A COMPELLING CONCEPT

Therapeutic cancer vaccines are all about equipping the patient’s own immune system to fight their cancer. It is a compelling concept on many fronts. On the risk-benefit front, vaccines are not associated with the sort of side-effects that make a patient’s life miserable and put their long-term health and quality of life at risk – a big plus.

On the scientific front, after millions of years of evolution the immune system has more than a few sophisticated tricks up its sleeve. The concept of working to support and focus this system seems an attractive alternative to current strategies of using our patchy understanding of the molecular biology of cancer to outwit fiendishly elusive cancer cells. And while cancer has proved itself adept at eluding the body’s own immune defences, increasing aware-

CuttingEdge

Therapeutic cancer vaccines – there’s a new kid on the block

Efforts to treat cancers using vaccines have seen many false dawns. Now the first therapeutic cancer vaccine has won approval for treating prostate cancer, with more waiting in the wings. Could compounds that teach the immune system to fight tumours be about to achieve their promise?

The approval of the prostate cancer treatment Provenge in the US in May appears in many respects to be nothing to shout about, offering an extra three to four months survival at $93,000 a shot. But Provenge could win landmark status in medical history as the treatment that ushered in a major new tool for fighting cancer – after a twenty-year rollercoaster of great expectations and dashed hopes, the first therapeutic cancer vaccine has finally made it to the market.

Among the small corner of academic cancer researchers who have focused on this highly specialised area, and the growing sprinkling of biotechs who have bet their future on cancer vaccines, the approval of Provenge – developed by the Seattle-based Dendreon Corporation – is seen as having broken through a glass ceiling. It has proved the concept for cancer therapeutic vaccines in much the same way as Herceptin did for monoclonal antibodies. These researchers expect new vaccines to be flooding through the regulatory portals in the coming years – as happened with targeted therapies. However, given the chequered history of this type of cancer treatment, there is an understandable caution about sounding too confident in public. The molecular biologist behind Herceptin, interestingly, has no such qualms; Axel Ullrich is openly tipping immunotherapy as the most likely field for the next major breakthrough in cancer – “Only the immune system is so clever that it can track down a cancer cell wherever it is in the body” (see Masterpiece Cancer World May–June 2010).

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ness that many very small cancers or precancerous lesions disappear without any intervention supports the idea that immune systems do have a role to play. And a growing body of information about how cancer can suppress – or even hijack – the immune system is providing leads on how to get around these evasions.

Then there is the question of cost. While $93,000 for three to four months extra survival may not look like a bargain, Provenge is in some ways highly unrepresentative of the field, as it is engineered for each patient individually using whole cells taken from their tumour. By contrast, most of the therapeutic cancer vaccines that are likely to enter the market in coming years will be ‘off the shelf’, with many targeted at antigens such as MUC-1 and MAGE-A3 that are present across a wide spectrum of cancers. The potential for pushing down costs in these cases is clear.

Compelling though this may sound, moving from concept to proof of concept and delivery has been exceptionally frustrating, with a series of exciting phase II trials routinely followed by disappointing phase IIIs. Many vaccines and small companies have been numbered among the fatalities, and weariness and scepticism inevitably took their toll.

After millions of years of evolution the immune system has more than a few sophisticated tricks up its sleeve
Picking up the pieces
The past five years have been testing times for those who have kept faith with the concept of cancer immunotherapy, as they struggled to make sense of a string of failures. Among them is Angus Dalgleish, Professor of Oncology at St George’s Hospital, London, and founder of the UK Cancer Vaccine Institute and the vaccine biotech company Onyxax. Dalgleish first became interested in immunology during his training as a medical oncologist at Prince Albert’s Hospital in Sydney, Australia. His subsequent career has spanned the two disciplines, but while his work in HIV and AIDS has been well recognised, it is his work in cancer that he feels will prove far more significant, helping pave the way for fundamental changes to the way this disease is understood and treated.

As we talked, he was signing off the final patient to be enrolled in a phase I trial for a melanoma vaccine whose story neatly encapsulates the dashed hopes and current rebirth of therapeutic cancer vaccines. This vaccine was first developed at St George’s around 10 years ago. Having gone on to prove itself in phase II trials in lung cancer at one of the UK’s top cancer centres, it was then dropped when a multicentre phase III trial showed no benefit. It owes its current revival to a wealthy friend of a melanoma patient, who was impressed at the survival of some of the patients on the early melanoma trials.

