



## By Dr Anthony Walker, CEO of Onyvax Ltd

Prior to co-founding Onyvax in 1997, Anthony Walker spent 10 years as a Management Consultant, specialising in the pharmaceutical and biotechnology industries. During his eight years at Arthur D. Little, Anthony was appointed a European Director, responsible for the London-based pharmaceutical practice that he founded, and at The Wilkerson Group (London) he had responsibility for the UK, Benelux and Scandinavian markets. Anthony has consulted to 12 of the top 25 Rx companies and has also worked closely with over 20 biotechnology companies. In addition, he has produced expert reports for a number of UK biotech IPOs.

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# Harnessing the Immune System Against Cancer

Cancerous cells contain numerous mutations, qualitative and quantitative, spatial and temporal, relative to their normal, non-cancerous counterparts. At certain periods during tumour cells' growth and spread, a proportion of these are capable of being recognised by the hosts' immune system as abnormal. This has led to numerous research efforts worldwide to develop immunotherapies that harness the power of the hosts' immune system and direct it to attack the cancerous cells, thereby eliminating such aberrant cells at least to a level that is not life-threatening (1,2). The market has recognised the potential of this approach, and the cancer vaccine revenues alone are forecast at US\$3 billion by 2008 (3).

Numerous approaches have been taken in the quest for cancer immunotherapies, which can be classified under the five categories covered in this article:

### NON-SPECIFIC IMMUNOTHERAPY

Efforts to stimulate the immune system non-specifically date back over a century to the pioneering work of William Coley (4). Although successful in a limited number of cases (such as BCG for the treatment of urinary bladder cancer and IL-2 for the treatment of melanoma and renal cancer), it is widely acknowledged that non-specific immunomodulation is unlikely to prove sufficient to treat the majority of cancers. Whilst non-specific immune-stimulants may lead to a general enhanced state of immune responsiveness, they lack targeting capability and subtlety. Many tumour lesions have mechanisms that allow them to evade or resist immune-surveillance.

### ANTIBODIES AND MONOCLONAL ANTIBODIES

Passive immunotherapy in the form of antibodies, and particularly monoclonal antibodies, has been the subject of considerable research and development as anti-cancer agents. Originally hailed as 'magic bullets' because of their exquisite specificity, monoclonal antibodies have failed to live up to their expectation in the field of cancer immunotherapy for a number of reasons. These include immune responses to the antibodies themselves (thereby abrogating their activity), and the inability of the antibody to access the lesion through the blood vessels. To date, two products have achieved broad market success, namely Rituxan for non-Hodgkin's lymphoma (IDEC/Genentech/Hoffman la Roche) and Herceptin for Her-2 positive breast cancer (Genentech/Hoffman la Roche), with over 50 other projects in the research and development pipeline. Although elegant in concept, the utility of antibody-

based approaches may ultimately prove limited by the phenomenon of 'immunological escape', where a subset of cancer cells mutates and loses the antigen recognised by the particular antibody.

### SUBUNIT VACCINES

Drawing on their experience in vaccines for infectious diseases and other fields, many researchers have tried to identify antigens that are exclusively or preferentially associated with cancer cells – namely tumour-specific antigens (TSA) or tumour-associated antigens (TAA), and to use such antigens as the basis for active-specific immunotherapy. Over 50 such subunit vaccine approaches, which consist of a single protein or antigen, are in development for the treatment of a wide range of cancers, although none has yet received marketing authorisation for use as a human pharmaceutical product. In a similar manner to that described for antibody-based approaches above, subunit vaccines may also be limited by the phenomenon of immunological escape.

### GENE-BASED IMMUNOTHERAPY

The majority of gene-based immunotherapy trials in human subjects have been in the area of cancer treatment, and of these, a substantial proportion have been designed to trigger and/or amplify patients' immune responses. The approach involves immunising the patient with a viral vector, such as the recombinant poxvirus vector, Modified Vaccinia virus Ankara (MVA), and/or a DNA-based vector carrying the genes for TAAs. In preclinical studies, DNA-based vectors have been shown to produce a highly specific response and can be potent in stimulating a cellular immune response – the branch of the immune system believed to be most important in tumour immunotherapy.

At the present time, it is too early to judge whether gene-based immunotherapeutic products in commercial development will ultimately prove successful, but it is widely accepted that commercial utility of these approaches are likely to be more than a decade away.

