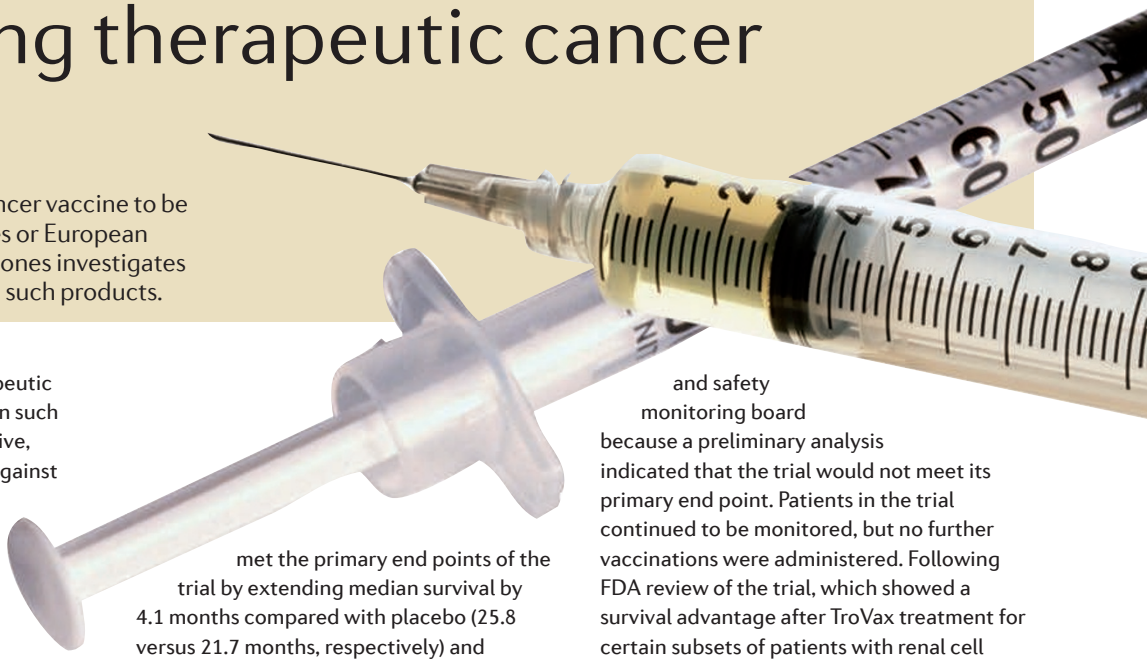
NEWS FEATURE

Rethinking therapeutic cancer vaccines

With the first therapeutic cancer vaccine to be approved in the United States or European Union eagerly awaited, Dan Jones investigates the challenges of developing such products.



In 2005, hopes were high for therapeutic cancer vaccines, with more than ten such products — designed to confer active, specific immunotherapy directed against tumour-associated antigens — in Phase III trials (*Nature Rev. Drug Discov.* **4**, 623–624; 2005). But, nearly 5 years later, several of these vaccines have failed completely, and none has yet been approved by the US FDA or the European Medicines Agency (EMEA).

"The clinical experience with cancer vaccines has been disappointing, especially the Phase II–III trials completed in the past 5 years," says Eli Gilboa, a professor of immunology at the Miller School of Medicine, University of Miami, USA. Steven Rosenberg, Chief of the surgery branch of the US National Cancer Institute, offers a similar assessment: "This area has not progressed very well at all, and nearly all cancer vaccines evaluated so far have not demonstrated clinically meaningful benefits, though that's not to say that they'll never work."

One therapeutic cancer vaccine that has remained in development is sipuleucel-T (Provenge; Dendreon) (TABLE 1), which was widely expected to receive approval in 2007 following a positive vote from the FDA's Office of Cellular, Tissue and Gene Therapies Advisory Committee. However, in a Complete Response Letter, the FDA requested more information, including additional clinical efficacy data.

