

Therapeutic Cancer Vaccines:

THE ROAD TO COMMERCIALIZATION

>>> A summary and analysis of the different approaches companies are taking to develop immunotherapies and the hurdles they face when manufacturing these products.

By Mac Parmar, PhD



Cancer vaccines are entering an exciting stage of growth with a number of products nearing the finish line. The success of these products will represent a major shift in the treatment of cancer. Uncovering the means for priming the body to fight its own disease will be a remarkable advancement to add to the traditional cytotoxic chemotherapy and radiation modalities. However, positive clinical results alone will not be enough to make cancer vaccines a success; they will also have to be commercially viable. The high cost and the complex manufacturing and processing required for patient-specific autologous and ex vivo dendritic cells present significant challenges that must be overcome

for commercial success, whereas the synthetic vaccine approach mirrors already established practices in the industry and therefore may have an easier road to market.

Traditional therapies in oncology have focused on cytotoxic chemotherapy and radiation modalities for treating and controlling cancer growth. These cytotoxic agents are designed to kill rapidly dividing tumor cells; however, they also kill and harm healthy cells and tissue. This indiscrimination causes a wide range of side effects for the patient. Over the last decade, the search for newer and more precise therapies has led to the exciting discovery and development of monoclonal antibodies that target specific up-regulated proteins on the tumor. Herceptin[®], Avastin[®], Erbitux[®] and, more recently, Vectibix[™] have emerged as the leading agents in this class of biologics now being integrated into practice. Similarly, small molecule drugs, such as Gleevac[®], Sutent[®]

and Nexavar®, have also emerged as effective agents against up-regulated enzymes. While the small molecule products target the tumor, they attempt to minimize collateral damage to healthy cells.

For years researchers have been on a journey to find a therapeutic cancer vaccine approach to train the body to combat the disease. A therapeutic cancer vaccine that primes the immune system to recognize, attack and control tumor growth would be a phenomenal advancement that may one day turn a terminal disease into a chronic condition. However, the road to developing cancer vaccines has been a bumpy one with a number of failures and missteps, in part due to inadequate trial designs and regulatory hurdles.

Historically, cancer vaccines have been lumped into the category of cytotoxics, thus clinical trials have been limited to the sickest patients who have undergone multiple cycles of chemotherapy and radiation. Patients at this stage have a compromised immune system, and therefore the chances of the vaccine having a meaningful impact are next to impossible. However, the FDA's recent Critical Path Initiative has identified cancer vaccines as a therapeutic area requiring new guidance for development and clinical testing. This new initiative will hopefully increase the chances of clinical success of cancer vaccines and provide patients with a new treatment option.

The various vaccine products and approaches of the leading companies in the therapeutic cancer vaccine field are summarized as follows.

Autologous Approaches

As discussed elsewhere in this issue, Favrilite (FavID®) and Genitope (MyVax®) are two companies with autologous vaccine products in Phase 3 testing for B-cell NHL. Both vaccines follow a very similar manufacturing process and vaccination strategy that involves the creation of patient-specific idiosyncrasy in combination with KLH and GM-CSF. The manufacturing runs for the vaccines are estimated to take at least 8-weeks (FavID) and ~3.5 to 6.5 months (MyVax) for each patient vaccine. The chief merit of a patient-specific method is that by using antigens specific to the individual patient these vaccines would theoretically lead to robust, targeted immune responses against their own tumor. With that being said, the vaccine would have to be continually modified to match the mutations in tumor biology that commonly appear over time.

...clinical results alone will not be enough to make cancer vaccines a success...

The manufacturing process for these vaccines is a multiple step procedure involving surgical extraction, idiosyncrasy identification, gene transfection, recombinant protein synthesis and conjugation. One can envision that a number of in-process

controls will likely be required to ensure that a level of quality and safety is maintained under cGMP (code of Good Manufacturing Practice),

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especially considering the use of plasmid vectors and cell lines.

Product manufacturing on a patient-by-patient basis suggests a high degree of variability from run-to-run, which will also need to be addressed. Although the idiotypic may not be the same, the recombinant protein must meet certain standard criteria prior to proceeding to the final product conjugation step. Standard-release testing methods for final product criteria such as potency, purity, sterility and pH may make gaining regulatory approval of a patient-specific vaccine additionally challenging. The FDA raised this very issue for final product characterization of autologous vaccine programs, namely those of Antigenics and Dendreon.

The 8-week processing time and resources required suggests a very high manufacturing cost, and a lack of scalability and commercial feasibility. Manufacturing costs will have serious implications on reimbursements, an area where the cost-to-benefit ratio will most certainly need to be addressed. Product tracking and safety controls will need to be implemented to ensure that manufacturing lines and equipment are dedicated to a particular patient's product and that the product is correctly administered to its intended recipient. The potentially challenging development and commercial path for an autologous program was cited by Cell Genesys in their decision to terminate their patient-specific lung cancer agent GVAX®, and instead focus on allogeneic whole cell vaccine technology.

The complexity of the manufacturing process is a major disadvantage from a commercialization, cost and regulatory perspective. The FDA will require a comprehensive Chemistry,

Manufacturing and Control (CMC) section in the NDA filing that outlines the detailed manufacturing processes and controls in place to ensure product quality, uniformity, reproducibility and safety. Since each vaccine is specific to the patient, the CMC section for these vaccines will likely be most challenging and it will be interesting as to how the processes are viewed by the FDA.

