OncoImmunology 2:1, e23687; January 2013; © 2013 Landes Bioscience

Victories and deceptions in tumor immunology
Stimuvax®

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Keywords: CTLA4, ipilimumab, L-BLP25, mucin 1, non-small cell lung carcinoma, PD1

Abbreviations: MUC1, mucin 1; NSCLC, non-small cell lung carcinoma; TAA, tumor-associated antigen

The last year closed with negative news for tumor immunology. Stimuvax®, an investigational therapeutic anticancer vaccine that Merck licensed from the US biotech firm Oncothyreon, failed to increase overall survival in a Phase III clinical trial designed to evaluate its efficacy in a cohort of non-small cell lung carcinoma (NSCLC) patients.[1] Stimuvax®, also known as L-BLP25 or BLP25, is a liposomal vaccine conceived to generate an immune response against mucin 1 (MUC1), a cell-surface glycosylated phosphoprotein that is frequently overexpressed by epithelial tumors, including NSCLC as well as breast, colorectal and pancreatic carcinomas.[2] The failure of this Phase III clinical trial may be attributed to multiple distinct causes.

First, it may be an illusion to achieve therapeutic effects with anticancer vaccines in patients affected by advanced tumors without simultaneously employing checkpoint inhibitors (such as anti-CTLA4 or anti-PD1 antibodies)[3,4] or without attempting to re-establish immunosurveillance by other manipulations.[5,6] Indeed, the progression of neoplastic lesions until an advanced (metastatic) stage is believed to require the subversion of natural anticancer immune responses, either as malignant cells actively inhibit immune effectors or upon the generation of escape variants that are not recognized by the immune system or are resistant to its attack.[7]

Second, NSCLC may represent a class of tumors that is particularly resistant to all sorts of immunotherapy. Indeed, there are relatively few studies postulating that the intra- or peritumoral infiltration of NSCLC by effector memory T cells would influence patient prognosis.[8] In this sense, NSCLC differs from many other tumor types in which the density, composition and architecture of the immune infiltrate does affect the course of disease at both the prognostic and predictive level.[8–10] Unfortunately, individuals affected by NSCLC are usually treated with chemotherapeutic regimens based on cisplatin, a platinum derivative that is rather inefficient, as (1) it is often associated with the development of chemoresistance,[11] and (2) it induces a non-immunogenic form of cell death.[12] Thus, chemotherapeutic regimens against NSCLC cannot be expected to stimulate major anticancer immune responses.

Third, Stimuvax® may have been designed in a suboptimal fashion. Indeed, given the propensity of malignant cells to undergo immunoediting and generate escape variants,[7] it may be a mistake to conceive vaccines that target one single tumor-associated antigen (TAA) instead of attempting to generate a broader immune response. Along similar lines, the adjuvant employed for Stimuvax® (a monophosphoryl lipid A-based formulation) might have negatively influenced its clinical performance, as adjuvants dictate both the intensity and the type of immune responses to considerable extents.[13,14]

Fourth, the design of the clinical trial may have been overoptimistic, as NSCLC patients have not been filtered at enrollment based on biomarker-based exclusion criteria. For instance, it might have been worthwhile to monitor MUC1 expression levels on surgical/bioptic material (and to exclude patients bearing MUC1-negative tumors); to determine the general immune status of patients (and to exclude individuals exhibiting low peripheral T lymphocyte counts or high levels of circulating or intratumoral immunosuppressive cells); and/or to evaluate immune responses against MUC1 or other TAAs at baseline (and to exclude patients with poor TAA-specific responses).[15]

In a press release, the coordinating investigator of the study, Frances Shepherd (University of Toronto, Canada) stated that "notable treatment effects were observed in certain subgroups of patients." Obviously, such subgroup analyses will not reverse the deception of this trial in its legal aspects (FDA approval is precluded at this stage). However, they may convert this defeat into a long-term victory, provided that additional prospective, carefully designed Phase III trials yield positive results. Hopefully, Merck's competitor GlaxoSmithKline, which has also launched a clinical study to investigate the efficacy of a therapeutic vaccine against NSCLC, will be more fortunate and learn the lessons exemplified by the Stimuvax® case.

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Submitted: 01/14/2013; Accepted: 01/14/2013
http://dx.doi.org/10.4161/onci.23687
Citation: Kromer G, Zitvogel L, Galluzzi L. Victories and deceptions in tumor immunology: Stimuvax®. OncoImmunology 2013; 2:e23687

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