAP); regulatory T cells (Tregs); xenotropic murine leukemia related virus (XMRV)

There are several possible explanations for the overwhelming predominance of this therapeutic vaccine approach against tumors and the rather modest outcomes achieved. There is a long embedded history of boosting latent tumor-specific immune responses. The appeal for confining immunotherapy to antigenic targets specific for the tumor itself lies in the exquisite specificity of such responsiveness and the inherent avoidance of collateral tissue damage and non-specific side effects that complicate less precise approaches. However, the trade-off for such tumor-specific immunotherapy is the increased likelihood that the selected tumor antigen, often derived from mutated, defective, ectopic, or dysregulated protooncogenes, or perhaps altered splice or frame shift variants of normal proteins may not elicit a clinically effective immune response. This may be due to the efficient cortical thymic deletion of T cells responsive to ubiquitously distributed proteins that are not expressed with any tissue specificity (11,12). Such resultant nondominant or cryptic T cell repertoires and autoimmune responses are a dynamic component of self-recognition plasticity in autoimmunity and may collectively provide clinically significant immunity. However, as isolated individual targets, non-dominant self-antigens often elicit responses that have limited clinical consequences and as such may provide insufficient regulation of tumor growth. Alternatively, unique tumor specific antigens may be highly immunogenic but their expression is generated from hyper-mutable regions of the tumor genome causing their production to be ephemeral and easily substituted with other variants when targeted immunologic pressure is applied. Thus, a vigorous response may be initially elicited, but it is against a phantom target that rapidly disappears.

In addition to being predisposed to eliciting nondominant suboptimal immune responses, putative oncogenic proteins and other tumor-specific antigens may also have a low frequency of over-expression in the overall intertumor population as well as substantial intratumor heterogeneous expression predisposing to ineffective therapeutic targeting. For example, the epidermal growth factor receptor tyrosine kinase (HER2), has been targeted for vaccination in HER2+ ovarian and breast cancers despite its limited frequency of overexpression in breast and ovarian tumors and its substantial irregular intratumor distribution (13–15). Thus, it is not surprising that selection of target tumor-specific antigens that have restricted tumor overexpression and are inherently predisposed to elicit suboptimal responsiveness may often provide inadequate tumoricidal results in the broad tumor-bearing population.

It should be noted that antigens ubiquitously expressed during development may in some cases have available T cell repertoires sufficient to provide effective tumor immunotherapy. Recent studies have shown that protection against the development of autochthonous tumors may be induced by vaccinating mice with embryonic or stem cell antigens overexpressed in tumor tissues and that this tumor protection occurs in the absence of any detectable autoimmune sequelae (16,17). However, it may be presumptuous to assume that autoimmune sequelae may manifest solely as parenchymal inflammation and organ failure, particularly when the stem cells expressing the targeted antigen are sparsely distributed within each organ. Targeted autoimmunity to embryonic or stem cell antigens may possibly manifest only when organs are challenged to repair or regenerate and may not be evident during normal organ function. Thus, the failure to observe autoimmunity following immunization with stem cell antigens may simply reflect a current lack of understanding of the likely non-traditional phenotype of embryonic or stem cell autoimmunity, and therefore, an absence of established experimental conditions under which such unique pathology may be observed.

In addition to deficiencies in repertoire and antigen availability, the effectiveness of therapeutic cancer vaccines is limited by the well documented immunosuppression commonly occurring in cancer patients (18). Tumors create a microenvironment that fosters

immune tolerance through a variety of mechanisms that include inhibition of antigen presentation, activation of negative costimulatory signals, secretion of factors that cause anergy, deletion, or suppression of invading T cells, and skewing of immunity toward regulation through regulatory T cells, natural killer cells, and myeloid derived suppressor cells. Thus, the induction of effective tumor immunity after tumors emerge and become established is a formidable challenge that requires overcoming the inherent ability of tumors to inhibit the immunity directed against them and to select against any immune pressure targeted to them by simply not making the targeted antigen.

