

## Therapeutic Cancer Vaccines

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In the past decade there have been a number of attempts to develop biological therapies against cancers by means of vaccines or adoptive immunotherapy. Clinical trials usually accrue cancer patients with advanced stage disease who need an effective therapy. Considering that vaccines against infectious diseases have been successful mainly in prophylactic settings rather than in therapeutic settings, the question is whether there is any hope for the development of therapeutic vaccines against cancers. Unlike infectious diseases, cancers arise from our own cells towards which the immune system has been tolerized. Therefore, an effective immune responses against cancer would be most difficult than it is against infectious diseases.

Recent reports by our group and others have shown that the status of the immune response can determine the outcome in cancer patients. For instance, we have shown that presence of a signature of immune function genes at the tumor microenvironment can predict relapse free survival following conventional therapies in breast cancer patients [1]. Interestingly, these patients concomitantly upregulated the expression of genes involved in primary immunodeficiency signaling, T-cell apoptosis, CTLA4 signaling and production of NO, and reactive oxygen species [1]. Such paradoxical findings as to simultaneous presence of immune effectors and immune suppressors suggest that tumor-derived factors may be responsible for the expression of immune suppressor genes thereby facilitating tumor growth even in the presence of the immune effectors. However, removal of breast tumors by conventional therapies may eliminate the source of immune suppressive factors and result in the decline of suppressor cells; subsequent rescue of the immune effectors would then protect the patients from their residual micrometastases and relapse. This possibility is supported by recent report as to the association of myeloid-derived suppressor cells (MDSC) with the stage of breast cancer [2] as well as the observation that primary tumors were the source of increases in MDSC [3]. A successful immunotherapy was not possible unless MDSC were depleted or reduced by chemotherapy or shrinking of the primary tumors [4].

There are also reports challenging immunosveillance theory by showing that immune compromised mice were not at a greater risk of developing spontaneous breast cancer compared to their immune

competent counterparts [5]. In fact, immune competent mice were not able to mount an effective immune response against their tumors.

Controversial reports as to the positive role or neutral role that immune system may play in controlling cancer development suggest the key role for tumor immunogenicity. While immunogenic tumors may elicit anti-tumor immune responses weakly immunogenic tumors may fail to do so. In this case, vaccination in a neoadjuvant setting may induce immune responses against weakly immunogenic tumors, and when combined with conventional therapies for the removal of primary tumor as a source of driving suppressor cells, can protect cancer patients from recurrence of metastatic tumors. In summary, therapeutic cancer vaccines preceding conventional therapies may show more promising results compared with vaccines alone.

### Acknowledgements

This work was supported by Virginia Commonwealth University Presidential Research Incentive Program (PRIP). We gratefully acknowledge the support of VCU Massey Cancer Center and the Commonwealth Foundation for Cancer Research.

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Received August 24, 2011; Accepted August 31, 2011; Published September 05, 2011

Citation: Manjili MH (2011) Therapeutic Cancer Vaccines. *J Clin Cell Immunol* 2:e101. doi:10.4172/2155-9899.1000e101

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