Dalgleish believes he can now explain most of the disastrous failures of the past. It took several years to piece together this complex picture, but it can be roughly summarised as follows:

The wrong cancer
Most early trials of vaccines were done in melanoma, partly because there was no effective drug treatment (though promising targeted therapies are now in the pipeline) and partly because spontaneous remissions were noted in melanoma, indicating immune system activity. Dalgleish believes this was not an ideal target. “It is too capricious, it can mutate and has a high proliferation rate, so it can outrun any vaccine if it wants to.” In the end it was as a treatment for prostate cancer that a vaccine first proved itself. The next approvals are widely expected to be in non-small-cell lung cancer and lymphoma. Melanoma vaccines have continued to disappoint, although there are now hopes that they may be more effective in combination with low-dose chemotherapy, says Dalgleish.

The wrong adjuvant
Vaccines are composed of the entity you want to teach the immune system to recognise (e.g. a tumour antigen or a whole tumour cell) plus an adjuvant, which sends a danger signal to the immune system. Getting that signal wrong was the main factor behind the high-profile fiasco of the phase III Megavax trial in melanoma, in which the control arm did better than the vaccine arm. The trial team at the Sloan Kettering decided to change the adjuvant from the BCG (traditionally used to vaccinate against tuberculosis), which they had used in phase II, to one that was deemed to be better, but turned out to be worse.

Immune responses associated with a good clinical response and good outcomes are all cell-mediated Th1-type responses, as opposed to antibody-mediated responses which are associated with a poor clinical response, says
Dalglish. “The adjuvant they switched to in the Magavax trial is known to be a very powerful initial Th1 booster, but it then boosts Th2, signifying an antibody-mediated response associated with a poor outcome,” he explains. “Retrospectively it wasn’t too surprising.”

**The wrong stage**
As with cancer drugs, the early vaccine trials tended to be in very late-stage disease, but experience has shown that vaccines struggle to have any impact in this setting. With vaccines, it will always be the earlier the better, says Dalglish. “Somebody asked me, ‘At what stage would you put the vaccine in?’ I said, ’Before I started staging them; before I send them off for the CT.’”

**The wrong patients**
Immunotherapy works best in patients with healthy immune systems. Dalglish describes being struck by the difference in general health (e.g. weight, smoking) he saw between patients enrolled at some centres doing phase III vaccine trials and the patients he had encountered at phase II – the result, he suggests, of the above average fitness of patients who actively seek to get on phase II trials, and the selection operated by the trialists at this stage. “There’s no doubt that in phase II studies you select – consciously or subconsciously – the most appropriate patients. Anyone who denies that is in denial!” Evidence to support the importance of a well-functioning immune system in determining benefit from cancer vaccines comes from gene array profiling studies done by GSK. They have found a set of genes that reflect spontaneous immune response to the tumour – associated with a healthier immune system – which distinguish with some accuracy melanoma patients who respond to their MAGE-A3 cancer vaccine from those who do not (in terms of both disease progression and survival). GSK will be proposing these genes as a marker to select patients for treatment with the vaccine.

**Poorly conducted trials**
Some phase III vaccine trials have suffered from a lack of understanding and commitment from many of the participating centres. Dalglish cites his experience with the vaccine that had shown promise when trialled in lung cancer at the Royal Marsden cancer centre in London. When, later, the multicentre phase III results showed no benefit, he took a closer look. It turned out that, in spite of training, staff in the various centres had given the vaccine spontaneously in the majority of patients, rendering it completely ineffective. “It doesn’t get picked up by the Langerhans cells and passed on to lymph nodes.” Furthermore, while a minimum of eight shots was needed to allow the vaccine time to do its work, few patients received anything like this, with just under half of them only receiving two shots or less. “A lot of centres were not familiar with vaccines for cancer,” says Dalglish. Scepticism about the novel therapy may have also influenced the way the trial was carried out. “The only conclusion was that the people who did the trial failed to do the study. These are lessons that we’ve learnt and we are not going to repeat.”

**Impatient investors**
Unlike most cytotoxic and cytostatic drugs, therapies that involve reprogramming a body’s immune system and sending it into action need a bit of time to take effect. Dalglish believes his prostate cancer vaccine Onyvax could have beaten Provenge to the market had the investors held on for survival figures rather than pulling the plug at nine months, when no real difference had emerged between the vaccine and control arms. “Dendreon [manufacturers of Provenge], who had the same good results as we did in a small group, also had nothing at nine months when they did the randomised study. But they had deep pockets, and they kept going. And between 9 and 12 months the survival curve starts splitting in favour of the vaccine.” This is a pattern, he adds, that has also emerged from a number of recent lung cancer trials: “I think you can almost superimpose the survival graphs.” So this is another lesson. “Especially in the randomised studies, you don’t get the earlier split you get in the phase II studies.”

