University of South Florida physicians have developed a promising anti-cancer vaccine. Safety has been demonstrated in a Phase I clinical trial and three Phase II clinical trials to treat a variety of malignancies have been completed and show promising results.

Over the past several decades, the use of conventional chemotherapy has yielded incremental progress in the treatment of advanced cancers. More recently, developments in anti-cancer research have elucidated the potential of using cancer vaccines as anti-cancer immunotherapeutic strategies. The immune system has the ability to recognize and eradicate tumor cells; however, many tumors have developed mechanisms to evade recognition.

The cancer vaccine developed by our researchers aims to overcomes tumor cell evasion from immune recognition. This vaccine utilizes cells engineered to secrete granulocyte-monocyte colony-stimulating factor (GM-CSF) and CD40L, which stimulate differentiation and activation of dendritic cells (DCs; see Figure). These genetically engineered cells are mixed with irradiated allogeneic (“off the shelf”) or autologous tumor cells and administered to the patient. The GM-CSF and CD40L stimulate differentiation and activation of DCs, which are hypothesized to present the tumor proteins (antigen) from the irradiated tumor to the patient’s T cells and stimulating the T cells, thereby eliciting tumor-specific immune responses.

Advantages:
- Vaccine utilizes both GM-CSF and CD40L to recruit and activate dendritic cells and can elicit tumor-specific T-cell responses in vitro and in vivo.
- Uses allogeneic (“off the shelf”) or autologous tumor cells as source of antigen.
- Phase I and three Phase II clinical trials now completed.

Vaccine stimulates tumor regression and anti-cancer immune activity.

22 of 23 vaccinated patients with mantle cell lymphoma had partial responses (15) or molecular and pathologic complete responses (7). Two patients with partial responses also demonstrated eradication of molecular disease within the bone marrow only after vaccination (one patient response shown above). Vaccination followed chemotherapy for all patients in study.
The technology is a tumor vaccine developed by USF faculty that has demonstrated safety in Phase I clinical trials, and has also demonstrated positive results in Phase II trials for a variety of cancer types.

This novel vaccine combines cells genetically engineered to secrete GM-CSF and express CD-40L (GM.CD40L bystander cells) with irradiated autologous or allogeneic tumor cells to stimulate anti-tumor immune responses in cancer patients.

**Preclinical:** In preclinical studies, significant anti-tumor T cell responses were generated in vitro when human lymphocytes derived from tumor-draining lymph nodes were stimulated with autologous tumor cells in the presence of the GM.CD40L bystander cells. Dendritic cells were also demonstrated to be activated following incubation with the vaccine. *Journal of Surgical Research* 2005 May 15; 125(2): 173-81. Epub 2005 Jan 28. PMID 15754671

**Phase I:**
In the first Phase I clinical trial, patients with a variety of stage IV cancers received 3 intradermal vaccine injections at 28-day intervals. The results of this trial demonstrated that the vaccine was safe, and that it elicited immunological and clinical responses in some patients. *Annals of Surgical Oncology* 2007 February; 14(2): 869-884. Epub 2006 Nov 14. PMID 17103257

Recently another Phase I dose escalation pilot study using GM.CD40L vaccine in combination with lenalidomide in International Prognostic Scoring System (IPSS) intermediate and high risk myelodysplastic syndrome (MDS) patients who failed hypomethylating agents was also conducted. In this study, the irradiated GM.CD40L transfected K562 cells themselves were the source of tumor antigen as they were originally derived from a CML patient. GM.CD40L was subcutaneously injected in the axillary nodal basin of subjects on days 8 and 22 of a 28-day cycle for a total of four cycles. Lenalidomide was administered at a daily dose of 10mg on days 1 through 21 every 28 days until disease progression or limiting toxicity. The dose escalation of vaccine was 10 x 10^6 cells in cohort 1, 30 x 10^6 in cohort 2, 60 x 10^6 in cohort 3 and 120 cells x 10^6 in cohort 4. Responses were measured using the international working group criteria (IWG) 2006 for MDS. Dose limiting toxicity (DLT) was reached in cohort 4 (120 x 10^6). One patient developed grade 3 dyspnea and fatigue after one injection of vaccine. Grade 1 toxicities were observed in all cohorts (rash, myelosuppression, nausea, vomiting, and fatigue). The IWG response rates were complete response (CR) in 2/11 (18%), marrow CR (1/11) (9%), and partial response (PR) in 1/11 (9%). The overall response rate was 4/11 (36%). In all patients who achieved a CR the median duration of response was 367 days (136-490). Complete durable responses suggest a therapeutic signal outside of lenalidomide alone. *Poster presented at American Society for Hematology 2010 meeting*

**Phase II:** Three Phase II clinical trials have been completed. The studies were designed to test the impact of this vaccine on anti-tumor responses, tumor progression, and overall survival of patients with: 1) malignant melanoma, 2) lung cancer (adenocarcinoma), and 3) mantle cell lymphoma. The results of these trials are summarized below:

Patients with Stage IV melanoma, a highly aggressive form of cancer, received 3 intradermal vaccine injections (irradiated autologous tumor cells plus GM.CD40L) at 28-day intervals. Patients with no disease progression received 3 additional vaccines at 28-day intervals. 28 patients were vaccinated on protocol. 18 received at least 3 injections, and 8 of these had stable disease by RECIST criteria after the third vaccine. ELISPOT analysis of PBMCs revealed measurable increases in anti-tumor immune responses after the third vaccine dose in 3 patients. One patient developed a partial response after the sixth vaccine, correlating with enhanced IFN-γ production in ELISPOT assays. Another patient developed transient vitiligo-like depigmentation that was associated with measurable expansion of MART-1-reactive CD8 T cells in the peripheral blood.

Patients with extensive stage non-small cell lung cancer were treated with vaccine (GM.CD40L combined with irradiated allogeneic lung cancer cells), cytoxan, and all-trans retinoic acid (ATRA). There were no clinical responders according to RECIST criteria, however there are two long term survivors.

In the Mantle Cell Lymphoma trial, patients were treated with vaccine (GM.CD40L combined with irradiated autologous tumor cells) after chemotherapy, a minimal residual disease setting. Vaccinated patients demonstrated a prolonged overall survival rate. Furthermore, the five year survival rate of the vaccinated patients was 75% as compared to 50% of what is predicted by the MIPI prognostic index. This effect was observed even amongst high risk subgroups. An increased tumor-specific immune response following vaccination was observed in several patients, as determined by IFN-γ ELISpot. This response was associated with an increase in progression free survival.