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Improving the efficacy of cancer immunotherapy

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ABSTRACT

A series of cancer vaccines have been evaluated in clinical trials with encouraging results, but the demonstration of clinical benefit in confirmatory studies has so far proven to be difficult. The development of cancer vaccines is hampered by a range of issues particular to this field of research. On 12th March 2008, the Biotherapy Development Association convened a workshop to discuss issues faced by scientists and clinicians involved in the development of cancer vaccines. This paper is a review of the field, based on discussions held at the BDA workshop, and describes biological barriers encountered in generating effective immune responses to tumours, methodological obstacles encountered in the improvement of immunological monitoring which aims to improve inter-laboratory and inter-trial comparisons, challenges in clinical trial design and problems posed by the lack of specific regulation for cancer vaccines and the impact on their development. Ultimately, a number of general solutions are posed: (1) better patient selection, (2) use of multi-modal treatments that affect several aspects of the immune system at once, (3) a requirement for the development of good biomarkers to stratify patients for selection prior to trial and as surrogates for clinical response and (4) harmonisation of SOPs for immunological monitoring of clinical trials.

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1. Introduction

The study of immunotherapy in cancer spans several decades with hundreds of clinical trials, using many different immunostimulatory strategies and modalities for vaccine delivery. A wealth of knowledge is now available that suggests that immunotherapy has potential application in the treatment of cancer, where it has been demonstrated to induce both clinical responses and robust immunological responses in sub-groups of treated patients. Cancer vaccines display a favourable toxicity profile compared to many standard cancer treatments, making them an attractive potential alternative to chemotherapy. However, none of the clinical development programme for therapeutic cancer vaccines have been successful in obtaining a centralised marketing authorisation in Europe or the United States of America (USA).[1]

On 12th March 2008 a workshop, organised by the Biotherapy Development Association (BDA), brought together clinicians and clinical scientists from industry, academic and regulatory backgrounds to discuss reasons for failure of immunotherapy and potential ways to improve its development. In this review, these issues are explored, and problems that are central to development of an effective immunotherapy are discussed, along with some preliminary solutions.

2. Background

The first example of immunotherapy for cancer applied in a clinical setting was credited to William Coley at the end of the 19th century.[2] Coley hypothesised that immunity raised in response to bacterial infection may be an important factor in the rejection of established tumours, an idea that led him to the development of the killed streptococcal preparations which later became known as Coley's Toxins. Although the principles used to develop Coley's Toxins are still around today (bladder cancer is treated with intravesicular Bacillus Calmette Guerin (BCG)[3], and there is evidence for the efficacy of Mycobacterium vaccae in melanoma and lung cancers[4,5]), the majority of immunotherapy research focuses on the 'vaccine' approach and targets tumour-specific antigens. One of the major breakthroughs in the field was the identification of first tumour antigens in mice and humans that could be specifically recognised by lytic T-cell clones.[6] In the following years, a broad variety of new tumour-specific antigens were identified that can be divided into different groups with unique features.[7] The availability of specific targets expressed on tumour cells led to the initiation of countless clinical trials, testing a plethora of different vaccines in a large number of solid and haematological malignancies.[8,9]

Nearly a century after the pioneering work of Coley, it is now widely accepted that immune responses play a part in the control of certain types of human cancers. Immune suppression, used for preventing rejection of organ grafts, has been shown to increase predominantly lymphomas, leukaemias and head and neck cancer as well as lung cancer.[10] Further evidence for a role of the immune system in tumour surveillance against common solid human tumours has been obtained in colorectal cancer, where the presence of T-cells in the tumour could predict the clinical outcome better than the tumour stage and nodal status,[11]and similar observations have also been made in several other types of human tumours. Rare, spontaneous tumour regressions are also thought to be due to anti-tumour immune responses. However, despite success with prophylactic vaccines for cancers with known viral aetiology (Gardasil and Cervarix have been licensed for use against Human Papilloma Virus (HPV), and thus prevention of cervical cancer[12]), there are no therapeutic vaccines licensed for humans in Europe or the USA. Three products achieved at least temporary regional marketing authorisations: Melacine® for melanoma in Canada; M-Vax™ for melanoma in Australia and recently Vitespen for Renal Cell Carcinoma in Russia. The first therapeutic cancer vaccine to receive conditional approval is the canine oral melanoma vaccine, produced by Merial Ltd., based on a significant improvement in overall survival of animals treated with a xenogeneic DNA vaccine targeting the tumour antigen tyrosinase.[13] This provides the proof of principle that therapeutic cancer vaccines may be successful in mammals.

