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Human Vaccines: Policy

Next generation of therapeutic cancer vaccines require smart vaccine design

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Despite the recent revival in the field of cancer therapy with the FDA approval of Dendreon's Provenge (Sipuleucel-T, a cell-based cancer vaccine) and the promising data from phase III studies with Bristol-Myers Squibb's Ipilimumab in melanoma [a monoclonal antibody mAb that enhances the immune system], investor skepticism toward cancer therapy lingers. This continues to translate into a profound reluctance to inject funds into the biotech industry to progress research and clinical development of such products. Despite the progress being made in clinical research, there is an underlying concern that current cancer therapies in late-stage clinical testing typically demonstrate a limited response rate (e.g. 20% of treated patients) and only an incremental benefit in these patients (e.g. modest extension of life). Such incremental successes contradict the investor's expectations of a miracle cancer therapy with profound impact on patients.

There is now a realization that a dramatic impact on cancer will only be realized by combining therapies. The evidence for this is substantial. GVAX (a vaccine prepared from a patient's own cancer cells) for example failed to meet clinical endpoints in Phase III clinical testing, which only exacerbated recent sentiment,[1] but several lines of evidence suggest that combining GVAX with other therapies can be synergistic and may be effective in treating tumors.[2] Anti-CTLA4 mAb therapy (e.g. ipilimumab) have completed Phase III clinical testing in single therapy modality showing limited yet significant efficacy on its own,[3] however it is contemplated that such a therapy will have considerably more impact if combined with an effective vaccine.

Avastin (bevacizumab, anti-VEGF mAb) has been approved for metastatic breast cancer based on incremental efficacy data; however, a combination therapy of bevacizumab and paclitaxel recently received accelerated approval from the US Food and Drug Administration (FDA) as it doubled median progression-free survival from 5.9 months to 11.8 months.[4] The approval came despite no effect on overall survival and the manifestation of several side effects including grade 3 or 4 hypertension.

Why the limited success in cancer therapy? The answer comes from a better understanding of cancer immunology in general and the mechanisms of these therapies in particular. GVAX relies on the use of GM-CSF as a built-in adjuvant; however, we now know that GM-CSF can easily inhibit or promote tumor growth, depending on the context in which it is used. GM-CSF can enhance T cell activation but its prolonged and sustained production can also activate regulatory T cells that negate the effect of the effector T cells we are trying to activate.[5] Anti-CTLA4 therapy removes the breaks on effector T cells, but it is now evident that it also enhances regulatory T cell function as well. Other members of the CTLA4 family have been discovered and their role in cancer immunotherapy is still to be elucidated.[6] Dendritic cell (DC)-based vaccination strategies look promising, however, the benefit they exert is incremental. For example Provenge, the first DC-based vaccine to receive FDA approval for the therapy of advanced stage prostate cancer, increases overall survival an average of 4.1 months.[7] The efficient activation and maintenance of an immune response capable of providing a strong anti-tumor effect is bound to be more complicated than a short- lived burst of partially activated antigen presenting cells, particularly in the presence of cancer-induced suppressive mechanisms.

Is targeted cancer immunotherapy capable of killing cancer? Absolutely! The most dramatic example is the experiment by Rosenberg using homologous T cells engineered in vitro to kill MART-1 expressing melanoma.[8,9] T cells were injected in melanoma patients and achieved a 50% response rate, following lympho-depletion. This revolutionary experiment proved that a targeted cellular immune response is capable of killing cancer in a human subject and that negative regulatory signals must be removed from the system for a cellular response to be effective. Unfortunately, the Rosenberg experiment is too complicated to be amenable to large-scale production and commercialization.

Most cancer vaccines have failed to achieve similar dramatic responses because the immune response they generate is not strong enough to overcome the regulatory mechanisms imposed by growing tumors or overcome the immune escape strategies that tumors employ. The design of these therapeutic vaccines has been suboptimal on two fronts: antigen selection and the use of an adequate vaccine delivery technology.[10] They also have not used strategies to dampen the regulatory mechanisms that have been placed by the cancer.

A plethora of cancer-specific antigens have been described to date and tested in the clinic. Most vaccine designs rely on the use of a limited number of the antigens at a time (most use only one) and they have invariably failed. Notwithstanding the problem of delivering these antigens properly, there is a realization that cancer cells manage to evade the immune system by downregulating the presentation of these antigen targets on their cell surface. While these antigens have been associated with the cancer, their presence is not critical to the survival of the cancer. MART-1 for example is downregulated on melanoma cells as a result of vaccine-induced immune pressure.[11] Her2-positive breast cancer cells can become Her2-negative following Herceptin treatment which causes a patient to become unresponsive to treatment.[12] Similar observations have been made for anti-EGFR therapy. GSK's MAGE-3 vaccine, now considered a strong contender in the cancer immunotherapy field, is lost in melanoma cells of vaccinated individuals.

