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# Dendritic cell vaccines to combat glioblastoma

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**“Dendritic cell-based vaccine therapies represent a novel experimental approach to treat malignant gliomas.”**

The dismal prognoses suffered by malignant primary brain tumor (glioma) patients remain unchanged over the past two decades despite significant improvements in the treatment of distinct tumors. Dendritic cell (DC)-based vaccine therapies represent a novel experimental approach to treat malignant gliomas. Clinical and related studies in glioma patients over the past 8 years have documented the great promise of DC vaccines to deliver low toxicity, potentially effective therapy to brain tumor patients, but major challenges still remain to establish clinical efficacy and render them more accessible to patients. The purpose of this editorial is to discuss how some of these challenges may be met through refinements at the technological, organizational and regulatory levels, provide a view of how vaccine therapy may evolve when this occurs, and illustrate how building on current findings from glioma vaccine trials may serve the cancer vaccine field generally.

Gliomas are among the gravest forms of cancer. The most common of these fatal tumors is grade IV astrocytoma or glioblastoma multiforme (GBM). The most effective standard treatment against GBM is surgical resection followed by radiation and chemotherapy, which does not dramatically improve clinical outcome. GBM diagnosis carries an average survival of approximately 15 months, with less than 5% of patients surviving more than 2 years. Consequently, less toxic and more effective therapies for GBM are desperately needed.

Therapeutic vaccination, and DC vaccines in particular, represents an emerging GBM therapy. DC vaccines are attractive because these most potent of immune stimulators can activate adaptive immune T cells that can then survey peripheral

tissues, including the CNS, at the cellular level and with exquisite specificity. Activated T cells have the added potential to mount secondary memory responses with increasing rapidity and intensity long after vaccine administration, which is crucial to safely eliminate microscopically disseminated GBM tumors that evade surgery and invariably cause recurrence.

Early Phase I and II DC vaccine trials in GBM patients demonstrated mild side effects, including localized rash and influenza-like symptoms, as well as induction of anti-tumor T-cell responses in most patients. Multiple DC vaccine trials continue to report favorable outcomes and minimal toxicity in GBM patients, with 40–70% of patients surviving longer than 2 years [1–7]. Moreover, objective tumor regressions, particularly after post-vaccine chemotherapy, continue to be observed, suggesting clinical efficacy and synergy with chemotherapy [8–10].

Several studies of non-CNS cancers have reported qualitative correlation between immunological and clinical metrics after DC vaccination [11–13]. The ideal evidence that T-cell responses directly improve cancer outcomes would be a continual (progressive) correlation between vaccine-induced T-cell responses and clinical outcomes. In this context, a recent Phase II DC vaccine study presented evidence of progressive correlations between clinical and immunological metrics in GBM patients [9]. This renews hope that effective vaccine therapies can be developed for at least some human tumors, and suggests that immunological targets to improve vaccines for GBM patients may be within reach. However, substantial challenges must first be met if such hope is to be transformed into reality.

First and foremost, the promising findings in early glioma DC vaccine trials must now be validated in randomized controlled trials. The current absence of Phase III vaccine trial results may reflect the relatively small size of the GBM patient population compared with non-CNS cancers. This undermines patient recruitment into larger clinical trials by any single institution, and necessitates costly multicenter trials. Multicenter Phase III trials are difficult, if not impossible, to conduct without ample corporate sponsorship, and such sponsorship requires favorable potential for commercialization. At present GBM DC vaccine manufacturing is individualized to each patient, most commonly combining DCs differentiated from autologous blood with the patient's own tumor lysate as an antigen source. The resulting manufacturing process requires the collaboration of personnel with surgical, blood bank, cell culture, quality control and cGMP/regulatory expertise that typically only coexists at large academic medical centers. The prospect of organizing and orchestrating such a consortium across several institutions, coupled with the relatively high cost of manufacturing cellular products, may further dampen corporate enthusiasm for Phase III trials. The regulatory environment also integrates into this equation. Specifically, although DC vaccine efficacy has now been established for Provenge<sup>®</sup>/sipuleucel-T in randomized controlled trials for prostate cancer patients [14], the US FDA has been reluctant to expedite its approval. The cancer vaccine community is eagerly awaiting further FDA consideration of Provenge in mid-2010, and it is no understatement that its approval as the first therapeutic cancer vaccine would change the immunotherapy landscape. Such an outcome would likely fuel considerable corporate interest in DC vaccines in particular. In summary, the primary challenge to advancing DC vaccine therapy for GBM to its next developmental phase hinges on proving its clinical efficacy, which is intertwined with potentially difficult corporate sponsorship, technological, organizational and regulatory issues. Solutions to this challenge must likewise address these issues.

In the context of this editorial, general remedies and/or alternatives can be envisioned. First, it should be accepted that regulatory approval of Provenge/sipuleucel-T is by no means guaranteed. In this context, potential FDA reluctance to approve new therapeutics labeled 'vaccine' could conceivably be related to vociferous public concern over the safety of preventive vaccines against infectious diseases. Scientists and clinicians involved in therapeutic vaccine development have a special responsibility in this regard to educate their public, and their government, as to the safety and benefits of cancer vaccines. Nevertheless, since such a strategy is long-term in nature, alternatives must be considered in the event of Provenge non-approval.

