Cancer Immunol Immunother (2002) 51: 409–416
DOI 10.1007/s00262-002-0293-3

PERSPECTIVES

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Antitumor vaccines: is it possible to prevent a tumor?

Received: 2 April 2002 / Accepted: 19 April 2002 / Published online: 25 June 2002

Abstract The main medical use of vaccines is to induce a state of immunity in healthy individuals to protect them from deadly or dangerous diseases. In the field of cancer immunology, however, vaccines are being used in patients as therapy, often with a very poor success rate against advanced disease. This paper reviews recent preclinical evidence in favor of the prophylactic use of immunological approaches to cancer. Successful attempts at immunological cancer prevention in HER-2/neu transgenic mice are described as an example. The specific properties of the HER-2/neu gene product as a tumor antigen, and the nature of the immune responses induced by effective preventive treatments are reviewed. Although the very high rate of mammary carcinoma prevention in mice has generated enthusiasm, it should not be forgotten that such treatments, when administered to healthy humans at risk of cancer, may carry the risk of inducing autoimmunity. These issues can be addressed in preclinical studies in appropriate animal models.

Keywords Breast carcinoma · Cancer prevention · HER-2/neu · Immunity · Vaccine

Why do cancer vaccines not cure cancer?

Vaccination is the most successful practice in preventive medicine [1] but in spite of this, the notion of using vaccines to prevent tumors has never been universally accepted by immunologists [21]. This is not surprising when viewed in the context of the highly emotional issues associated with the diagnosis of cancer and the strong desire to provide a form of treatment, even one that is only sporadically and marginally successful. Poor prognosis associated with neoplastic disease and only temporary efficacy of several aggressive therapies are compelling reasons to use an alternative and less toxic approach for therapy. In this setting, several sophisticated vaccines are being developed with the aim of curing cancer [41]. Some of these have been found to be very effective in protecting immunized mice against lethal tumor challenge [33]. Unfortunately, however, when these vaccines are employed in clinical trials, sporadic tumor regression and temporary stabilization of disease are the only general positive outcomes [3, 19]. These disappointing clinical results are not surprising, considering that the efficacy of a cancer vaccine is commonly assessed experimentally for the protection it is able to provide healthy mice against a subsequent lethal tumor challenge. The ability of cancer vaccines to cure existing tumors has hardly ever been investigated experimentally [34]. In cases where this was done, it was found that only a minority of tumor-bearing mice were cured, and even this limited efficacy was achieved only when the vaccine was administered in the first few days of tumor growth. The results of using cancer vaccines for cancer cure in experimental mice are no more encouraging than those obtained with cancer patients [34].

The efficacy of vaccines administered to a cancer patient is countered by a combination of multiple immune evasion strategies some of which are general and others that are particular to each tumor [18, 24]. An established tumor can escape an immune attack by outgrowing the destructive potential of the immune system, forming a microenvironment which is impenetrable to immune attack [45], and by orchestrating a large array of immunosuppressive activities [50]. Moreover, in an established tumor, cell clones that no longer express the antigen target of the immune attack can be easily selected [37]. This selection is favored by the genetic instability that follows neoplastic transformation

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[7]. An established tumor can be seen as an aggregate of many millions of genetically different and unstable cells, each one possessing enormous clonogenic potential. The time frame necessary for the progressive establishment of immune defenses elicited by vaccination may provide the perfect conditions for the selection of tumor cell clones that no longer express target antigens. After an initial shrinkage due to the killing of tumor cells expressing the antigen, the immune attack may result in a more anaplastic tumor that is capable of regrowing with a higher proliferative and metastatic potential.

A full assessment of the various tumor evasion mechanisms may be useful in determining whether current efforts on the improvement of vaccine efficacy are a rational way to proceed, or whether therapeutic vaccines should be considered limited in their efficacy because the mechanisms elicited by immunization, no matter how potent, may never be able to cure established tumors [3].

Could cancer vaccines prevent cancer?

