

Is there a Need to Identify Novel Tumour Antigens as Targets for Immunotherapy Clinical Trials for The Removal of Minimal Residual Disease in Haematological Malignancies?

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ABSTRACT

Despite the identification of many tumour antigens with the potential to act as targets for cancer vaccines and/or T-cell therapies very few have been used in clinical trials to date. This led to the timely development of a criteria which identified the ideal characteristics of tumour antigens which should be actively pursued for use in immunotherapy clinical trials. A list of 75 antigens were assessed against these criteria and although none harboured all of the characteristics identified as desirable, a number did show many of the characteristics identifying them as worthy of further pursuit to enable an organised development towards immunotherapy clinical trials. The study highlighted the benefit of focussing on a short list of antigens which would enable the rapid progress of a smaller number of antigens into clinical trials as targets for immunotherapy. However the antigens expressed by solid tumours often differ to those expressed by haematological malignancies, leading to this editorial which states the need for a similar study prioritising tumour antigens for use in clinical trials of haematological malignancies, independently of solid tumours. We also debate the importance of looking for new antigens in cancers in which few targets are known and discuss the importance of tumour antigens as biomarkers of disease diagnosis, stage and survival.

Abbreviations

CML: chronic myeloid leukaemia;

Ph: Philadelphia chromosome;

AML: acute myeloid leukaemia.

EDITORIAL

Despite the many tumour antigens (mutant, overexpressed or abnormally expressed proteins found in cancer cells), which can serve as targets for cancer vaccines and/or T-cell therapy, very few have been used in immunotherapy clinical trials. This was highlighted by Stephen Rosenberg et al's publication in *Nature Medicine*^[1] which summarised the outcomes of 440 patients with metastatic cancer who were treated with 541 different cancer vaccines at the Surgery Branch of NCI between February 1995 and April 2004. The group found that only 2.6% of participants showed an overall objective response rate.

This indicated a need for a standard criteria for recording clinical responses and demonstrated that many cancer immunotherapy treatments were falling short of their desired impact on patient outcomes. However immune therapy is not the same as chemotherapy and so the Response Evaluation Criteria for Solid Tumours (RECIST) response evaluation criteria was developed^[2].

Although a major improvement, which standardises the response criteria, like all guidelines it also has limitations. These include the time it takes to see a complete remission in a clinical trial, the need to consider immunological criteria including immune infiltration, the absence of symptomatic deterioration and the occurrence of new lesions (described by Tony Reid in^[3]). In addition it's counterpart for haematological malignancies does not exist in the same format. In leukaemic disorders, treatment with antibodies have been shown to lead to an initial increase in the number of tumour cells in the peripheral blood associated with lymph node shrinkage and/or delayed responses due to the antibody-dependent cell-mediated cytotoxicity and natural killer cell activation^[4] which also need to be considered.

The high failure rates of patients in immunotherapy clinical trials is no doubt heightened by the restricted eligibility criteria which limit phase I clinical trials to patients who have predominantly failed all conventional therapy. These patients often have late stage metastatic and/or difficult to treat disease and although I recognise that in Phase I clinical trials this patient group is only examined for safety of new drugs, it is the beginning of a long process before a therapy can be used to treat patients who are well enough to respond immunologically and we have a reasonable chance of demonstrating a clinical impact. Thus it becomes apparent that if cancer immunotherapy is to progress from bench-to bedside at a rate conducive with a notable impact on patient outcomes, then there is a need for clinicians/scientists to inform the public of the current limitations on our work and secure financial support from charities and governments on this basis. There is a need to focus our efforts on therapies with the most promise which are often, but not always, the ones which have received the most investment.

However the issue remains how to decide which immunotherapy treatments we should focus on in terms of getting more of them to the clinic. A consideration is the vast number of different types of cancer immunotherapeutic protocols being investigated such as whole cell vaccines, peptide vaccines, DNA vaccines, viral vectors, dendritic cells fed with tumour mRNA, tumour cells or apoptotic cells as well as the vast number of potential immunogenic targets. In 2009 Martin Cheever and colleagues published the prioritisation of tumour antigens^[5] in which they identified 75 antigens and prioritised them on a set of characteristics. Although none of them had all of the ideal characteristics, for example only 46 were immunogenic in clinical trials, the study highlighted the benefits of funding research on a limited number of antigens to enable some to make it to a profitable end – both for patients and funding bodies whose support relies on demonstrating clinical advances. The Cheever *et al* paper was emphasised as being a pilot study and enabled a focus for ensuing debates on how the translational research community, who fill the seats on grant review committees, can prioritise limited funding and ensure we do not just keep extending a growing list of antigens as possible targets for immunotherapy without many getting to the clinic and making any impact. Considerations include which disease (cancer types), outcomes (clinical endpoints) as well as which antigens have the best chance of translating into health benefits for patients if we are to keep patients and funding bodies interested in immunotherapy as a treatment option.