**The proof of the pudding**
To the non-believer, this may of course read like a litany of excuses for failure. And while Dalglish has been surprised by negative attitudes he has met within the medical oncology community, he accepts that vaccines will only prove themselves when more of them join Provenge in making it through the approval process. There are a few candidates now standing in line.

**MUC-1**
Near the front of the queue is Merck Serono’s Stimuvax, in a phase III registration trial for stage III unresectable non-small-cell lung cancer. The vaccine showed a small survival benefit at phase II, when it was trialled in 171 patients with later stage disease – stage IIIb/IV. But when the results for the locoregional stage IIIb patients were looked at in isolation, patients with the vaccine showed an additional 17 months survival over the control arm. “If you are treating patients with NSCLC this is really outstanding,” comments Oliver Kisker, head of Merck’s Global Clinical Development Oncology unit. The phase III eligibility criteria were therefore adjusted to include only patients with stage III unresectable disease.
“These type of immunotherapies have the potential to become effective and low toxic treatments in the future”

If the phase III results bear out the promising phase II data, and if the trial remains on track, Kisker believes Stimuvax could be the next vaccine to make it to market. “Certainly it has the potential to be the first active anti-cancer vaccine — true anti-cancer vaccine,” he says.

Stimuvax primes the immune system to lock on to MUC-1 (or mucin-1), which was one of the antigens used as a target in the very early experiments with immunotherapy done in the 1970s by Cancer Research UK, among others. Because MUC-1 is present in a high proportion of tumours not only in NSCLC, but also in breast, prostate, colorectal, ovarian and other cancers, the hope is that if and when the treatment gets approval for lung cancer, it will be possible to take the vaccine forward across a number of other cancers as well.

Merck Serono obtained the exclusive worldwide rights for development and commercialisation of Stimuvax from the former Canadian and now American biotech Oncothyreon, who did the early development under the name L-BLP25. Growing confidence in the therapeutic potential of MUC-1 targeted vaccines is also seen, for instance, in the decision by Novartis to sign a $10 million deal with the French biotech Transgene, for exclusive development and commercialisation rights on a similar vaccine, TG4010, also in trials for use in NSCLC.

Unlike some cancer antigens, MUC-1 is also expressed by normal secreting cells — in the intestines, for instance — giving rise to the theoretical possibility that an anti-MUC-1 vaccine could trigger an autoimmune response and turn the body’s immune system against itself. However, ten years of experience using the vaccine in more than 1000 patients seems to indicate that the vaccine is selective for tumour MUC-1 expression, says Kisker. “It has not shown any side-effects that point to unwanted activity against the physiological expression of MUC-1.”

The Stimuvax NSCLC trial was put on temporary hold in March this year, when a myeloma patient developed encephalitis after receiving the vaccine. “We worked very closely with the FDA, and with the treating physician and neurology specialists. But overall it remains completely unclear what happened here, so we cannot rule out that Stimuvax might have had a role. We have not seen anything like this elsewhere, so we just don’t know,” said Kisker. So far there have been no reports of any MUC-1 expression in the tissue of neural or central nervous system organs.

Merck got the go ahead to resume their NSCLC trial in June with some additional safeguards in place, and Kisker remains confident that cancer vaccines are on track to join established cancer therapies. “These types of immunotherapies have the potential to become effective and low toxic treatments in the future. In the past it has been shown that development is not that easy, and we must be prepared for setbacks also in ongoing research, because we don’t understand fully all the details of the factors that are required to generate an effective immunotherapy. I think, in principle, all these therapies, like MAGE-A3 and other cancer vaccines currently in phase II and III, have the potential to become effective treatments in the future. We need to await the results from the clinical trials.”
MAGE-A3
The MAGE-A3 antigen is also present across a range of cancers, but unlike MUC-1, it is present only on cancerous tissue. Currently the target of registration trials in NSCLC and melanoma (where it is expressed in about one-third and three-quarters of tumours respectively), it is also present in various proportions of bladder cancers, myelomas, and gastric and oesophageal tumours.

GSK licensed the antigen from the Ludwig Institute for Cancer Research in the mid-1990s, a few years after the Institute had identified the first antigen that was specific only to cancer cells. At the time, GSK was looking at how to put to good use its extensive experience in developing prophylactic vaccines (the HPV vaccine, Cervarix, for instance, is one of theirs).

Vincent Brichard was brought into GSK eight years ago to evaluate whether moving into cancer immunotherapy might be a viable strategy, and he now heads the company’s cancer immunotherapies programme. He explains, “Most infectious diseases already had vaccines and they believed it was the right time to capitalise on the research on immunological adjuvants that had been done for prophylactic vaccines.”