In cancer prevention, the target is not the tumor mass but the potential risk of cancer (primary prevention), a preneoplastic lesion (secondary prevention), or a small number of isolated neoplastic cells remaining after a temporarily successful therapeutic treatment (tertiary prevention) [21]. Each condition raises distinct issues, but in each case the potential for immune evasion is markedly diminished. The low proliferative rate of the relatively few cells forming a preneoplastic lesion and residual tumor cells along with the still limited genetic instability of preneoplastic cells do not particularly favor the selection of cell clones able to escape the immune attack [30]. Furthermore, the suppressive activities of this small number of cells are reduced, since the extent of suppression is directly proportional to the tumor burden [50]. Lastly, preneoplastic lesion and residual tumor cells have not yet been isolated from the body by a fibroblastic stroma that can provide protection from the immune attack [45].

Another major issue in favor of preventive vaccination is that the immune system may not yet be aware of the presence of the altered cells. This permits the avoidance of specific immunosuppression, and tolerance linked to the inappropriate exposure of tumor antigens to the immune system, as takes place when they are presented by proliferating tumor cells [20, 24]. When the target antigen is first recognized through "optimal" presentation in the vaccine, the possibilities of eliciting an efficacious immune response are much higher. This is probably what can be expected in the case of the vaccination of a "not-yet-patient" at risk, or a person with a preneoplastic lesion. Whether or not the immune system of an individual in whom a tumor mass has been cured could recover the ability to respond to the tumor associated antigen (TAA) originally expressed by the tumor probably depends on the length of time from tumor removal and the intensity of tumor-induced tolerance.

While these theoretical considerations suggest that an antitumor vaccine could induce a more efficient immune reaction in cancer-free individuals, and that the effector arm of the immune response would be more efficacious against preneoplastic lesions and residual tumor cells, does there also exist direct proof from animal models that endorses this? Since the potential of a cancer vaccine is commonly assessed in vaccination-protection tests, there is plenty of data showing how effective the immunity elicited by many different vaccine formulations in healthy rodents is in inhibiting a subsequent challenge. In the last 20 years a large variety of tumors have been used while the vaccines have been developed in several ingenious ways. Even tumors that in more conventional experiments were unable to induce significant immune responses are rejected when the syngeneic recipients are efficiently preimmunized [5, 28]. New vaccines based on dendritic cells [51], or tumor cells engineered to release cytokines [15] elicit very effective immunity. Cytokine gene engineered cancer vaccines permit a selective elicitation of the most effective immune memory mechanisms [33]. These data suggest that it is possible to preimmunize against almost any kind of tumor. Somewhat inappropriately, these data have been (and still are) considered as an indication of vaccine curative potential. In effect, immunization-protection type experiments show how effective the immunity induced against nonexisting tumors is. However, the great preventive potential these vaccines display has been dismissed as being of no interest, since neither the type nor the antigenic makeup of a future tumor can be foreseen.

Predictive oncology and tumor immunology

In developed countries cancer has replaced infectious disease in incidence and prime cause of death, and the current scenario of immunoprevention of cancer is beginning to resemble that presented by the immune prevention of infectious diseases a century ago [21]. The repertoire of infectious agents against which human populations are vaccinated is mainly decided on a statistical basis, because populations in distinct environments have different probabilities of developing a specific infectious disease [1]. A change in the environment may alter the risk and require the development of new vaccines. The same kind of probabilistic reasoning can be applied to the risk of cancer. It can be assessed in a healthy population as a function of sex, age, family history, genetic makeup and lifestyle [17]. While the individual profile of cancer risk can be assessed by predictive oncology, immunological and molecular biology studies outline the probability of a specific TAA being expressed by certain type of tumor [12]. The combination of risk and specific TAA expression reduces the number of individuals with a significant probability of developing a tumor whose progression can be limited by a specific vaccination. Nevertheless, the population selected through these two kinds of predictions should not

be too small since the same TAA is often expressed by tumors originating in different organs [12].

These considerations radically transform the issue of preventive vaccines against cancer, since the central problem is no longer that of the unpredictability of cancer, nor that of the TAA expressed. Instead, it is now the balance between tumor prevention efficacy and the risk of inducing autoimmunity associated with the vaccine administration. The importance of this risk increases progressively by shifting the vaccination from patients with advanced cancer to patients with a preneoplastic disease, and normal individuals at a greater risk of developing cancer. However, even if the autoimmunity risk poses a major threat in a possible unrestricted use of preventive cancer vaccines [10], the basic question is whether a specific type of cancer can really be prevented through vaccination.