Cheever *et al*^[5] had identified some of the best antigens in the field, which met to some extent or another the following criteria “(a) therapeutic function, (b) immunogenicity, (c) role of the antigen in oncogenicity, (d) specificity, (e) expression level and percent of antigen-positive cells, (f) stem cell expression, (g) number of patients with antigen-positive cancers, (h) number of antigenic epitopes, and

(i) cellular location of antigen expression”. However we know that many of the antigens which are important in one cancer are not so in another^[6] and there are more than 200 cancer types. Of course we are all heterogenous (apart from identical twins) and our tissues develop along similar paths but not always the exact same route with environment having its own impact on our gene expression and physical development. Similarly few tumour types are homogenous in their initiation and progression with additional variation in tumour antigen presentation, co-factors and the status of the immune system – making the case for personalised therapies based on in-depth knowledge of a patients' specific cancer. Rare exceptions with regards to homogeneity and cancer are chronic myeloid leukaemia (CML), typified in almost all cases by the Philadelphia (Ph) chromosome and a t(9;22) translocation which produces the BCR-ABL chimeric protein. Indeed the BCR-ABL translocation has been shown to cause the initiation of leukaemia in myeloid precursor cells^[7]. Although >95% of CML patients harbour the Ph+ chromosome at disease detection, immunotherapy targeting of the BCR-ABL translocation product have led to mixed and often disappointing results^[8-10]. In acute promyelocytic leukaemia targeting the PML-RAR α translocation showed exciting results when delivered in combination with conventional chemotherapy in small mammals^[11] and more recent studies targeting mutated BCR-ABL epitopes have shown promise^[12].

And so we reach our conundrum. What about haematological malignancies such as acute myeloid leukaemia (AML) which represents a very heterogeneous group of disorders with many subtypes^[13]? Until 2005 few targets for the immunotherapy of acute myeloid leukaemia were known and many were found in a subset of patient samples^[14]. In AML we know that the leukaemia associated antigen WT1 is found in 73% of patient samples at diagnosis^[15] while mutated NPM1 is found in 53% of samples^[16]. The cancer-testis antigens PASD1 and HAGE are found in 30%^[17] and 23%^[14] of patients at disease presentation, respectively, although AML remains heterogenous as a disease especially in patients who lack one of the typical cytogenetic rearrangements^[13,16]. NPM1, CEBPA and FLT3 remain important survival markers for AML in addition to cytogenetic rearrangements^[18]. The most promising AML antigen for clinical trials to date has been WT1^[19-21], one matching most of the Cheever *et al* criteria and ranking as number 1 on the cancer pilot prioritization list. Other antigens have shown varying amounts of promise, including the cancer-testis antigen PASD1^[22] and the leukaemia associated antigens (LAAs) NPM1^[23] but none alone would ensure effective treatment of all AML patients and the choice of several leukaemia associated antigens would allow escape mutants to be targeted following immunotherapy. There is an increasing appreciation of epitope spreading^[24] and the most effective treatment is likely to be personalised. Hopefully one day off-the-shelf immunotherapies for patients, will be personalised, change with disease progression and will effectively remove MRD in first remission, which is a state achieved by most AML patients post-conventional treatment.

To date there has not been the same level of investigation to identify new targets for immunotherapy in the leukaemias, especially ALL and MDS although these investigations have the capacity to increase our understanding of the pathobiology of these diseases. So do I believe there is room for more investigation to identify new tumour antigens in some cancers? Yes. Of course! New targets for immunotherapy have also been shown to be biomarkers of survival, disease stage, progression and indeed disease detection. They provide new insights into cancer initiation and progression (including

minimal residual disease and relapse prediction) and new targets will enable personalised therapy for a wider patient population to be realised sooner. There is little funding available for the search for new antigen targets and limited funding for the validation of new targets. However the search for new antigens has its place in modern immunotherapy studies, where evidence of the need for improved targets provides the justification for continued searching.

CONFLICT OF INTERESTS

The author has no conflicts of interest to declare.

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