3. Escape mechanisms used by tumours

The development of strategies to overcome the natural tendency of tumours to vary their antigenic profile and to suppress immune responses is a key issue in the design of immunological therapies for cancer. It is well established that tumours down-regulate many of the molecules involved in processing and presentation of peptide on major histocompatibility complex (MHC) class I, and that changes occur in the antigenic profile of tumours as they progress and metastasise.[14] For example, it has been shown that human leukocyte antigen (HLA) -A2 expression on ascitic cells from ovarian carcinoma, and transporters associated with antigen processing (TAP) and β-2 microglobulin (β2m) expression on tumour cell lines, is highly variable.[15] These 'escape mechanisms' allow tumours to evade therapies based on antigen-specific, monovalent therapy. A better understanding of the mechanisms and dynamics of such changes may lead to the development of more effective immunotherapeutic treatments. It is well known, for example, that natural killer (NK) cells target tumours that lack MHC,[16] and a high degree of NK cytotoxicity in the peripheral blood of healthy individuals can predict a significantly lower risk of cancer of any type, as compared to individuals with a low NK cytotoxicity in their blood.[17] Thus, vaccine-driven tumour escape (through MHC or antigen down-regulation) may be compensated through manipulation of innate immune responses.[18] Such interventions are currently being investigated.

The tumour microenvironment is generally immunosuppressive due to mechanisms such as hypoxia, induction and recruitment of suppressor cells (e.g. regulatory T-cells (T-regs), myeloid-derived suppressor cells (MDSCs) and immature dendritic cells), appearance of immunoregulatory immune complexes, oxidative stress and an enhanced proteolytic activity.[19] Changes in the expression of receptors and cytokines by tumours contribute towards the immunosuppressive tumour microenvironment, e.g. through upregulation of transforming growth factor-β (TGF-β) and interleukin-10 (IL-10). Furthermore, MDSCs, in the tumour microenvironment,

are known to produce immunosuppressive factors such as nitric oxide and reactive oxygen species.[20] Thus, although tumour-specific cytotoxic T-lymphocytes (CTLs) are often found to invade tumour tissue, they are frequently anergic and unresponsive due to the presence of immunosuppressive factors and regulatory cells.

Obviously, mechanisms that suppress the immune system provide a fundamental reason why immunotherapy fails to induce consistently robust immune responses. The investigation of immuno-suppression by tumour-infiltrating cells has become of utmost importance since a comprehensive understanding of the mechanisms involved will provide new directions for therapies complementary to immunotherapy. Thus, Talmadge et al. investigated new quantitative approaches for isolation of tumour-infiltrating cells. The analysis of immune cells purified from tumour in murine models has demonstrated that tumour volume is related to the absolute number of MDSCs and that this number is inversely correlated with numbers of tumour-infiltrating lymphocytes (TILs) (Talmagde et al., unpublished data). This leads to the hypothesis that perhaps MDSCs in the tumour microenvironment inhibit T-cell migration into the tumour. Since numbers of TILs are associated with positive outcome in a number of cancer backgrounds, this provides a rationale for the negative effects of MDSCs. Talmadge et al. further demonstrated that Celecoxib treatment could reduce numbers of MDSCs indicating a potential drug intervention that might synergise with immunotherapy. Kiessling et al. demonstrated that NK cells of the $CD56^{dim}$ phenotype, which is the subset mediating efficient anti-tumour cytotoxicity, are particularly sensitive to oxidative stress by H_2O_2.[21] This mirrors a similar sensitivity of T-effector/memory cells to oxidative stress.[22] A novel approach to the protection of such effector cells has been suggested in which *ex-vivo*-cultured TILs or LAK cells are modified with a catalase-encoding retrovirus, which would protect them against the effects of oxidative stress. These studies exemplify the ways in which a fundamental understanding of the underlying biology of tumour immuno-suppression may lead to new treatments, which aim to synergise with immunotherapy.