Therapeutic Cancer Vaccination against Tissue Restricted Differentiation Antigens

As alternative targets for cancer vaccination, organ-specific differentiation antigens often show high expression frequencies in tumors derived from the organ and appear to be very capable of eliciting immunodominant responsiveness and effective tumor immunotherapy as evidenced by their ability to target tissue-restricted destruction or by their ability to elicit high frequencies of type-1 proinflammatory T cells. For example, melanoma antigen recognized by T-cells (MART-1) is a normal differentiation antigen expressed on most melanomas, and its ability to induce autoimmune vitiligo has been associated with its effectiveness as a melanoma cancer vaccine in advanced clinical trials (19,20). In addition, vaccination against glycoprotein100 (gp100), a differentiation protein expressed in melanocytes and melanomas, has been shown to prolong survival in melanoma patients in advanced clinical trials (21). Recently, the U.S. Food and Drug Administration has granted approval to treat patients with advanced prostate cancer with Sipuleucel-T (Provenge®), an autologous dendritic cell (DC) vaccine targeted against prostate acid phosphatase (PAP), a protein expressed in normal prostate tissues and in most prostate cancers (22). Sipuleucel-T has been shown to induce high frequencies of proinflammatory interferon-gamma producing T cells and prolong survival in patients with metastatic androgen-independent prostate cancer (10,23). Thus, normally expressed differentiation antigens may be both effective and acceptable targets for cancer vaccination particularly if the potential autoimmune sequelae resulting from such self targeting are tolerable. Such conditions occur in breast cancer since tumor affected breasts are often removed or ablated as part of therapy, and their removal, though traumatic, is not life-threatening.

One possible explanation for the success of PAP vaccination may lie in the likelihood that a substantial T cell repertoire would be available for responding to such a tissue restricted differentiation protein compared to more ubiquitously expressed antigens. Thymic expression of tissue specific proteins occurs in medullary thymic epithelial cells (mTECs) under control of the autoimmune regulator transcription factor (AIRE; 24–26). Although, mTECs are poor antigen presenting cells, they are known to transfer the AIRE dependent tissue specific proteins to thymic medullary DCs capable of presenting these proteins to developing T cells. Upon engagement of these self proteins, T cells with high affinity receptors undergo deletion, anergy, receptor editing, or become regulatory T cells (Tregs) that prevent the development of autoimmunity (27). In contrast, ubiquitously expressed proteins are constitutively presented by thymic DCs, and T cells responding to such proteins are deleted or regulated in a relatively AIRE independent manner even as they develop and migrate through the thymic cortex (11,12).

In addition, the AIRE dependent process critical to deletion or regulation of T cells that recognize tissue restricted proteins, predisposes to a variety of ways in which high affinity T cells can escape deletion including AIRE mediated expression of splice variants that do not contain disease inducing peptides (28), the formation of unstable short-lived complexes involving peptides bound to major histocompatibility complex (MHC) proteins that preclude

apoptotic deletion of disease inducing T cells (29), and the availability of an extremely narrow neonatal window for completing the AIRE dependent deletion process (30). Thus, differential shaping of autoreactive T cell repertoires may make it more likely that a clinically relevant immune response will develop against proteins expressed in a tissue restricted manner compared to proteins with ubiquitous multi-organ expression profiles.

Viral Targets for Prophylactic Cancer Vaccination

Viral targeted vaccines have already been shown to protect against cancers that arise as complicating sequelae of chronic viral infection. As indicated above, cervical cancer occurs following chronic infection with defined strains of HPV including strains 16 and 18 that account for the majority of cases (31–33). However, recent evidence also implicates chronic HPV infection in cancers of the anus, vulva, vagina, penis, as well as oropharyngeal cancer often with a predominant involvement of strain 16 thereby suggesting HPV vaccination may ultimately provide protection against many cancers in addition to its intended and proven protection against cervical cancer (33–37). The most prominent risk factor for developing liver cancer is chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV; 38), and the broad use of the hepatitis B vaccine in children resulted in significantly reduced incidence of childhood associated liver cancer (39). This immunity persisted even after the disappearance of viral titers suggesting long-lived cell based memory (40).

Several other viruses have been implicated in the development of cancers but vaccines designed to protect against these viruses are currently unavailable. Chronic infection with Epstein Barr virus is associated with the development of lymphomas including Hodgkin's lymphoma, Burkitt's lymphoma, post-transplantation lymphomas, as well as nasopharyngeal cancer (41). Chronic infection with Herpes virus 8 has been implicated in the development of lymphomas but is also associated with the development of the Kaposi sarcoma skin cancer (42). Human T cell leukemia virus-1 (HTLV-1) is a prominent risk factor for developing adult T cell leukemia and cutaneous T cell lymphoma (43), and very recent evidence has implicated the xenotropic murine leukemia related virus (XMRV) in 27% of prostate cancers compared to 6% of normal prostate tissue (44,45). However, the XMRV association with prostate cancer remains quite controversial (46,47). Chronic bacterial infections may also induce tumor formation as indicated by the high incidence of gastric adenocarcinoma in patients chronically infected with *Helicobacter pylori* (48).