If FDA approval of Provenge is withheld or delayed, there are still scientific means to increase enthusiasm for GBM vaccines. For example, evidence that key aspects of brain tumor behavior or malignancy are significantly impacted by T-cell activity could conceivably increase GBM vaccine enthusiasm even without solid Phase III trial data. Such evidence may well come from global genetic analysis of brain tumors using microarray or related technologies. Potential immune metrics already exist within many

GBM microarray databases, and have already contributed to detailed information on GBM etiology [15,16]. Further studies could identify genetic subgroups likely to benefit from DC vaccination, and provide insight into how immune metrics relate to GBM therapeutic sensitivity, malignancy and prognosis. For example, the relationship between immune and chemosensitivity metrics could demonstrate the mechanism of apparent synergy between DC vaccination and chemotherapy in GBM [8,9]. Moreover, the relationship of immunity to elimination of tumors exhibiting stem-like gene expression could be clarified [17,18]. Global genetic analysis may thus provide a means to test whether immunity impacts or is impacted by multiple GBM phenomena in unprecedented detail.

Relatively minor refinements in technology and/or focus could also enhance corporate as well as scientific enthusiasm for GBM DC vaccines. For example, dispensing with the use of tumor lysate could significantly decrease both manufacturing costs of DC vaccines, while increasing antigen definition and allowing pinpoint immune monitoring. Unfortunately, single peptide antigens that are universally expressed on GBM cells and are indispensable for tumor growth have yet to be identified, although clinical testing of the single antigen vaccine paradigm is underway [19]. Synthetic peptide antigen cocktails may be a useful compromise in this regard. Clinical studies to assess the feasibility of this approach are also underway.

**“...a recent Phase II dendritic cell vaccine study presented evidence of progressive correlations between clinical and immunological metrics in glioblastoma multiforme patients.”**

Establishing the best immunological monitoring strategy to employ after vaccination would represent another technological refinement that could heighten corporate and scientific enthusiasm for DC vaccines as well, since this could also profoundly impact assignment of clinical benefits to treatment specifically. The current lack of consensus over immune monitoring in cancer immunotherapy is likely to be influenced by a predominant lack of correlation between any immune metric and clinical outcomes in non-CNS cancer vaccine trials. In this context, the progressive correlation between immune assay and clinical parameters observed in recent GBM vaccine trials could conceivably guide the development of more informative immune monitoring methods. For this reason, studies to further characterize immune effectors measured in such assays are underway.

The ultimate technological advance to increase access to therapeutic cancer vaccines would come from converting to molecular-based technologies as effective as DCs. Strategies to mobilize and activate endogenous DCs to tumor antigens *in vivo* via administration of synthetic antigen plus endogenous DC-promoting factors such as *TLR* agonists or heat shock proteins may eventually make this a possibility, but their development is only at an early stage. Owing to this, it is anticipated that the biggest expansions in glioma vaccine accessibility over the next 5 years will come from consolidating, optimizing and/or adapting existing

manufacturing paradigms beyond academic medical centers. From an organizational standpoint, this can be achieved through greater partnering of clinical operations with established centralized facilities capable of performing key manufacturing, quality control and/or immune monitoring functions associated with DC vaccines.

When, or if, convincing evidence is provided that DC vaccines and/or T-cell activity significantly improve clinical metrics in GBM, the field can reasonably expect greater acceptance of immunotherapy. This is simply owing to the lack of minimally toxic and effective treatments currently available for this disease. Greater acceptance will include greater financial support for advanced clinical trials, accompanied by proliferation of centralized cellular manufacturing entities at strategic locations, provided their technological and organizational shortcomings can be minimized. We should also expect a shift in the vaccine science community from characterizing what is wrong with the immune system in these patients, to identifying effectively working components of beneficial immunity after vaccination. This is arguably a safer strategy for immunotherapeutic improvement even in the absence of solid clinical findings, because there are myriad ways that anti-tumor

immunity can fail in this patient group [20–22]. Conversely, there may be far fewer ways anti-tumor immunity can succeed in GBM patients, and identifying them may allow us to further enhance GBM immunotherapy. Similarly, a more subtle scientific shift from studying how tumors prevent induction of beneficial anti-tumor immunity, to how GBMs acquire resistance to immune activity, can also be expected as these tumors readily acquire resistance. In an ideal world, such a scenario would lead to progressive improvement of GBM immunotherapy over the next 5 years, to the extent that we may for the first time be able to reasonably expect GBM treatment, rather than GBM demography, to best predict disease outcome.

#### Financial & competing interests disclosure

*The author is the holder of patent WO/2005/043155, 'System and method for the treatment of cancer, including cancers of the central nervous system', which describes combining dendritic cell vaccination with chemotherapy to treat high-grade gliomas. 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 apart from those disclosed.*

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• of interest

•• of considerable interest

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