### CELL-BASED VACCINES

Tumours have the remarkable ability to counteract the immune system in a variety of ways. These include the down-regulation of the expression of potential target proteins and receptors, or down-regulation of MHC class I and II expression, stopping direct presentation of TAA or TSA peptides. They may additionally down-regulate co-stimulatory molecules, leading to incomplete stimulation of T-cells and anergy, or shed selective, non-representative membrane portions to act as

decoys to the immune system. Although this list is by no means exhaustive, it indicates just how well-equipped tumour cells can be when it comes to beating the immune system. What is clear is that the immunological heterogeneity and plasticity of tumours in the body will have to be matched to a degree by immunotherapeutic strategies that similarly embody heterogeneity. The use of cell-based approaches to cancer immunotherapies can be viewed as analogous to the use of whole inactivated or attenuated viruses as vaccines against viral disease, and has several potential advantages:

- ◆ Cell-based vaccines contain a broad range of antigens, providing an antigenic profile of sufficient heterogeneity to match that of the lesions as described above
- ◆ Multivalency (that is, containing multiple antigens) reduces the risk of immunological escape, as the probability of cancer cells 'losing' all of these antigens is remote
- ◆ Cell-based vaccines include TSAs and TAAs that have yet to be identified as such; it is possible that currently unidentified antigens may be clinically more relevant than the relatively small number of TSAs/TAAs that are already known

#### Autologous Cell Vaccines

Cell-based vaccines fall into two categories. The first, based on autologous cells, involves the removal of a biopsy from a patient, cultivating tumour cells *in vitro*, modifying the cells through transfection and/or other means, irradiating the cells to render them replication-incompetent and then injecting the cells back into the same patient as a vaccine. Although this approach enjoyed considerable attention over the past decade, it has been increasingly apparent that this individually tailored therapy may face a number of challenges. The approach can be time-consuming and expensive, and lead-times for producing clinical doses of vaccine often exceed the patient's life expectancy. Additionally, as a 'bespoke' product, only the procedure, not the product, can be standardised and hence optimised and quality controlled. Furthermore, the tumour biopsy used to prepare the autologous vaccine will have certain growth characteristics, interactions and communication with surrounding tissue that makes it somewhat unique. This means that a biopsy providing the initial cells represents an immunological 'snapshot' of the tumour, in that particular environment and at that point in time. As the cancer cells are continually evolving, this may prove to be an inadequate immunological representation over time for the purpose of a

vaccine that may be given over the entire course of the disease.

#### Allogeneic Cell Vaccines

The second type of cell-based vaccine uses allogeneic cells that are genetically (and hence immunologically) mismatched to the patients. Allogeneic cells benefit from the same advantages of multivalency as autologous cells, giving them a broad spectrum of activity. In addition, allogeneic cell vaccines are based on immortalised cell lines that can be cultivated indefinitely *in vitro*, removing the lead-time and cost disadvantages of autologous approaches. Similarly, the allogeneic approach allows combinations of cell types to be used that match the disease profile of an individual in terms of the stage of the disease, the location of the lesion and potential resistance to other therapies. Therefore, this may represent a more comprehensive approach than autologous cell vaccines.

There are numerous published reports describing the utility of cell-based cancer vaccines (5). These studies range from the basic procedure of using cancer cells as an immunotherapy antigen, to transfecting the cells to produce GM-CSF, IL-2, interferons or other immunologically active molecules, or the use of 'suicide' genes. Researchers have used allogeneic cell lines that are HLA-matched or partially matched to the patient's haplotype, as well as cell lines that are mismatched to the patient's haplotype and transfected with GM-CSF. Clinical studies using this approach have suggested such vaccines can significantly increase survival rate, with patients experiencing both humoral and cell-mediated immune responses.

#### CONCLUSIONS

Immunotherapy is increasingly being seen as an attractive approach to treating a wide spectrum of cancer types. However, cancer remains a difficult disease to treat because so many druggable targets are still unknown to science. The fact that cancer-associated antigens change continuously over the course of the disease, and that the cancer cells themselves mutate, compounds this clinical problem. Therefore, it is becoming increasingly evident that by decreasing the chances of immunological escape, a multivalent approach represents a strong likelihood for success in stemming tumour growth. Allogeneic cell-based vaccines that incorporate a wide range of cancer-associated antigens representative of different disease stages, offer strong potential in harnessing the immune system to attack cancer cells, with the potential of significantly prolonging survival whilst improving quality of life for cancer patients. ◆

#### References

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