Dendreon recently completed the analysis of data from its pivotal Phase III IMPACT (immunotherapy for prostate adenocarcinoma treatment) trial of Provenge, which could address this issue. "We're confident that we've gathered the required additional evidence to support our efficacy claim," says David Urdal, Chief Scientific Officer at Dendreon. The data presented at the annual meeting of the American Urological Association in April showed that sipuleucel-T met the primary end points of the trial by extending median survival by 4.1 months compared with placebo (25.8 versus 21.7 months, respectively) and improving 3-year survival by 38%. These results will be incorporated into a revised Biologic License Application that the company expects to file with the FDA in the fourth quarter of this year.

The history of sipuleucel-T illustrates a number of the challenges for developers of cancer vaccines. The company recognized at an early stage that a robust potency assay for the effects of sipuleucel-T would be essential and developed such an assay during Phase I–II development. They also communicated with the FDA to understand the likely regulatory requirements.

"We worked with an FDA division that specializes in the development of cell and gene therapies and looked at the development programme with a regulator's eye to identify the important issues that sponsors need to monitor to ensure the safety and reproducible potency of the product," says Urdal. "The characterization work we did in our Phase I–II programme was crucial in this respect, as was working closely with our product reviewers — we walked with them down a path that would ultimately lead to generating the kind of clinical data that support the product having an impact on overall survival."

Discussions with the regulators also recently enabled Oxford Biomedica to proceed with the clinical development of TroVax (TABLE 1). Last year, Oxford Biomedica's Phase III trial in renal cell carcinoma, known as TRIST (TroVax Renal Immunotherapy Survival Trial), was stopped by an independent data and safety monitoring board because a preliminary analysis indicated that the trial would not meet its primary end point. Patients in the trial continued to be monitored, but no further vaccinations were administered. Following FDA review of the trial, which showed a survival advantage after TroVax treatment for certain subsets of patients with renal cell carcinoma, Oxford Biomedica have been invited to submit adaptive Phase II–III trial designs in metastatic colorectal cancer.

A key challenge for the regulators is that cancer vaccines are a diverse array of therapeutics with several mechanisms of action (TABLE 1). One consequence of this diversity is that there are no standardized ways to preclinically characterize new therapies, particularly those based on human cells. "A human-specific product will be rejected by an immunocompetent animal, so it is difficult, if not impossible, to obtain a relevant animal model in which you can preclinically assess pharmacology and toxicity," says Thomas Hinz of the Paul Ehrlich Institut, Langen, Germany, and member of the Cell Products Working Party of the EMEA.

Therefore, it is crucial to devise ways of characterizing cancer vaccines in terms of potency and toxicity that will satisfy regulators and enable testing of the product in Phase I studies. To assist with this, the EMEA and FDA have released guidance on cell-based and gene therapy products. "It's very important that sponsors get in touch with regulatory authorities, and at an early stage, so that we can find solutions together," says Hinz.

The selection of the maximum tolerated dose of a cancer vaccine is also difficult, particularly compared with traditional anticancer agents. For example, in the development of cytostatic or cytotoxic agents, Phase I studies typically determine a maximum tolerated dose of the drug, which

Table 1 | **Therapeutic cancer vaccines in late-phase development in the European Union or United States**