Experimental data on tumor prevention

As mentioned above, overwhelming proof of the concept of the preventive efficacy of tumor vaccines has been provided by the numerous publications showing that in immunized rodents antitumor vaccines allow the inhibition of growth of a subsequent lethal challenge by a syngeneic tumor. In the last 20 years a large variety of tumors have been transplanted into animal recipients immunized with different vaccines. Even tumors that in more conventional experiments were unable to induce significant immune responses are promptly rejected when the syngeneic recipients are effectively preimmunized [5, 33]. In addition, appropriate vaccination following the surgical removal of the transplanted tumor can block recurrence of the tumor in the form of minimal residual disease or its metastatic diffusion [9, 38].

However, a series of major conceptual issues are inherent in experiments of this kind. In most cases, immunization-challenge experiments are performed by injecting fast-growing tumors that have already been transplanted several times. This allows an experiment to be performed under well standardized conditions in which the minimal lethal dose, the latency, the growth, and the metastatic pattern of the tumor in syngeneic recipients are defined accurately and reproducibly. Unfortunately, as the experimental system becomes better established, the information provided is more and more unrelated to the features of natural tumors. Tumor clones are selected to grow under unnatural experimental conditions, and to grow fast. The time required for experimental observations is shortened through the selection of aggressive fast-growing tumors, while it is commonly accepted that if immunity inhibits fast-growing tumors, it would be even more efficacious against slower ones. On the other hand, the very rapid growth kinetics of transplantable tumors minimizes the consequences of tumor genetic instability. Slow progressing tumors favor the immune selection of clones that no longer express the target TAA, and sneak through the mesh of immune reactions. Models based on fast-growing tumors require an immune reaction which proceeds at full speed. Only a swift immune counterattack can control a rapidly developing neoplastic growth capable of killing a mouse in 2 to 3 weeks. To be effective, the elicited immune mechanisms have to be so fast as to inhibit the challenging tumor while it is still at the stage of monodispersed cells. The destructive ability must be so rapid that it does not even allow the tumor to form a compact aggregate and to build its protective extracellular matrix [33].

Human tumors become clinically apparent in aged individuals, while almost all immunization-challenge experiments are performed in young animals whose immune system can be significantly different from that of older animals. In addition, the TAA against which the animal is vaccinated may be a totally foreign entity for a young healthy recipient. In this case the ability of the vaccine to induce protective immunity does not have to overcome tolerance, nor are risks of autoimmunity possible. Even in the case of a vaccine breaking tolerance against a TAA overexpressed by the tumor and expressed by a few normal tissues at a lower level, the short duration of the experiment may prevent any assessment of the risk of autoimmunity associated with vaccination.

More recent experiments in mice transgenic for the target TAA provide a more accurate indication of vaccine efficacy and the risk of autoimmunity [19]. For instance, transgenic mice expressing the human CEA under its own promoter have shown that vaccines can break tolerance to CEA and protect mice against a subsequent tumor challenge by a tumor cell expressing CEA without inducing any autoimmune reactions against CEA positive normal tissues [49]. Several lines of mice transgenic for the human MUC1 gene driven by its own promoter have been generated. In these mice, various vaccine preparations can break tolerance to MUC1, and confer a long-lasting protection to a challenge from a MUC1 tumor without inducing autoimmunity [46]. In a similar way, in different lines of Her-2/neu transgenic mice an effective reaction against syngeneic Her-2/neu-positive transplantable tumors can be elicited with several vaccine preparations [19].

Inhibition of oncogene-induced carcinogenesis in transgenic mice

It is sobering to consider that almost all of what we know and believe about the ability of a vaccine to prevent tumor growth is based on experiments with highly artifactual transplantable tumors of this kind. Distortion of the information is the price that must be paid to obtain easily reproducible models that display the influence of the immune reaction on tumor growth.