GSK is a bit unusual in that it likes to use the term antigen-specific cancer immunotherapy (ASCI) rather than cancer vaccine, to make clear the distinction between prophylactic vaccines and these therapeutic products. This might be seen as slightly ironic, as their cancer vaccine strategy appears to be more focused than most on the post-surgical disease-free setting (the adjuvant setting), where the concept of prophylaxis does have a relevance. As Brichard puts it, “This is a non-oncology product in the oncology landscape. We are just in-between prophylactic vaccines and oncology drugs.” So while Merck is trialling their vaccine in patients with unresectable NSCLC, GSK is in phase III trials to see how well its vaccine prevents recurrence in NSCLC patients whose tumours have been completely resected.

About half of all NSCLC patients whose tumours have been completely removed by surgery have a recurrence within two years. A phase II trial of the MAGE-A3 ASCI in these patients with completely resected NSCLC expressing MAGE-A3 showed 25% fewer recurrences among patients at the final analysis, and the difference between the two arms has held now for almost six years.

The phase III trial, which aims to enrol around 2300 NSCLC patients positive for the MAGE-A3 antigen – “the largest lung cancer trial ever conducted in the adjuvant setting” – is being carried out using a ‘new and improved’ immunological adjuvant, which GSK hopes will give even better results. To guard against repeating the Megavax experience, where the ‘new and improved’ adjuvant turned out to be a disaster when used against cancer, this adjuvant has had to prove itself in a phase II melanoma trial in comparison to the standard adjuvant used by GSK. It is now being used in both the NSCLC registration trial and another registration trial for melanoma patients with regional lymph node involvement.

Brichard is also highly conscious of the need to avoid the trials being undermined by a lack of understanding or commitment among the clinicians at the many trial centres (450 centres in 33 countries for lung cancer and 250 centres for melanoma). “There is a lot of communication with doctors and patients, and also a different mindset in the team here. We are here to support them. It is not: ‘We have a study and we have a product, and please do the study and enrol your patients.’ It is more: ‘You are part of this story.’ We do not hesitate to go to the sites, so this is a lot of effort. But when we are successful, this is going to pay. Those centres will really be part of the history of innovation.”

GSK has now licensed a further five tumour antigens – “almost the whole Ludwig portfolio” – all of them expressed only by cancer cells. It will be looking at ways in which these can be combined in the future to target tumours with different antigen profiles.

HELPING VACCINES DO THEIR THING
With the lessons learnt from the past decade, Provenge on the market, and 212 therapeutic active vaccine trials...
Across a very wide spectrum of cancers now listed on clinicaltrials.gov – six of them in phase III (and two in II/III) – vaccines look set to find a place in the mainstream of cancer therapy. The next step, says Dalgleish, is to focus on making them much more effective. How to do this has been the focus of his attention for the past five years, and he is very confident. “I really know how we are going to do this.” The challenge, he explains, is threefold:

**Boost the immune system**
This has traditionally been done by interferon, and more recently IL-2 – a much underestimated drug says Dalgleish. “Historically, IL-2 has been given in high doses, which is very toxic for patients. It’s not necessary. You can give them tiny amounts subcutaneously, and if you give it after a vaccine or after another treatment you get a really nice ongoing immune response.”

**Deprive the tumour of the environment that feeds it**
Dalgleish, along with a growing number of researchers who are focusing on the tissue around the tumour, points to chronic inflammation as a key factor in allowing a mutated cell to survive and then flourish – he calls it the ‘rose bed of cancer’. It has a proven association with local immune suppression, “so the immune system is not going to go anywhere near the tumour to see the mutated RAS or p53 or whatever else,” and it attracts lots of growth factors, including angiogenesis, “which help the cancer grow and spread.”

Combatting the inflammation and the angiogenesis should help cancer vaccines work better, says Dalgleish, who has demonstrated as much in mouse models.

**Disarm the shield that cancers use to hide from immune attack**
The ability of cancers to avoid detection by the immune system has been suspected for some time. Dalgleish and co-workers have now documented one way in which this happens. “We have a paper, not published yet, that shows that, particularly in advanced stages, the cancer produces factors that convert normal lymphocytes that would like to beat the cancer up into ones that protect it. It puts on hats that shield it from various things.”

The reason why metastases are able to survive and flourish, says Dalgleish, is that they take the environment of the primary cancer with them. “What I mean is that if I were to go to the moon I would only survive if I took the atmosphere from earth with me. That is what it does… As soon as it starts metastasising it pours out immunosuppressive cytokines so the immune system can’t get locked on to attack. We’ve documented that for colorectal cancer.”