The immune "editing" capability of cancer cells is the Achilles heel of targeted immunotherapy. This is why the expression of antigens that are cancer-specific, and required for the survival of the cancer cell, cannot be lost without dire consequences. These antigens are critical elements of smart vaccine design.

There has been much activity in developing vaccine delivery systems. These include DC vaccination, MVA-based vaccination, Listeria monocytogenes-based delivery, heat shock protein delivery, and particulate vaccines that use "special" antigens such as p53 or MAGE-3. The research activity in the field is immense, with entire journal issues dedicated to describing these emerging technologies. The field has progressed to increasingly complicated

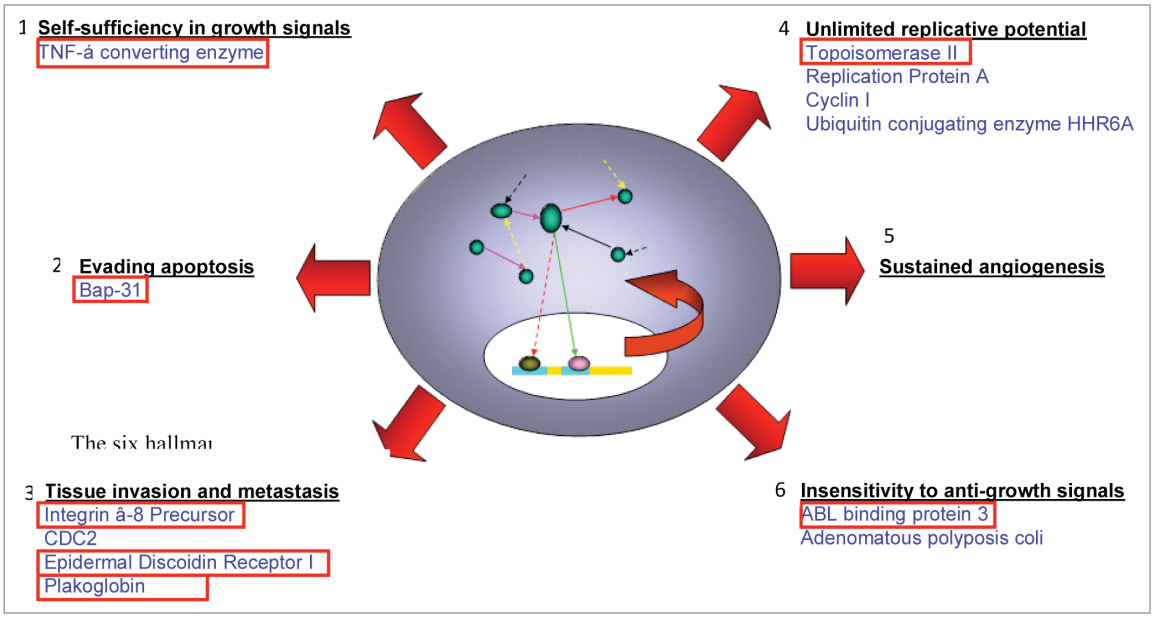

Figure 1. DPX-0907 targets five pathways critical to tumor immune evasion. The six hallmarks of cancer, first described by Hanahan and Weinberg,[18] allow the tumor to avoid immune detection through multiple mechanisms. By relying on multiple pathways, the tumor can adapt to the loss of a single protein with relative ease. DPX-0907 simultaneously targets multiple proteins associated with different pathways, making it difficult for the tumor to adapt quickly.

approaches that range from developing and maturing immune cells ex vivo (e.g. DC vaccines) to injecting cancer antigens directly into lymph nodes to induce a stronger immune response. Intra-lymph node vaccinations currently performed by MannKind Corp. have shown that an over-abundance of antigen can easily dampen a cellular immune response.[13] If this concept is true, then all vaccination platforms in development today risk delivering a bolus of antigens that eventually drain into a lymph node where a cellular immune response is expected to be generated.