Recently, tumors developing as a natural consequence of an artificial gene defect and insertion in transgenic mice have formed an alternative experimental system (reviewed in [19]). Many of the issues that

rendered the data derived from preimmunization-challenge experiments inappropriate have been overcome. In transgenic mice the expression of the transgene is commonly driven by a tissue-specific promoter and causes the onset of tissue or organ specific tumors. These become clinically evident in aged mice after a long period during which progressive preneoplastic lesions were detectable. The relationships between the incipient tumor and the surrounding tissues are preserved in several of these models, while the progression of carcinogenesis mimics what is observed in humans.

Despite these important analogies, these mouse models of cancer are not devoid of subtle but important pitfalls. In most transgenic mouse lines neoplastic transformation is due to the insertion of an oncogene, while the tumors appearing in humans are mostly due to a defect of a tumor suppressor gene. However, the most important immunological issue is related to when the transgene expression takes place. If the transgene product is a protein that is not commonly expressed by normal mice, the time of its first expression induces an immune tolerance of a different type. Transgenic proteins overexpressed during late pregnancy, or by young mice, should elicit a more profound tolerance than those that appear during puberty. The immunological context is different since an effective vaccine has to break central tolerance in certain transgenic mice, while in others it has solely to activate a significant reaction to an ignored foreign antigen. The elicited immune reactivity has to deal with multiple and multifocal tumors when the neoplastic transformation is directly induced by the transgene, or has to deal with a single or few tumors resulting from a progressive accumulation of transforming events. In some lines of transgenic mice tumors are aggressive and metastatic, while in other lines tumors display slower growth. A difference in aggressiveness can be observed even among lines of mice transgenic for the same oncogene driven by the same promoter. Variations in the transgene insertion and the genetic background of the mice modulate the aggressiveness of the tumors. Several background genes have been found to profoundly modify carcinogenesis in mice and in humans [11, 29, 47]. The action of some cancer modifier genes, for example polymorphic oncogenes [47], is easily explained, but in many instances the mechanisms linking the genetic background and neoplastic transformation are still hypothetical and obscure.

The idiosyncratic characteristics of each transgenic mouse model may account for the opposite results in the case of vaccination. C57BL/6 transgenic mice expressing SV40 T antigen under probasin promoter regulated by androgens and restricted to the prostate epithelial cells develop prostate carcinomas with a carcinogenesis progression resembling the human disease [8]. A preventive immune response against primary prostate carcinomas that naturally appear in these mice could be elicited by using an irradiated tumor cell vaccine and CTLA-4 blockade [26]. TG.ACxC57BL/6 F1 mice carry in the germline a mutant *Ras* oncogene. In these mice wounding or chemical promotion induces papillomas that progress to cancer. Immunization with the mutant rat peptide induces T cell reactivity and specific delayed-type hypersensitivity (DTH). However, immunization not only failed to protect against papillomas, but it induced a remarkable enhancement of their growth [44].

HER-2/neu transgenic mice

Thanks to the pioneering work of Leder and Muller [32] there are now several models of transgenic mice that start to over-express the rat (r) Her-2/neu non transforming proto-oncogene or its transforming mutated form under the transcriptional control of the mouse mammary tumor virus at a distinct period of their life. In some of these mice rHer-2/neu carcinogenesis takes place in virgin females, while in others it comes after pregnancy. Moreover, at 1 year of age (advanced maturity in mice) carcinomas can be evident in one, a few or all mammary glands depending on the model system [25].

Important direct comparisons are made possible by this large array of models. Both the slow carcinogenesis driven by rHer-2/neu proto-oncogene and the aggressive tumor growth due to the transforming oncogene are inhibited by vaccination with proteins, peptides, DNA plasmids, and $p185^{neu}$ positive allogeneic cells [21]. Inhibition appears to be mostly dependent on interferon-gamma (IFN-γ)-based DTH and antibody, as suggested by pathological findings and in vitro tests [22, 35, 42]. In several lines of transgenic mice, anti $p185^{neu}$ vaccination appears to be unable to elicit a strong cytotoxic T lymphocyte (CTL) killing of $p185^{neu}$-positive cells [22, 35, 39, 42], probably due to the difficulty of fully breaking their tolerance [39]. Vaccination-induced antibodies appear to block carcinogenesis by inhibiting $p185^{neu}$ receptor function and down-regulating its membrane expression in preneoplastic cells [42]. Their activity appears to be similar to that of passively administered anti-$p185^{neu}$ monoclonal antibodies [16]. Thus, multicomponent mechanisms other than a "straightforward" CTL activity may inhibit carcinogenesis driven by the expression of oncogenic growth factor receptors on the cell membrane [2]. These mechanisms, interestingly, do not play a major role in the inhibition of the growth of transplantable tumors [42].