4. Immunological biomarkers

Immune parameters that can be established to predict clinical outcome may be developed as biomarkers. The overwhelming message from most tumour biomarker research is that no single parameter is likely to achieve any significant degree of use and that a broad profile of markers will be more informative. Immunological biomarkers have the potential to predict clinical outcome, and thus to reduce the development time and the length of clinical trials. Furthermore, prescreening of patients for immune status may identify patients who are more likely to respond to vaccination. However, despite some interesting immunological data and new approaches to integration and interpretation of the complex immunological data, no validated biomarkers exist for cancer immunotherapy or vaccines as yet, reflecting the need for rational and consistent approaches to the measurement of anti-tumour immune responses.[23]

One reason for the lack of correlation between immunological response and clinical outcome may be the complexity of the responses required for an anti-tumour response. For example, cytokine production (usually Interferon (IFN)γ) by T-cells *in vitro*, in response to antigen-specific or polyclonal stimuli, is measured in an attempt to demonstrate T_H1 responses. Although in cancer immunotherapy there is a dogmatic acceptance of the need to provoke a T_H1 cellular response, this does not always correlate with clinical outcome. The advent of multiplex cytokine assays combined with new methods, such as artificial neural networking (a programme that may be used to analyse complex data), allows for more sophisticated interpretation of cytokine data. In this way, it may be possible to generate immunological profiles which act as biomarkers for clinical response.

Most immunological monitoring is done on peripheral blood-derived effector cells. However, the lack of a response in the periphery may reflect the movement of effectors to the tumour. The type and activity of tumour-infiltrating cells (either cellular and humoral effector cells, innate immune cells or regulatory cells) may provide a deeper understanding of key anti-tumour effector mechanisms.[11] Certainly, there is evidence that the presence of both $CD4^+$ and $CD8^+$ T-cell infiltrates predicts improved clinical outcome in melanoma[24,25], and that the presence of tumour-infiltrating regulatory cells correlates with poor prognosis in ovarian cancer.[26] Moreover, improved overall survival of melanoma patients was seen where tumour-associated antigen (TAA)-specific cells were detected by tetramer analysis, indicating an effective antigen-specific response.[27] These data indicate the importance of determining responses within the tumour microenvironment and suggest that it is these immunological parameters that may determine clinical response. Thus, establishing immune parameters in the tumour and secondary lymphoid organs may be important in understanding the responses to immunotherapy.

5. Standardisation of immunological monitoring

Harmonisation of methods for monitoring the induction of antigen-specific T-cell responses in clinical vaccination trials has been identified as a key area of development within the field. The purpose of monitoring immunological outcomes in response to immunotherapeutic treatments is fourfold. (1) To determine the effectiveness of a vaccine to elicit the correct type of immune response. This will further aid in understanding the nature and dynamics of the response elicited by a particular modality and provide proof-of-principle for ensuing trials. (2) Determination of elements of the immune response that correlate with a clinical response. This is vital in order to understand the dynamics and magnitude of immune responses that are required to elicit clinical responses. (3) Armed with such knowledge, immunological responses may be used as surrogate markers for clinical responses which may ultimately be useful, if validated, as end-points in the later clinical trials. (4) There is an increasing recognition of the importance of obtaining immunological data that are comparable between different clinical trials.