In a slightly strange twist that brings the fields of chemotherapy and immunotherapy together, it turns out that some of the more commonly used chemotherapy drugs can in fact combat these T-suppressor cells – if used in low doses. Gemcitabine, oxaliplatin, docetaxel and cyclophosphamide have all shown this ability.

**A drug that ticks all the boxes**
Useful though these chemotherapy agents may be in helping to give vaccines a clear view of their enemy, it is a class of drugs that has wandered into cancer from the field of immunotherapy that Dalgleish believes could turn vaccines from a useful addition to something much more.

Lenalidomide is an analogue of thalidomide, the first immunomodulatory drug (IMiD) ever approved for cancer (for multiple myeloma patients ineligible for high-dose chemotherapy or as a first-line treatment in patients over 65 years). Lenalidomide is like thalidomide but with much lower risk (particularly to the unborn child), and a second analogue, pomalidomide, is now in phase II trials, also for multiple myeloma.

What makes this class of drugs so exciting, says Dalgleish, is that they work alongside the vaccine and tackle all the problems needed to allow vaccines to work to their full potential:
- they are anti-inflammatory,
- they stimulate immunogenic response,
- they are anti-angiogenic.

Added to all of this is what Dalgleish sees as the real killer blow. It turns out that they can also switch off T-suppressor cells. Dalgleish, who has just published a paper on the topic (Cancer Immunol Immunother 58:1033–1045), describes this as “a lovely surprise”. He believes lenalidomide/pomalidomide could open the door for vaccines to become effective even in metastatic disease.
**IS THE FUTURE LENALIDOMIDE + X?**

Confirmatory evidence for the benefit of this drug comes not only from previous studies Dalgleish has done in mouse models, but also from the results of a study of the use of Prevnar – a vaccine normally used to prevent infection caused by pneumococcal bacteria – in treating myeloma patients. Early data presented at this year’s American Society of Hematology (ASH) meeting showed that patients who were also being treated with lenalidomide responded really well, while others who were on different treatments benefited far less. The findings came as a surprise to the investigators – but not to Dalgleish. He is now openly postulating that, “The future of cancer treatment may be lenalidomide (or other thalidomide analogue) plus X,” where X is a vaccine plus adjuvant.

Provocative though all this may sound, Dalgleish is not really predicting the end of medical oncology, radiotherapy or any other treatment modality – at least not outside an adjuvant setting. Quite the contrary in fact, he anticipates vaccines will tend to be used very early in treatment strategies to magnify the impact of other treatments.

“One of the things that is quite staggering is that once patients have been primed with immunotherapy – and this seems to work with any sort of non-resectable tumour – the sensitivity to radiotherapy is just unbelievable. It says in the book that melanomas are notoriously resistant to radiotherapy, less than 20% respond, but that’s only for palliative care. We regularly get complete responses in people who have been on vaccines.”

The same goes for chemotherapy. “I’ve always suspected that what the Provenge study really shows is that vaccine+chemotherapy gives a survival benefit over chemotherapy alone,” he says (though the Provenge trial tested vaccine against placebo, many of the patients in both arms will have been treated with docetaxel on progression, says Dalgleish).

Predicting the future direction or success of cancer treatments has always been a rash and thankless exercise, but as Brichard from GSK points out, new therapies have always had to overcome scepticism. “This is a field that has suffered from failures. But let’s look back to monoclonal antibody development. It was extremely fashionable in the ’70s and then there was a big downtime. Nobody believed in it until Herceptin came out. And now it is a no-brainer that when you test a monoclonal, this will translate into clinical efficacy. I believe we are at this stage with the ASCI programme. We are in a landscape today of, ‘OK, let’s try.’ A lot of scepticism. But probably five or eight years from now, I believe it will be a no-brainer that when people do put their patients on board a cancer immunotherapy study, this will be a product and a treatment for their patients in the following years.”

“We have learnt a lot,” adds Merck Serono’s Kissker. “The first vaccine is now approved by FDA, we have tried to understand and are understanding more about vaccination in general. Mistakes were made in the past and all treatments were somewhat different. I truly believe there will be a place for treatment for cancer patients with vaccine.”

On the evidence of today, therefore, it would seem safe to say, at the very least, that the multidisciplinary teams of the future will not be complete without having at least one member thoroughly versed in cancer immuno-therapeutics. Vaccines are the new kid on the block. As they come to maturity, they will start to demand their place at the top table of treatment modalities.

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