The aggressiveness of the carcinogenesis directly modulates the degree of protection afforded by vaccination [4]. While all these transgenic mice appear to be genetically predestined to die because of rHer-2/neu carcinogenesis, the rate of tumor progression, the time limit of the experimental observations, as well as the occurrence of death due to natural causes may prevent multiple carcinomas from arising in all models [30]. Aggressive carcinogenesis not only makes its inhibition more challenging, but influences the time and the intensity of the expression of $p185^{neu}$. In turn, this affects the intensity of mouse tolerance to $p185^{neu}$. This is a crucial issue in antitumor vaccination, as discussed above.

Probably the most aggressive model of rHer-2/neu carcinogenesis is displayed by BALB/c inbred mice transgenic for the transforming activated rHer-2/neu oncogene (BALB-neuT mice) [4]. Foci of atypical hyperplasia appear in all 10 mammary glands, first in the terminal buds and then as lateral buds sprouting from ducts and ductules. The lateral side buds give rise to foci of carcinoma in situ around the 15th week, and these progress to invasive lobular carcinomas by the 20th week. Ten weeks later, these carcinomas are present in all the glands and are palpable before the 33rd week of age [14]. A significant delay in carcinogenesis was sought by administering allogeneic carcinoma cells expressing $p185^{neu}$. Moreover, their administration in combination with systemic IL-12 reduced tumor incidence by 90% and more than doubled mouse lifetime [35]. Six-week-old BALB-neuT animals received twice weekly for 2 weeks $p185^{neu}$ positive allogeneic $H\text{-}2^{q}$ cells, followed by five daily administrations of IL-12 in the third week. After 1 week of rest, this 3-week course was repeated for the entire lifetime of the mouse. The mammary glands of mice receiving this chronic combined treatment displayed a markedly reduced epithelial cell proliferation, angiogenesis and $p185^{neu}$ expression, while the few hyperplastic foci were heavily infiltrated by granulocytes, macrophages and $CD8^{+}$ lymphocytes. Specific anti-HER-2/neu antibodies and a non-polarized activation of $CD4^{+}$ and $CD8^{+}$ cells secreting IL-4 and IFN-γ were evident. A central role for IFN-γ was shown by the lack of efficacy of the combined treatment in IFN-γ gene knockout HER-2/neu transgenic BALB/c mice and the IgG2a and IgG2b isotype of anti-HER-2/neu antibodies.

These data constitute important proof of the validity of the concept that a very aggressive carcinogenic process can be inhibited by chronic immunological treatment. Preneoplastic lesions appear to be an appropriate and rational target for a specific immunological attack. A more analytical view is provided by BALB-neuT mice immunized at the 6th, 12th, 18th and 24th week of age with plasmids coding for the extracellular (ECD) and transmembrane (TM) domain of mutated rat-$p185^{neu}$. Following this treatment, 57% of the immunized mice did not display any palpable tumor at week 33, when all control mice were dying due to an outgrowth of the 10 mammary carcinomas [42]. Unpublished data showed that almost the same protection was afforded by only two immunizations at the 6th and 12th week. Vaccination with plasmids encoding only the $p185^{neu}$ ECD were less effective, whereas their protective potential was increased by their association with a small nonapeptide from human IL-1β [43].