In spite of its clear importance, finding a consensus on assays and protocols for immunological monitoring is a huge challenge, and there remains no standard within the field. To meet this challenge, there are now several programmes of research to improve the harmonisation of immunological monitoring, including the Immunoassay Proficiency Panel organised by the Cancer Vaccine Consortium (CVC) and the Cancer Immunotherapy (CIMT) Monitoring Panel (as part of the Association for Immunotherapy of Cancer). These organisations bring together laboratories to assess the current working standards for immunological tests and to identify areas that may be harmonised, with a view to optimising protocols and developing standardised assays.

Data shown by CIMT demonstrated the variability in tests between laboratories. Concentrating on ELISPOT and HLA peptide-tetramer staining CIMT did external validation studies on assays, from up to 13 different laboratories across Europe, using model antigens. In these studies, peripheral blood mononuclear cells (PBMCs) and peptides or tetramers were produced centrally, while the individual laboratories used their local version of the test. Tremendous variation was observed in the percentage of antigen-specific cells detected in peripheral blood. Moreover, in comparisons of ELISPOT data, where six possible reactivities were detectable, 5 of 12 laboratories were unable to detect more than 2, and one laboratory could detect none. This well exemplifies the degree of heterogeneity that exists in antigen detection between contributing laboratories that use different conditions in their assays; many differences in methodology were identified which clearly influence the outcome of these tests, including numbers of cells used, types of antigen-presenting cells, sources of reagents and readout platform for the assay. Of further concern is the degree to which criteria for data acquisition were seen to vary between laboratories, as small changes in the acceptance criteria can already lead to significant differences in the number of reported responses. These data exemplify the way in which local variation can lead to profound differences in interpretation of the immunological outcome of vaccination, and thus reduce the ability to compare data between laboratories. This initiative also highlights the importance of quality assurance within each laboratory in order to obtain precise and accurate results. It is of great concern that otherwise successful strategies may be abandoned due to false-negative data.

The solution to these problems lies in the standardisation of immunological measurements: a large undertaking given the variety of assays involved and the diversity of approaches employed for each assay. It is for this purpose that organisations such as CVC and CIMT are focusing on harmonisation of standard operating procedures (SOPs), a process that has started with the establishment of common SOPs for ELISPOT.[28] In principle, having determined optimal assay procedures the final step in this process will be to validate the procedures by inter-laboratory comparisons.

A number of key recommendations have been posed for the standardisation of ELISPOT and HLA-peptide multimer staining.[28,29] Despite these initial advances, there are many issues to address. While ELISPOT and HLA-peptide multimer analysis assess the responses to defined antigens, questions about which standard assays will determine the immune response to undefined antigens will ultimately need to be tackled given the efficacy of whole cell vaccines and other multivalent approaches.

6. Regulatory challenges

In the increasingly strict regulatory environment that surrounds all clinical developments, there is no specific regulatory framework for cancer vaccines in Europe. While there is no specific guidance document issued from FDA in the US, representatives from this agency have recently gone on record during academic or government initiated meetings providing certain references that might be considered when developing these products.[30] Specifically, the applicability of several regulations pertaining to clinical development as part of the Code of Federal Regulations (CFRs), including the relatively new 'Guidance for Industry, Clinical Trial End-points for the Approval of Cancer Drugs and Biologics',[31] has been reaffirmed. Thus, at present there is no single source of advice for those seeking to do clinical trials of these treatments.

The definition of vaccines, as referred to in the guidelines of the Vaccine Working Party of the Committee for Medicinal Products for Human Use (CHMP) of the EMEA, covers preparations that are 'intended to provide pre- and post- exposure prophylaxis against infectious diseases'. While this definition may include vaccines used to prevent tumours with viral aetiology (e.g. HPV in cervical cancer), it does not address the development of therapeutic cancer vaccines that target TAAs.

