Commentary (Fox)—Melanoma Vaccines: What We Know So Far

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Drs. Bystryn and Reynolds present an overview of melanoma vaccines, including a theoretical rationale to support the approach, criteria for an effective vaccine, and a discussion of the challenges to optimal vaccine design. Results of clinical trials where vaccine-induced immune responses correlated with improved clinical outcome are discussed, as well as limitations of monitoring vaccine-induced immune responses. A series of randomized, concurrently controlled trials with complex, polyvalent whole-cell vaccines, extracts, lysates, or shed antigens are reviewed. The authors conclude that melanoma vaccines' "potentially most significant application" may be the prevention of melanoma in individuals at high risk of developing the disease. Their review discusses the generally accepted rationale for selecting vaccine antigens and does a thoughtful job of reviewing the current state of complex melanoma vaccines.

Vaccine Shortcomings

My own perspective is that while such complex vaccines are the "correct" antigen source, these vaccines will not reach their therapeutic potential, because, alone, they cannot overcome tolerance or tumor-induced suppression. The authors describe preclinical studies in which whole-tumor vaccines protected naive animals from a subsequent lethal tumor challenge. However, at the beginning of 2005 there is essentially no evidence that therapeutic vaccination alone can cure animals with large established (7- to 10-day old) poorly immunogenic tumors. Why does vaccination work in naive "tumor-free" animals but not in animals with established tumor burden? While tumors have the capacity to directly or indirectly suppress the antitumor immune response, this is only part of the answer.

What is needed for immune-mediated tumor destruction? As noted by Bystryn and Reynolds, preclinical models generally document that CD8 T cells are the primary mediators of a curative immune response. However, it is becoming increasingly clear that CD4+ T cells are essential for longterm persistence of tumor-specific CD8 T cells and "cure" of animals with established tumors.[1]

While many vaccine studies report a significant increase in the frequency of tumor-antigen-specific T cells, these frequencies are generally below 1% of the total T-cell population. Our Institute's view, supported by preclinical data and recent clinical reports, is that this level of response will not provide a curative effect, explaining why melanoma vaccine strategies have not delivered on their promise.[2]

Improving Vaccine Therapy

What can be done to overcome these tumor-induced roadblocks and increase the frequency of tumor-specific T cells in melanoma patients?

(1) Use complex antigen vaccines: While class I-presented peptide vaccines have provided proof of concept and opportunities for sophisticated immunologic monitoring, vaccines utilizing CD8 epitopes alone should be broadened to include CD4 epitopes or switched to complex vaccines. Immune responses composed of CD4 and CD8 T cells against a spectrum of tumor antigens will be required
to maintain long-term curative immunity.

(2) Provide costimulation: At least three costimulation approaches are in or nearing the clinic. The most clinically advanced is anti-CTLA-4, which interferes with a natural “braking” system that limits costimulation. While serious autoimmune reactions have been noted following anti-CTLA-4 administration, they have been controllable and their detection is seen as evidence of a fundamental change in the nature of the induced immune response.[3] Additional antibodies that provide costimulatory signals and directly augment immune cell function are anti-4-1BB and anti-OX-40. Our Institute has developed an anti-OX40 antibody that should enter clinical trials in 2005.

(3) Block suppression: Antibodies, small molecules and/or receptor antagonists that interfere with these suppressive cytokines and molecules are becoming available and should soon find their way into cancer vaccine trials.

(4) Eliminate "suppressor" regulatory T cells (T_{reg}) cells: Since T_{reg} cells express interleukin (IL)-2 receptors, investigators are attempting to eliminate them, using an IL-2-toxin fusion protein (Ontak). In the near future, we expect that reagents will be available to selectively deplete and/or transiently regulate these cells or their function.

(5) Restructure the "environment" for immune cells: Manipulating costimulation, suppressive molecules and/or T_{reg} cells may augment the immune response to vaccination, but homeostatic mechanisms may limit the increase in tumor-specific T cells. Building on the findings of Mackall and colleagues,[4] our Institute has developed a strategy that may overcome the homeostatic controls that maintain a fixed number of lymphocytes. In preclinical models, this strategy—which involves vaccinating a lymphopenic mouse that has been reconstituted with 1% to 10% of their normal lymphocytes—results in higher frequencies of tumor-specific T cells and increased therapeutic effects in vaccine and adoptive transfer models.[5,6]

Ongoing Research

In collaboration with colleagues in Xi'an, China (Drs. J. Ma, Y. Wang, and colleagues at Xi'an Jiaotong University, studying ovarian cancer) and Munich, Germany (Drs. D. Ruttinger, M. Schlemer, R. Hatz, and colleagues at Klinikum Grosshadern, studying non-small-cell lung cancer), our Institute is participating in four planned clinical trials of this reconstituted lymphopenic patient (RLP) approach.[7] These investigations include a trial for HLA-A2+ metastatic melanoma patients (Drs. W. J. Urba, B. Curti, and H. Ross, Earle A. Chiles Research Institute, Providence Portland Medical Center, Portland, Oregon). The RLP trial design involves the processing and storage of an apheresis product, administration of chemotherapy to induce lymphopenia, infusion of the apheresis product, and vaccination.[7]

Conclusions

Ultimately, the "success" of melanoma vaccines will require a multifactorial approach, which will not be easy to establish. Combining new agents from different companies will result in a need to deal with intellectual property issues as well as corporate concerns regarding possible adverse events when agents are combined. Success in the area will require a positive perspective and collegial relationships between corporate, academic, funding, and regulatory agencies. The Cancer Vaccine Consortium of the Sabin Vaccine Institute recently initiated a series of working groups to address these and other issues, in an effort to facilitate development of "cutting edge" vaccine trials that combine multiple agents and may increase objective clinical response rates.

Another roadblock to cancer vaccine development is the paucity of translational investigators, specifically, scientists who are actively involved in translating their basic science observations to the clinic. In my opinion, this is a crisis that severely limits the application of new technology to the clinic. Recognizing this, the International Society for Biological Therapy of Cancer (iSBT) is working to increase participation by PhD scientists and students. However, solving this crisis will require the institution of translational medicine training programs that develop scientists interested in transferring good basic science to patient care and the establishment of mechanisms to recognize, support, and reward scientists that pursue this career path.

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Disclosures:
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