These findings are leading to an exploration of how wide the time frame is in which a preneoplastic lesion can be inhibited. Should it be envisioned as a preventive maneuver in mice bearing very early preneoplastic lesions, or can it also be of benefit once overt preneoplastic lesions are diagnosed? This is a significant question because genetic screening programs are detecting healthy not-yet-patients [27], but early diagnosis programs lead to the identification of patients with preneoplastic lesions. Unpublished preliminary data suggest that the efficacy of vaccination decreases when its commencement is delayed, though substantial protection is still provided if it is started at week 14, when initial invasive carcinomas are detectable. A further 2 weeks' delay, i.e. to the time when the first carcinomas become palpable, results in zero protection (Quaglino and Forni, unpublished results). The definition of which immune mechanisms are responsible for the inhibition of the preneoplastic lesions, and how the efficacy of these vaccinations can be increased, are the questions guiding ongoing investigations.

What are the right antigens?

One of the major reasons for the success of the immunopreventive approach in rHER-2/neu transgenic mice stems from the choice of $p185^{neu}$ as the target antigen, and from its distinct immunological advantages in comparison with other tumor antigens. Such advantages are partly due to the fundamental differences between immunotherapy and immunoprevention as far as the choice of the target antigen is concerned. In the past decade the preferred choice for immunotherapy was a tumor rejection antigen recognized by T cells in the context of a MHC class I molecule on the surface of tumor cells [5, 6]. This type of target is highly useful to direct a relatively rapid attack of the immune system against tumor cells which are known to be already present, readily expressing both the antigenic peptide and the MHC molecule. Switching now to the long-term perspective of tumor immunoprevention, it is easy to see why most tumor rejection antigens are not suitable targets.

Tumor antigens are usually not required for tumor cell proliferation or survival. To the best of our knowledge, in the absence of immune attacks, melanomas thrive whether or not they express MAGE or tyrosinase; the same applies to carcinomas and CEA. In a sense it is ironic that, beginning with CEA itself, the true physiological function of many tumor antigens is still not fully understood, thus indicating that their presence or absence has a very limited influence on the biology of normal cells, and is practically negligible as far as neoplastic transformation is concerned.

Obviously if the antigen is not required for tumor cell growth and survival, then it is easily lost when progression from normal to neoplastic occurs in the presence of an antigen-specific immune attack. On the contrary, as in the case of rHER-2/neu, if oncogene and antigen are one and the same, then antigen loss variants inevitably will lose their tumorigenic potential as well.

A case in point is the establishment from in vitro cultures of rHER-2/neu transgenic mammary carcinoma cells having lost, for as yet unknown causes, the expression of $p185^{neu}$ [36]. It is interesting to note that such loss variants exhibited only minimal differences from

daughter cells expressing p185^{neu} as far as cell proliferation in vitro is concerned, but after in vivo injection, they displayed a complete loss of short-term tumorigenicity. A few tumors eventually grew after a very long latency, but such tumors invariably re-expressed high levels of p185^{neu} [36]. In short, in the rHER-2/neu transgenic system one can count on the presence of p185^{neu} throughout tumor progression from normal to metastatic mammary carcinoma, and a successful immunological targeting of p185^{neu} will inevitably result in the block of tumor growth and progression as well.

A second reason for the unsuitability of conventional tumor rejection antigens for tumor immunoprevention is their dependency on MHC expression for T cell recognition. Down-modulation of MHC glycoprotein expression, or of endogenous antigen processing machinery results in a severe impairment of tumor cell recognition and lysis by T cell immunity, even in the presence of a high expression of the antigenic protein. Defects in antigen processing or in MHC expression are exceedingly common in tumors, their overall frequency is estimated to be well above 50% of all cases [23], on a par with essential carcinogenic events such as telomerase reactivation or p53 inactivation. The advantage of integral surface molecules like p185^{neu} is quite obvious because they remain good targets for immune defenses, in particular antibodies and ADCC, even if tumor cells reduce or completely lose the ability to express MHC class I glycoproteins.

It has been shown that mammary carcinoma development in rHER-2/neu transgenic mice does indeed lead both to an overall reduction in MHC class I expression and to a selective loss of D-region specificity [31], possibly related to the restriction element for T cell recognition of relevant p185^{neu} antigenic peptides. However, the success obtained in establishing highly effective immunological prevention protocols demonstrates that p185^{neu} remains a viable target for the immune system, even in a MHC-unstable tumor progression system.