Since there are no specific regulations covering cancer vaccines, regulation might also be dependent on the product class. For example, whole cell vaccines are regulated under the Guideline on Human Cell-Based Medicinal Products[32], while gene-therapy cancer vaccines are regulated under guidelines for gene-therapy medicinal products. Relevant guidance for Europe is provided in the 'Guideline on the evaluation of anti-cancer medicinal products in man'[33], which recognises aspects of cancer vaccine development, besides its focus on conventional cytotoxic compounds.

7. Clinical challenges for immunotherapy

It is commonly believed that conventional anti-cancer drug development paradigms, which were established based on the experience with small molecule cytotoxic drugs, are not suitable for the assessment of immunotherapy. Consequently, novel, rational, clinical trial design methods have to be explored that might be better suited for the evaluation of clinical safety and efficacy in the field of immunotherapy.[34]

Specifically, in phase I trials the current paradigm involves the assessment of maximum-tolerated dose (MTD) and pharmacokinetics in order to determine safety, dose and schedule for phase II and III trials. However, in an immunotherapy setting the relationship between dose and immune response or toxicity is often not linear, and the MTD does not, in general, define the most effective dose with which to induce anti-tumour activity.[35] Likewise, some forms of immunotherapy do not lend themselves to classic pharmacokinetic studies. In circumstances where the cancer vaccine is a somatic cell therapy medicinal product, bio-distribution studies may be more appropriate.

Ethical considerations restrict clinicians in their choice of patient groups in first-into-man clinical studies. Thus, where alternative treatments exist in early stage disease, the only recourse is to use patients who are in end-stage disease, who suffer from high tumour burden and who are often immunosuppressed, either as a result of their disease (see above) or because of prior treatment. Therefore, advanced patients may not be suitable to demonstrate responses to immunotherapy. This exemplifies the regulatory catch twenty two situation in which the use of end-stage patients is unlikely to provide the evidence of immune augmentation and therapeutic efficacy that is required to support the use of such experimental therapies in the early stage patients, where efficacy is more likely to be demonstrated.

In order to show clinical efficacy, measurements of tumour progression are often made using the Response Evaluation Criteria in Solid Tumours (RECISTs), which defines the response of tumour according to changes in size.[36] However, there is a real concern that changes in tumour size do not reflect the efficacy of immunotherapy. Anecdotal data suggest that increases in tumour size may, on occasion, be due to increased intratumoural inflammatory infiltrates. Thus, increases in tumour size or even apparent stable disease may be misleading. Further data are required to demonstrate this, but in the meantime increases in tumour size after immunotherapy should be assessed with an awareness of the possibility that this may not always reflect tumour progression.

In the late phase studies, the choice of end-points must reflect the dynamics of response to cancer vaccines. Several phase III studies that have failed to meet their primary end-points have nonetheless demonstrated signs of late clinical effects (1). One possible explanation for such observations is the slow development of clinically relevant immune responses, which may take many months to develop. However, the parameters of clinical trial design do not always reflect this slow pace of patient response, and thus the choice of appropriate end-points in trials for cancer vaccines is critical to allow underlying clinical responses to become obvious. The 'gold-standard' for phase III confirmatory trials is overall survival (OS), but this increases the length and cost of clinical trials and makes the need for relevant surrogate end-points critical. A number of surrogate end-points for OS exist including time-to-progression (TTP), progression-free survival (PFS) and disease-free survival (DFS), but such surrogate end-points may not accurately predict the outcome of OS. This has been exemplified by the recent studies using the autologous, dendritic cell vaccine Sipuleucel-T.[37] In this phase III, placebo-controlled study on asymptomatic hormone resistant prostate cancer, the primary end-point of TTP did not reach statistical significance. There was, however, a trend towards improved OS in the treatment group which may indicate clinical efficacy.

8. Looking forward; improved clinical trial design

There are a number of immunotherapeutic approaches that have shown great efficacy in early phase trials but have failed to show efficacy in randomised phase III trials.[1] While this clearly reflects a lack of activity for some treatments, for others the problems may lie in inappropriate clinical trial design, selection of patient populations and/or a poor understanding of the underlying mechanism of action of the treatment. Although a complete solution to all the problems addressed in the sections above cannot be presented, we outline proposals made at the 12th March BDA workshop which were deemed to be necessary to develop a new paradigm for cancer vaccine development. There was a general agreement that a number of key areas should be addressed.