Delivery of adjuvants to a lymph node can also have a positive effect on T cell activity. We know now that adjuvants that activate innate immunity (non-specific) are critical for the generation and maintenance of adaptive immunity (targeted).[14] The context in which these adjuvants are used, however, can dramatically affect the efficacy of the vaccine. The beneficial use of adjuvants that target the Toll-like receptor (TLR) family has been clearly demonstrated. Adjuvant overload, however, can induce immune regulatory T cells known as T regs, alongside the effector T cells that the vaccine is trying to induce. Historically, the field has had limited access to these adjuvants, with only a few tested extensively in the clinic. The reliance of the cancer vaccine research field on adjuvants that are readily available, such as GM-CSF must be revisited. The use of the adjuvant with peptide-based vaccination is widespread and its use continues today, despite clear evidence that repeated immunizations with these vaccines result in progressively lower immune responses in cancer patients. Immunovaccine Inc. has shown in "humanized" transgenic mouse models that our DepoVax™ vaccine delivery technology can enhance and, more importantly, maintain a strong immune response after repeated immunizations, whereas GM-CSF based vaccines failed to maintain such a response.[15]

The therapeutic cancer vaccine candidate DPX-0907 incorporates all the elements of smart vaccine design (**Box 1**). The antigens are carefully selected with a multi-targeted approach that focuses on proteins involved in pathways that are critical for the survival of a cancer cell (**Fig. 01**). This reduces the likelihood of immune escape through loss of antigen expression/presentation as a tumor responds to vaccine-induced immune pressure. The select antigens are formulated with a T helper epitope to ensure activation of the appropriate T cells known to maintain a cellular immune response. A TLR agonist has been selected based on its activity in tumor challenge models. The depot concept, which incorporates all these critical vaccine components, ensures very slow and controlled release of the antigens and adjuvant so as not to overload the immune system. Experimental evidence, as reported in the April 2010 issue of the *Journal of Immunotherapy*, supports this hypothesis. The report concludes that DepoVax-based vaccines in preclinical studies have induced strong and sustained cellular immune responses without raising T reg levels beyond normal baseline levels.[15] Also, this superior control of antigen and adjuvant release likely contributes to the efficacy profile and the favorable safety profile that has been noted in Immunovaccine's histology-based safety studies.

Immunovaccine has compared the depot effect of DepoVax to that of other depot formulations (e.g. emulsions) and has observed dramatically different release profiles. No other depot formulation is capable of achieving the DepoVax™ effect. We are not aware of any technology that is capable of bringing water-soluble vaccine components (antigens and adjuvants) into a pure oil environment for the ultimate depot effect.

Cancer therapy is gravitating towards combination therapies out of necessity. mAbs have been successful at demonstrating incremental benefits, and combining passive targeted therapies has proven useful but potentially dangerous. Systemic side effects are common with monotherapies, let alone combination

Box 1. DPX-0907 differentiating features:
- Smart antigen selection
- Contains a T helper for maintenance of immune response
- TLR agonist to activate innate immunity, a pre-requisite for strong adaptive immunity
- Superior depot formulation to control the release of vaccine components to the immune system
- Ability to induce T effector cells without inducing T regulatory cells
- Easy to reconstitute and use in the clinic
- Safe

therapies.[16] Vaccines, on the other hand, are well known to be a safe alternative to systemically administered mAb therapy and chemotherapy. For this reason cancer vaccine development continues to be very strong today.

Cancer vaccines that can show some efficacy in clinical trials will ultimately be combined with some of these systemic therapies to control cancer cells effectively. The safety profile of such combinations is bound to be favorable to other combination therapies in clinical testing today. The best combination therapy is one that weakens the tumor directly, or indirectly, by limiting its angiogenic potential or the immune regulatory mechanisms they promote. This combination could be a mAb therapy or chemotherapy combined with a targeted immune therapy such as a vaccine with strong cellular immunity potential that targets the cancer cell directly through markers which cannot be lost by the cancer cell under attack. Experts in the cancer field are aware of this, and everyone is waiting for such a vaccine to be available for clinical testing.

A perfect example of this strategy being successful in the clinic is Avant/Celldex's CDX-110 brain cancer-specific vaccine.[17] This vaccine, when combined with the lympho-depleting drug temozolomide, dramatically extended the median survival in glioblastoma multiform (GBM) patients. CellDex has since signed a $390 million deal with Pfizer for CDX-110. Unlike CDX-110, which can only be used on GBM patients, DepoVax can be applied to any cancer by incorporating the right antigens in the vaccine enhancement platform. In addition to combining a vaccine with a lympho-depleting drug (CellDex's strategy), a DPX-0907 therapy is also perfectly compatible with anti-angiogenic therapies such as Avastin. DPX-0907, with its specific immune activating potential, is also compatible with general immune enhancing products such as ipilimumab (anti-CTLA4).

DPX-0907, which appears to be more effective and safer than other vaccine alternatives in clinical testing today, is mid-way through a Phase 1 clinical trial. Should the results of this Phase 1 trial prove encouraging, it opens the door for applying these smart strategies with the DepoVax vaccine delivery formulation to later stages of clinical testing.

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