Name (company)	Indication (Phase)	Description	Class of vaccine
Abagovomab (Menarini)	Ovarian cancer (II–III)	A murine IgG1 anti-idiotype monoclonal antibody that mimics the structure of a specific epitope on the ovarian cancer tumour-associated antigen MUC16	Antigen specific
Allovectin-7 (Vical)	Metastatic melanoma (III)	A DNA plasmid–lipid complex encoding MHC1 antigen	Antigen specific
Belagenpumatucel-L (NovaRx)	Non-small-cell lung cancer (III)	Allogeneic non-small-cell lung cancer cells transfected with a plasmid containing a TGFβ2 antisense transgene	Polyvalent
BLP-25 (Merck Serono)	Non-small-cell lung cancer (III)	A liposome-encapsulated peptide derived from the MUC1 antigen	Antigen specific
BiovaxID (Biovest/Accentia)	Non-Hodgkin's lymphoma (III)	An anti-idiotype patient-specific protein	Antigen specific
GSK1572932A (GlaxoSmithKline)	Human melanoma antigen A3-positive non-small-cell lung cancer (III)	Human melanoma antigen A3	Antigen specific
MDX-1379 (Medarex/ Bristol–Myers Squibb)	Melanoma (III)	gp100 melanoma peptides	Antigen specific
M-Vax (AVAX Technologies)	Metastatic melanoma (III)	Autologous melanoma cells that have been irradiated and then modified with the hapten dinitrophenyl	Polyvalent
Oncophage (Antigenics)	Renal cell carcinoma (Pre-registration)	Autologous heat shock proteins	Polyvalent
PR1 leukaemia peptide vaccine (The Vaccine Company)	Acute myeloid leukaemia (III)	A 9-amino-acid HLA-A2-restricted peptide derived from proteinase 3	Antigen specific
Sipuleucel-T (Dendreon)	Prostate cancer (Pre-registration)	Prostatic acid phosphatase-loaded autologous antigen-presenting cells	Dendritic cell-mediated
TroVax (Oxford Biomedica)	Renal cell carcinoma (III)	A recombinant modified *Vaccinia ankara* viral vector encoding the 5T4 oncofoetal trophoblast glycoprotein	Antigen specific

gp100, glycoprotein 100; HLA-A2, human leukocyte antigen A2; IgG1, immunoglobulin G1; MHC1, major histocompatibility complex 1; MUC16, mucin 16 (also known as CA125); TGFβ2, transforming growth factor β2.

leads to a recommended dose for exploration in Phase II–III trials. Cancer vaccines, however, are typically not very toxic, and so the optimum dose often has to be based on the immune response of patients, says Martina Schüssler-Lenz of the Paul Ehrlich Institut.

Such immune response measurements can be confounded by the fact that patients receiving cancer vaccines may have previously been heavily treated with other anticancer agents. This can lead to a compromised immune system that makes it difficult to detect an evoked immune response. "Companies have not always determined how they will define the immune response in Phase I to determine the best dose for later phases," says Schüssler-Lenz. This often has downstream consequences for development.

The transition from Phase II to Phase III trials also hinges on adequate product characterization, in particular with regard to efficacy. "Companies take a big risk if they have not sufficiently characterized the exploratory efficacy of their products to justify testing in Phase III trials," says Schüssler-Lenz. Furthermore, end points that are used in Phase III trials of cancer vaccines pose regulatory challenges. "We're often confronted with new end points in Phase III that have not been validated nor shown to be meaningful in terms of improving or prolonging the life of the patient," adds Schüssler-Lenz.

As well as identifying appropriate trial designs, a key strategy to improve the success of cancer vaccines is to combat the immunosuppressive pathways that are activated by tumours. "Understanding and manipulating these [regulatory] mechanisms are the key needs for cancer immunotherapy," says Lieping Chen, Professor of Oncology and Dermatology at Johns Hopkins University School of Medicine, Maryland, USA, suggesting that cancer vaccine approaches may benefit from being combined with immune-modulatory strategies that counter immune suppression. "In fact, rational design of a combined cancer immunotherapy is becoming a very important direction of research."

Such immune-modulatory strategies could include nonspecific immunotherapies, as well as immune-activating antibodies. Interleukin-2, for example, is a general stimulant of T cells that has been approved by the FDA for cancer treatment. It can cause regression of tumours in up to 15% of patients with melanoma and kidney cancer, says Rosenberg.

One example of an immune-activating antibody is ipilimumab (Medarex/ Bristol–Myers Squibb), a cytotoxic T lymphocyte-associated antigen 4 (CTLA4)-specific antibody that is currently in a Phase III trial in combination with the cancer vaccine MDX-1379. "The rationale for using a CTLA4-specific antibody is that it is thought to block the negative regulatory role of the immune system," says Chen. Other antibodies that can manipulate regulatory pathways or checkpoints of immune responses are also being explored, he adds (see page 688).

Whichever approach researchers, clinicians and sponsors take with future cancer vaccine development, Gilboa offers the following advice: "We have to identify the best antigen to vaccinate against; we have to identify the best way to vaccinate; and we have to optimize the schedule and the dose," he says. "If you optimize only one of these three aspects, clinical trials will still fail."