Concepts derived from the Cancer Vaccine Clinical Trial Working Group (CVCTWG) suggest a completely new approach to cancer vaccine trial design in which the three-phase structure of product development is replaced with a two-stage model.[34] In this model, the first stage of development would be a proof-of-principle trial with the objective of determining safety, dose and schedule, and the demonstration of biological activity, the later incorporating appropriate immune and molecular markers. This early phase of clinical investigation should include a minimum of 20 patients in a homogenous, well-defined population and should be carried out in an adjuvant setting, or one without rapidly progressive disease, to allow vaccines adequate time to induce biological activity. Evidence of biological activity should be demonstrated to provide a sound rationale for commencement of further trials: Activity is defined as any effect of the vaccine on the target disease or host immune system using biological markers as study end-points (for example, clinical, molecular or immune response markers). If none of these end-points are met, the clinical development plan should be reevaluated to decide whether further development is warranted. Successful proof-of-principle trials should be followed by efficacy trials, which would ideally be randomised, and should formally establish clinical benefit either directly or through use of appropriate surrogate end-points. This is in contrast to single-arm phase II trials used for cytotoxic agents, which often use tumour response rate as the primary end-point and historical controls as a comparator. Efficacy trials may use prospectively planned adaptive designs to expand from randomised phase II into phase III studies if well-defined trigger-point criteria are met, but the cost of incorporating such design elements should be carefully evaluated. The concept of efficacy trials allows for early assessment of vaccine efficacy based on credible prospective data. This two-phase development paradigm supports a more flexible, expeditious and focused clinical developmental process with early and informed decision making.

One area of change that is central to the improvement of immunotherapy clinical trials is that of patient selection. Historically, patients who are undergoing experimental vaccine therapy have late-stage disease with high tumour burden, and have already been exposed to first and second line chemotherapy and/or radiotherapy. Although many of the reasons for such patient selection are ethical, it remains a key area of contention since this patient group is the least likely to benefit from vaccination. Furthermore, the current dogma suggests that it is necessary to allow sufficient time for patients to build an immune response. However, patients in this group are less likely to survive long enough to develop a robust immune response. Thus, patients with early stage, low volume disease constitute a target group which may be most

suitable for the development of an effective immune response.

Another criterion for patient selection includes screening for the presence of target TAA and/or relevant MHC since the presence or absence of these markers may prevent patients from gaining benefit from immunotherapy. Especially, when using single antigen/epitope vaccines in clinical trials, screening for the presence of the target tumour antigens should be performed as their expression pattern might be variable and heterogeneous depending on the site and stage of the tumour. Likewise, patients should have a relevant HLA type, particularly when vaccinating with MHC-restricted peptide. It is noteworthy that, in addition to arguments for the use of early tumour stage patients due to low volume disease, early stage patients may have less tumour heterogeneity and so may be more amenable to single antigen/epitope approaches. Ovarian cancer patients, for example, display HLA haplotype loss in metastatic sites, which is not seen in primary tumours.[15]

It has been suggested that immunotherapy is unrealistic in the salvage setting since chemotherapy has a potential detrimental effect on vaccine efficacy. However, there is a substantial body of evidence to suggest that some combinations of chemo- or radiotherapy and vaccine treatment are synergistic.[38,39] Further study is required to determine the exact nature and mode of action of synergistic treatments, but it will become increasingly important to take this into account when designing clinical trials for cancer vaccines.

9. Improving cancer vaccines

Various strategies have been discussed to improve the immunological efficacy of immunotherapy. In addition to the inhibition of immunosuppressive mechanisms, which was discussed above, varying dosing regimen and the use of adjuvants may lead to a greater magnitude of immune response. While dosing regime may be extrapolated from murine studies and established in early phase trials the use of adjuvants and other therapies to boost immunological responses is a subject of some difficulty.