Viral etiopathogenesis has also been proposed for human breast cancer. Several groups have identified virus in human breast tumors having >95% homology with the mouse mammary tumor virus (MMTV), a retrovirus known to cause breast tumors in mice (49). One version of the human mammary tumor virus (HMTV) is a non-genomic infectious virus found in about 40% of human breast tumors (50,51). Alternative variants are genomic and overexpressed in up to 90% of human breast tumors but are also expressed in 15% of healthy cancer-free women and a variety of human lymphomas (52–55). It has been proposed that the infectious HMTV virus represents a variant of MMTV that jumped species since the distribution of breast cancer incidence corresponds to the native or introduced habitat of the house mouse, *Mus domesticus* (56), and MMTV can productively infect human breast cells (57).

The infectious HMTV virus would be a likely target for a conventional prophylactic breast cancer vaccine. However, it is less clear what viral specific proteins can be targeted against any endogenous HMTV for prophylactic breast cancer vaccination. In any event, it seems clear that the development of several new prophylactic pathogen-targeted vaccines may possibly provide substantial protection against cancers for which we currently have no

protection. These include several types of lymphomas, naso-pharyngeal cancer, Kaposi sarcoma, gastric adenocarcinoma, and possibly even prostate and breast cancer.

Self Targets for Prophylactic Cancer Vaccination

It is important to recognize that most cancers are not associated with any predominant viral or other pathogen risk factors. For example, colorectal cancer has no well defined link to any viral risk (58). Moreover, cancers associated with pathogen risk factors may still develop even in the absence of the defined pathogen. This development may be most evident from the fact that the infectious HMTV cannot be detected in about 60% of breast tumors (50,51) and XMRV cannot be found in at least 73% of prostate tumors (44,45). Thus, vaccines targeting these viruses may be inherently limited in their ability to diminish breast and prostate cancer incidence by no more than 40%. Clearly, this level of decreased tumor incidence would be a remarkable and admirable achievement, but would not be close to the >99% degree of disease inhibition often achieved by vaccines used against pathogens during childhood vaccination (Figure 1).

It is equally important to note that all cancers are characterized by unregulated overgrowth of dysfunctional cells. It is widely believed that tumors initially develop when cells undergo dysplastic changes showing abnormal size, shape, chromatin content, and mitotic activity. Severe dysplastic cells may evolve into a carcinoma *in situ* containing many immature non-differentiated cells and eventually may evolve into invasive and finally metastatic carcinoma. This evolving transformation of normal cells into malignant cells often takes years to develop and therefore provides an opportunity for effective immune intervention through prophylactic vaccination targeting self proteins expressed during dysplasia or in carcinoma *in situ* as a result of the transcriptional dysfunction that is clearly manifest during these early pre-malignant stages.

How then do we select self targets that can be used for prophylactic cancer vaccination? Clearly for effectiveness, the self protein target must be expressed during early tumor development in dysplastic cells and/or in carcinoma *in situ*. However, for safety considerations the self protein target must not be expressed in normal tissues so that autoimmune complications may be avoided.

Self Targets for Prophylactic Breast Cancer Vaccination

We have recently proposed an autoimmune mediated strategy for generating an effective and safe prophylactic breast cancer vaccine (59). We selected breast cancer for developing a prophylactic vaccine because it is a major global health risk in both the developed and developing world with an astounding 1.38 million new cases and 480,000 deaths worldwide in year 2008 (60). Our criteria for target antigen selection involved the following considerations: the antigen had to be constitutively overexpressed in the majority of targeted tumors, expression of the target antigen in normal tissue had to be conditional, and the condition determining expression of the target antigen in normal tissue had to be readily avoidable. We selected α -lactalbumin as our target antigen for several reasons. Despite two studies in the early 1980's indicating its lack of expression in human breast tumors (61,62), several subsequent investigations have found that α -lactalbumin is produced in many or most human breast tumors (63–68). Moreover, recent studies have shown that the α -lactalbumin promoter can be used for breast tumor specific targeting of several tumoricidal factors including the E1A transcriptional regulator (69) and the suicide genes thymidine kinase (70) and cytosine deaminase (71). Indeed, argyrophilia and ultrastructural dense-core granules are often observed in human breast tumors and may represent attempts to differentiate and lactate (68). We also selected α -lactalbumin for vaccine targeting because

its conditional breast specific high level expression occurs only during lactational differentiation (72–75).

