

Multifunctional vaccines in cancer: the 'triad' approach

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John Nemunaitis

Mary Crowley Cancer
Research Centers, Dallas,
TX 75201, USA

and
Texas Oncology PA, Dallas,
TX 75251, USA

and
Medical City Dallas Hospital,
Dallas, TX 75230, USA

Tel.: +1 214 658 1965

Fax: +1 214 658 1992

[jnemunaitis@](mailto:jnemunaitis@marycrowley.org)

marycrowley.org

“Over the last 50 years ... ‘single’ modality vaccines have been tested ... However, they have met with limited success and have not approached a level of efficacy ... necessary for US FDA product approval.”

Are we perhaps unlocking a mystery of cancer management that has eluded us for hundreds of years? Namely, the mystery of how we influence the immune system to control cancer? Tantalizing spontaneous tumor regression has been demonstrated since recorded medical history in 0.1% of melanoma and in rare renal cell cancer patients following primary surgery. Over the last 50 years, in an attempt to duplicate success with infectious disease and antigen awareness, ‘single’ modality vaccines have been tested (whole-cell vaccines, tumor lysates, activated effector cells, various protein small molecules, cytokines, antibody-directed vaccines, and DNA- or RNA-based vaccines). However, they have met with limited success and have not approached a level of efficacy (survival advantage) necessary for US FDA product approval. Why is this? There are many reasons, but one which is frequently mentioned is that our animal models are not effective and have minimal correlation to the human response. Another is that we have not identified a surrogate marker or assay consistently correlating immune activity with survival. Nevertheless, our knowledge has improved.

For example, there have been many advances in molecular biology that have led to identification of new antigens, cytokines and molecular mechanisms, thereby clarifying our understanding of how immunotherapeutic approaches may impact control over cancer.

Dendritic cells (DCs), for instance, engage in cell-mediated immunity and play a central role in the induction of

antitumor immunity in tumor-bearing hosts via antigenic cross-presentation [1–4]. DCs efficiently display antigens on MHC class II and stimulate proliferation and activation of CD4⁺ and CD8⁺ T cells. CD4⁺ cells augment the activity of natural killer cells and macrophages, in addition to amplifying antigen-specific immunity via local secretion of cytokines [5,6]. Through this process DCs have been identified as a pivotal component to engage for success of immune-based vaccine technologies.

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Over the last several years we have also explained reasons for the potential lack of activity, including ineffective priming of tumor-specific T cells, lack of high-avidity primed tumor-specific T cells, and physical or functional disabling of primed tumor-specific T cells by the primary host and/or tumor-related mechanisms. One inhibiting mechanism that is now well characterized involves tumor-infiltrating lymphocytes, which are immunosuppressive T regulatory cells that secrete TGF- β and express a high level of CTLA-4 [7,8]. These cells impede immune activation by facilitating T-cell tolerance to tumor-associated antigens rather than cross-priming CD8⁺ T cells. This results in the nonproliferation of killer T cells which recognize the tumor and will not attack it [7–10]. Another

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example of an inhibiting mechanism involves various cytokines (i.e., IL-10, TGF- β_1 and TGF- β_2) that suppress immune responses against cancer [11–14].

Virtually all clinical vaccines demonstrate remarkable safety and, furthermore, immune function assessment has demonstrated, albeit periodically and inconsistently, a correlation with response, survival or time to progression. Dramatic responses are described on a ‘case report’ basis in solid tumor patients and this has been encouraging. However, many oncologists would agree that this is a far cry from where we need to be. Nevertheless, a strategic use of vaccine technology to manage cancer and, in essence, enable patients to ‘live with the cancer’, is a step in the right direction – that is, to manage cancer similarly to how we manage diabetes or hypertension. These medical disorders are not cured but with the appropriate minimally toxic treatment, patients live long healthy lives with a minimal impact from these incurable diseases.

“...we do appear to be coming closer to understanding how to manage patients using immune-modulating therapeutics.”

Recently, Provenge® (Dendreon), an antigen-stimulated activated DC vaccine, demonstrated significant survival advantage in advanced disease prostate cancer patients. Following swiftly on from this, recently in the USA, ipilimumab made a landmark breakthrough demonstrating further survival advantage in advanced melanoma patients. Both products are now approved by the FDA as indicated therapies in prostate cancer and melanoma, respectively. Remarkable systemic responses have also been observed in advanced non-small-cell lung cancer patients receiving autologous tumor granulocyte–macrophage colony-stimulating factor (GM-CSF) gene-based vaccines (GVAX) [15] and dose-related survival advantage has been demonstrated through inhibition of the TGF- β_2 gene using the Lucanix® (NovaRx) vaccine [16]. Oncovex (BioVex), another GVAX, has also been tested in melanoma with similar results [17].

So why the recent success following such a frustrating road over the prior 50 years? Let us consider the key points of prior work. Cancer vaccines were originally designed to mimic success of infectious antigen-based vaccines as a single modality therapy or to stimulate antigen effector cell function (e.g., cytokines). We

now know that the immune system and its involvement in control (or lack of control thereof) of cancer is much more complex and dynamic. However, we have also learned over the last 50 years three key mechanisms by which the immune system can be modulated to control cancer – mechanisms that have been verified by clinical activity. These are antigen education, immune function enhancement and inhibition of immune inhibitors. Vaccines with success consider each of these mechanisms. Recently, we also described one vaccine that strategically controls elements of each of these three mechanisms. Phase I results of this novel vaccine named TAG (Gradalis Inc.) described autologous tumor antigen education, enhancement of immune function using GM-CSF gene and inhibition of tumor inhibitors through blocking of TGF- β_2 [18]. This could be considered the first ‘triad’ vaccine. Manufacturing design and Phase I trial initiation of a more comprehensive triad vaccine called FANG™ was more recently described [19]. Will these or others generate more fruitful results? We do not yet know, but we do appear to be coming closer to understanding how to manage patients using immune-modulating therapeutics. However, two technologies (Provenge and ipilimumab), despite limitations and some off-target toxicity, are now finally in the hands of oncologists and clinical researchers. In the future, we may expect to see utilization of immune-modulatory approaches in a variety of combination trials now linked to targeted therapy and low-dose chemotherapy. Vaccine technology as it now evolves into the clinical arena with its high safety profile will begin to impact adjuvant therapy, consolidative therapy and will engage patients with minimal disease at high risk of recurrence. It will also enable patients with less tolerance to chemotherapy as a result of other medical limitations or age to undergo a new method of therapeutic management. Some of the off-target issues, particularly involving T-cell regulators, need to be worked out, however, a focus on triad vaccine development appears reasonable.

Financial & competing interests disclosure

John Nemunaitis has a direct affiliation with Gradalis Inc., in which he owns stock. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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