A concept that is gaining a wide acceptance in the field of cancer vaccine research is that vaccine monotherapy is unlikely to deliver the necessary stimulus to generate robust and long-lasting (memory) immune responses that overcome tolerance, immune escape and the immunosuppressive microenvironment of the tumour. Thus, synergism between existing chemotherapy and immunotherapy may lead to more profound immunological and clinical responses.[39,40] However, many useful drugs, that might otherwise be tested for efficacy in combination treatments, have been shelved by the biotechnology industry after failure to prove effective in monotherapeutic approaches and split intellectual property introduces conflicts of interest and barriers to the development of otherwise useful combination therapies. For these reasons, the National Institute of Health recently canvassed scientists within the field to ask which drugs they felt would be the most useful for development in a cancer vaccine setting. From this, a short list of 20 drugs was developed for which the NIH intended to support development.[41] This list includes immunostimulatory adjuvants and cytokines which have great potential for use in combination with existing vaccine modalities. However, despite the uses of many drugs in monotherapy, the development of combination therapies is associated with unique challenges when bringing them to the clinic. There is often little preclinical data on the effects of such combinations and phase I trials are required to establish non-toxic combination regimens and to demonstrate immunological responses to vaccine.

There is a growing interest in combining strategies that alter the regulatory environment in the tumour (including the use of cytotoxic T-lymphocyte antigen-4 (CTLA-4) blockade and the depletion or control of T-regs) with immunotherapy. In addition, there is increasing evidence that the standard chemotherapy approaches may target regulatory cells. Gemcitabine and sunitinib have been implicated in the suppression of MDSC activity[42,43], and there is much evidence for the anti-Treg activity of cyclophosphamide.[44] Combining such approaches with immunotherapy may result in enhanced tumour-specific immune responses and clinical efficacy. Clinicians involved in immunotherapeutic studies should be aware of potential synergies since observation of patients undergoing sequential chemo/radiotherapy and immunotherapy may have responses which lead to serendipitous discovery of new combination treatments.

10. Conclusion

Despite a number of high-profile failures for immunotherapeutic treatments in oncology, there are indications that benefits may be seen for patients with a range of solid tumours including lung, breast, prostate, renal and colorectal cancers. A number of cancer vaccines show great promise, and are either currently in phase III or new studies are planned for the near future. Follow-up studies are planned for two of the most successful phase III studies to date; Liponova and Vaccinogen Inc are planning new phase III studies to support the previously reported benefit of their vaccines Oncovax (in stage II colorectal cancer) and Reniale (in stage II and III renal cell carcinoma), respectively. GSK is sponsoring a well-powered, phase III trial to assess a MAGE-A3 vaccine in resected stage IB, II and III NSCLC. This study is the largest vaccine trial to date. Dendreon will, later this year, announce the results of its phase III, randomised study of Sipuleucel-T (a dendritic cell vaccine designed to induce immune responses against the TAA prostatic acid phosphatase). If Sipuleucel-T meets expectations, it is likely to become the first licensed therapeutic cancer vaccine for use in humans in the US.

We have documented here many of the challenges to successful immune intervention in cancer patients as well as the views of scientists and clinicians working in cancer vaccine research. Ultimately, it is hoped that consensus can be reached on the optimal and most rational way to develop cancer vaccines. Harmonisation of approaches with regard to trial design and immune monitoring may thus help to encourage and promote the development of regulatory guidelines governing cancer vaccine development. The BDA has created a Cancer Immunotherapy Working Group to address issues in cancer immunotherapy where these issues can be discussed

in the hope of developing recommendations, which will bring more consensus into the field to expedite the process of developing effective and safe products.

Conflict of interest statement

The authors wish to state that the opinions expressed here represent personal perspectives, and are not necessarily representative of the institutes or companies that they represent.

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