We used two transgenic mouse breast cancer models including MMTV-*neu* transgenic mice that express the non-activated *neu* under regulation of the long terminal repeat of mouse mammary tumor virus (MMTV) and show a 50% incidence of spontaneous mammary tumors by 205 days of age (76), and MMTV-PyVT transgenic mouse that express the polyomavirus middle T antigen (PyVT) under MMTV regulation and develop very rapidly growing mammary tumors palpable by 5 weeks of age (77). We found that vaccination of 2 month old MMTV-*neu* transgenic mice with α -lactalbumin completely prevented the appearance of autochthonous breast tumors at 10 months of age whereas 100% of sham vaccinated control mice developed breast tumors. Additional experiments showed highly significant inhibition in the growth of transplantable 4T1 breast tumors in BALB/c mice prophylactically immunized with α -lactalbumin. Although α -lactalbumin vaccination significantly inhibited the growth of established transplantable 4T1 breast tumors as well as established autochthonous breast tumors in MMTV-PyVT mice, the ability to inhibit established tumors was modest in comparison to the impact of prophylactic vaccination. In addition, the efficacy of therapeutic vaccination decreased with increasing tumor load at the time of vaccination.

Prophylactic α -lactalbumin vaccination was clearly far superior to therapeutic vaccination in preventing or reducing tumor load. However, most importantly, prophylactic α -lactalbumin vaccination occurred in the complete absence of any detectable inflammation of normal breast tissues or any other tissues examined. Autoimmune inflammation occurred only in lactating breasts resulting in breast failure characterized by lactation insufficiency and decreased ability to nurture offspring. Pups nursed by α -lactalbumin immunized mice consistently showed significant growth inhibition often complicated by kwashiorkor-like nutritional abnormalities and runting. Thus, α -lactalbumin vaccination may provide safe and effective protection against the development of breast cancer for women in their post-child-bearing, premenopausal years, when lactation is readily avoidable and risk for developing breast cancer is high and ever increasing.

Next Generation of Prophylactic Breast Cancer Vaccines

The importance of our study lies in the fact that carefully selected self proteins may serve as targets for developing effective prophylactic cancer vaccines that are also safe in terms of inducing any unacceptable autoimmune inflammatory complications. These conditionally expressed self proteins would be most useful in serving as vaccine targets for cancers not predominantly associated with any definitive etiopathogenic infectious agent. These cancers would include breast cancer, ovarian cancer, prostate cancer, and colorectal cancer to name a few.

It is important to note that our study represents a very embryonic and prototypic form of the self targeted prophylactic cancer vaccine strategy in which a single targeted antigen provides vaccine protection against tumors in a limited number of mouse strains. It is possible that such a simplistic approach will not translate completely intact into a viable vaccine capable of providing the same observed safe and effective protection in a heterogeneous human female population. On the other hand, if safe and effective protection against breast cancer can be induced in mice, then it is also quite likely that it can be achieved for women. Given the breast failure and highly significant prophylactic protection against mouse breast tumors induced by targeted autoimmunity against the α -lactalbumin differentiation protein, there is minimal reason to think that similar prophylactic protection would not be induced against breast cancer in women particularly considering the substantial number of studies that have

shown expression of α -lactalbumin in human breast tumors. However, one primary concern here is whether prophylactic α -lactalbumin vaccination of normal healthy cancer-free women may result in autoimmune complications due to possible expression of α -lactalbumin in the normal breast tissue of some women as has been previously claimed (62). This occurrence may possibly be avoided by pre-screening candidate women for high serum prolactin levels required for induction of α -lactalbumin expression (68) and by excluding women using contraceptive hormone therapy associated with expression of lactational foci in normal breasts (62). In addition, this potential problem may be circumvented by targeting the vaccine to women with sufficient involution of their breast parenchyma to preclude expression of lactation dependent proteins, *i.e.* older women at ever increasing risk of developing breast cancer with age.

It must be noted that for therapeutic breast cancer vaccination, the frequency of expression of α -lactalbumin in human breast tumors would be a most important consideration because if the target antigen is not in the tumor, the vaccine would have limited clinical effectiveness in either inhibiting the growth of the established tumor or prolonging overall survival. However, it is very important to realize that for prophylactic breast cancer vaccination, the frequency of α -lactalbumin expression in established breast tumors is a completely moot point since prophylactic vaccination targets the expression of the antigen during mild and severe early dysplastic changes as well during the carcinoma *in situ* stage of the evolving breast tumor. Thus, one must select the target antigen in the context of its expression during the early stages of tumor emergence rather than during the later evolved stages of tumor maturation when the tumor cells have developed more sophisticated ability to invade, metastasize, and adapt to and thereby avoid any chemotherapeutic or immunologic pressure.