Ex Vivo Dendritic Cell Therapy

An alternative patient-specific approach has been developed by Dendreon using ex vivo dendritic cell technology to produce the prostate cancer vaccine Provenge®. The 5-day process involves in vitro loading of synthetic prostatic acid phosphatase (PAP) protein into patient-derived dendritic cells followed by intravenous infusion back into the same patient. The process is much simpler than the autologous tumor extraction method where the loading of dendritic cells, in theory, offers a more efficient presentation of the antigen to the immune system leading to a more robust immune response.

Although the process may be simpler, the same concerns regarding commercial viability, cost, regulatory compliance and safety exist. Ex vivo processing requires adequate controls for sterility, product tracking, and stability throughout the manufacturing process. The processing time, resources and logistical issues of product shipping to and from multiple sites on a patient-by-patient basis present significant challenges from a commercialization cost perspective.

A manufacturing site's capacity may be limited by the number of vaccines that can be prepared at any given time, thus significant

investments in additional manufacturing sites may be required. In addition, the cost-to-benefit ratio and Medicare reimbursement issues will need to be considered.

As with the autologous programs, the dual issues of release testing and potency determination will need to be established prior to commercialization. Validated assays will be required to determine if the vaccine was successfully manufactured by determining potency values after the antigen loading. In the case of Provenge, the potency measurement component was addressed and resolved by an assay for a cellular marker implemented to ensure that the product met this criterion.

Synthetic Vaccines

Traditional pharmaceuticals are “off-the-shelf” products that are manufactured on scale and, in a majority of cases, use completely synthetic starting materials. The active and inactive components are well defined by raw material specifications that add a level of control for quality and uniformity in manufacturing. The cost, quality and product characteristics would be easily controllable in large-scale manufacturing, much like conventional vaccines.

Stimuvax® by Biomira/Merck KGaA, in late-stage testing for lung cancer, is based on a synthetic platform. The vaccine is a synthetic peptide, encoding for a sequence on a tumor-expressed protein. The peptide is anchored to a lipid incorporated into a phospholipid

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matrix. The matrix also contains Lipid A, an immunostimulatory adjuvant. The product is manufactured as a liquid on a large scale and sterile-packaged into vials and then freeze-dried into a powder. The vaccine is reconstituted into a solution in the doctor's office prior to administration.

The vaccine is designed to induce a targeted immune response against the over-expressed MUC1 protein found on the tumor cells.

One major advantage of a completely synthetic vaccine is that it is an off-the-shelf product that does not require complex processing and manipulation on an individual patient basis. A significant advantage for Stimuvax is that it targets a protein found on a majority of solid tumors, thus it would have a broad-based application across a variety of different cancers.

Another synthetic peptide vaccine in development, GV1001 (Pharmexa), is currently in Phase 3 testing for pancreatic cancer. The vaccine targets the telomerase enzyme thought to be involved in the mechanism by which cells transform into rapidly growing cancer cells that lack the “off-switch” of normally dividing cells. The vaccine is administered intradermally with synthetic GM-CSF and has been shown to be immunogenic in mid-stage trials. A clear advantage of a peptide vaccine is that it can be produced on a large scale under cGMP with well-defined chemical purity and quality that are acceptable to the regulatory authorities. This is another example of an “off-the-shelf” vaccine product [cont. on pg 20 >>](#)

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with a clear advantage over patient-specific approaches. Moreover, the telomerase enzyme is widely expressed in a wide variety of cancers, thus it would represent a potentially universal cancer vaccine.

Synthetic vaccine programs are also being pursued by Bristol-Myers Squibb and Medarex in late-stage melanoma. The collaboration combines a monoclonal antibody, MDX-010, and a synthetic peptide cocktail, MDX-1379, which consists of two peptides against the gp100 melanoma-associated protein. The programs are designed to initially block the CTLA-4 on T-cells, which will then theoretically increase T-cell responses to the concomitant administration of MDX-1379. The net result would be a robust immune response directed at the melanoma cells.

Much like current vaccines on the market, a synthetic vaccine can be made using well-defined starting materials to produce a homogeneous, well-characterized and stable product in large quantities compared with the patient-specific approaches. The manufacturing processes are simpler and can be rapidly implemented early in the development of large, confirmatory trials.

Synthetic vaccine products would have significantly lower barriers in commercial manufacturing and regulatory approval once they are found to be successful in the clinical setting. Moreover, the ease of use in the

oncologist's office and feasibility of using in combination with current treatment modalities would be noted as another advantage of the "off-the-shelf" synthetic approach.

Products Poised for Success

As you can see, the industry approach to cancer vaccine development varies widely—from the patient-specific autologous and ex vivo dendritic cell methods to the whole cell and completely synthetic approach. Taking a cancer vaccine from the research and clinical testing stages to regulatory approval and commercialization will require that the feasibility and manu-

facturing costs of the treatment are sufficiently addressed. It will not be enough for a cancer vaccine to simply achieve clinical efficacy in order to be commercialized. The vaccine must be manufactured reliably on scale and meet the FDA's stringent quality and safety requirements. **MP**

Mac Parmar is Director of Pharmaceutical Sciences at a private biopharmaceutical company. He can be reached at macparmar@hotmail.com.

...a synthetic vaccine can be made using well-defined starting materials...

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Cancer drugs comprised 13% of the nation's drug spending in 2002; in 2007, that figure is expected to almost double, to 22%, accounting for almost a quarter of total U.S. drug spending. (*Wall Street Journal*, 3/15/07)



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