Finally, a definite advantage of targeting p185^{neu} derives from a combination of the properties outlined above. T cell target antigens invariably require a cytotoxic hit to eliminate tumor cells, but alternative, non-cytotoxic mechanisms can be equally effective in the case of p185^{neu}. For example, antibody binding can down-modulate p185^{neu} surface expression [42], thus leading to a decrease in phosphorylation of downstream kinase targets and ultimately to a powerful cytostatic effect. In fact, it has also been shown that three-dimensional growth in agar of HER-2/neu transgenic mammary carcinoma cells is severely hampered by anti-p185^{neu} antibodies in vitro, in the absence of complement or of ADCC effector cells.

To summarize, HER-2/neu and its protein product p185^{neu} present several distinct advantages over conventional, MHC-restricted peptide antigens recognized solely by T cells. The most important properties are the absolute requirement of p185^{neu} expression and kinase function for tumorigenicity, its surface localization and accessibility to a variety of immune effector mechanisms, both MHC-dependent and MHC-independent, and the existence of multiple tumor-blocking immune mechanisms in addition to cytotoxicity.

Risks inherent in preventive cancer vaccines: are they justified?

Can vaccines be used to prevent tumors? The accumulating experimental data in mouse models suggest

Fig. 1. The difficulty of assessing the risk of a new biotechnology is illustrated by this comic cartoon "The cow pock – or – the wonderful effects of the new inoculation!" (1802) by James Gilray showing a physician (possibly Edward Jenner) ready to vaccinate a young woman while several former subjects demonstrate the effects of the vaccine with cows sprouting from various parts of their bodies. Unfortunately, the potential and the risk of a vaccine aimed to inhibit carcinogenesis in a person diagnosed with a preneoplastic lesion or at specific risk of cancer cannot be predicted much more accurately. The picture is from the "Images from the History of Medicine" (IHM) collection of the U.S. National Library of Medicine, Bethesda, Maryland

that this is a plausible prospect, and justify the attention that is beginning to be paid to this new way of considering the exploitation of specific immunity against cancer. In several mouse models the genesis of tumors can be prevented immunologically. Vaccination could be envisaged as an effective new prospect in the prevention of carcinogenesis and inhibition of established preneoplastic lesions due to the overexpression of oncogenic growth factor receptors [2]. However, past failures and unrealized expectations have taught tumor immunologists to proceed with circumspection (Fig. 1). Despite significant similarities in the progression of carcinogenesis in transgenic mice and patients, the mouse data cannot be directly translated to humans because the mechanisms of tolerance to TAA may be different, and the escape mechanisms from immune control of human preneoplastic lesions may be more difficult to overcome. Vaccination of healthy individuals at risk of cancer is not the same as a compassionate attempt to help a patient with advanced cancer. Even where the expectation of a preventive vaccination may be to rescue a person at risk, the subject is a healthy person, and the risk is not equal to that posed by a rapidly progressing and deadly disease. For example, a promising attempt to develop a vaccine for Alzheimer's disease was recently blocked when the initial patients in the clinical trial developed inflammatory reactions of their nervous system [10]. This and several other issues linked to epitope presentation by polymorphic major histocompatibility antigens should be carefully evaluated beforehand, to ensure reasonable safety of a widespread antitumor vaccination. The old paradigm has been to take a promising new approach directly from successful proof-of-concept preclinical experiments to disappointing clinical trials, marred by ''unexpected'' side effects. Further studies in animals have usually demonstrated that most side effects were indeed already evident, or might have been discovered, during a more extensive preclinical phase [13]. It is hoped that this time around, immunoprevention of cancer will avoid this masochistic pitfall and will put animal models to good use in order to investigate the potential side effects and how to avoid them, before proceeding to clinical trials.

In conclusion, the potential of vaccines for tumor prevention may open a new medical dimension for managing this disease. We are close to the time when some of the most common tumors may be prevented by specific vaccines administered to patients with a preneoplastic lesion, to persons with a genetic risk of developing cancer, and eventually to the general elderly population.

Acknowledgements We wish to thank O.J. Finn (University of Pittsburgh Cancer Institute) for helpful comments and S.J. West for editing the manuscript. This work was supported by the Italian Association for Cancer Research, CNR Target Project on Biotechnology, and the Ministero dell'Università e della Ricerca Scientifica.

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