Although our study provides a proof-of-principle for safe and effective prophylactic breast cancer vaccination, it is clearly a prototypic vaccine that targets a single antigen likely involved in the transcriptional dysfunction that characterizes early breast cancer development. As such, this restricted targeting provides a limited monovalent amount of immunologic pressure against any impending tumor development and thereby precludes inhibition of tumors that do not express α -lactalbumin during their early development. Therefore, one could argue that optimization of prophylactic breast cancer vaccination may require a multivalent vaccine that targets several lactation dependent proteins with tumor expression features and conditional expression profiles similar to α -lactalbumin. This level of immunologic pressure against any emerging breast tumor would likely enhance the protective effect of the prophylactic breast cancer vaccine and hopefully do so in the absence of any increased autoimmune risk.

Alternative Self Variants for Prophylactic Cancer Vaccination

Our prototypic prophylactic breast cancer vaccine targets '*conditional self*' as a functional substitute for traditional '*non-self*' and thereby extends the concept of prophylactic vaccination to include safe self targets that are capable of providing vaccine protection in the absence of autoimmune sequelae. However, there are other self target concepts that could provide substitutes for conditional non-self and thereby provide safe and effective self targeted prophylactic cancer vaccination. One could view aging as a process that provides proteins that for all intents and purposes are no longer expressed due to metabolic termination or waning of former biologic processes. Certainly, tissue involution that occurs with age is accompanied by declining expression of proteins associated with such robust youthful tissue function. Such proteins may often be expressed during the early stages of tumor development as dysfunctional transcription manifests. Such '*retired or former self*' may also serve as viable targets for safe and effective prophylactic cancer vaccination. Additionally, one could select self protein targets that are overexpressed during tumor

development but whose targeted autoimmunity induces clinically irrelevant inflammation and nominal or insignificant autoimmune complications. Targeting such '*irrelevant self*' may also have the potential to provide powerful protection against the development of tumors in the absence of any clinically relevant autoimmunity.

Summary

The childhood vaccination program shows that prophylactic vaccination is a proven way to dramatically reduce the incidence of disease, yet there is no similar vaccination program to protect us as we age from adult diseases like breast, ovarian, prostate, and colorectal cancer. We propose that it is possible to develop a similar adult vaccination program designed to provide protection against adult cancers by extending our vaccine target selection to self proteins that are overexpressed during the early stages of tumor development but serve functionally as non-self viral-like substitutes because their expression in normal tissues either no longer occurs as we age (*'retired or former self'*), is restricted to defined readily avoidable conditions (*'conditional self'*), or is not capable of targeting any clinically relevant autoimmune sequelae (*'irrelevant self'*). Although prophylactic cancer vaccine must have a strong safety profile and cost-benefit ratio, such safety and cost factors may be quite tolerable particularly within high risk populations associated with strong family history and/or genetic predisposition for developing malignancies. The consequences of expanding the target range of prophylactic cancer vaccination to carefully selected self targets may dramatically effect the incidence of adult diseases like breast, ovarian, prostate, and colorectal cancer in ways previously unimagined and thereby re-define the concept of cancer prevention as far more than simply early detection.

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KEY MESSAGES

1. The childhood vaccination program shows that prophylactic vaccination is a proven way to dramatically reduce the incidence of disease, yet there is no similar vaccination program to protect us as we age from adult diseases like breast cancer.
2. We propose the development of a similar vaccination program for adults designed to provide protection against adult cancers by extending vaccine target selection to self proteins that are overexpressed during the early stages of tumor development but serve functionally as non-self viral-like substitutes because their expression in normal tissues either no longer occurs as we age (*'retired or former self'*), is restricted to defined avoidable conditions (*'conditional self'*), or is not capable of targeting any clinically significant autoimmune sequelae (*'irrelevant self'*).
3. Expanding target selection for prophylactic cancer vaccination to carefully selected self proteins will re-define the concept of cancer prevention as far more than simply early detection and lifestyle changes and has the potential to alter the incidence of adult diseases like breast, ovarian, prostate, and colorectal cancers in ways previously unimagined.

FIGURE 1.

Incidence of poliomyelitis, hemophilus influenzae B (Hib), measles, and mumps in the United States following licensing of vaccines for childhood vaccination. (adapted from: Centers for Disease Control and Prevention, The Pink Book: Slide Sets, Epidemiology and prevention of vaccine preventable diseases, 11th edition, 2009; <http://198.246.98.21/vaccines/pubs/pinkbook/pink-slides.htm>)