## Harnessing the immune system to treat cancer – A reality at last

**Kapil Dhingra MBBS, KAPital Consulting LLC, NJ, USA**

The development of cancer is in part related to an inability of the immune system to recognize cancer cells as foreign and eliminate them. Commonly used cancer therapies, such as chemotherapy and radiotherapy are associated with significant toxicities, especially as their non-selective mechanism of action leads to adverse effects on normal tissues. The immune system has evolved during the course of evolution to selectively destroy noxious agents. However, most attempts at harnessing the immune system to target cancer cells proved to be mostly a fond hope. In particular, systemic administration of broadly acting cytokines such as alpha interferon and interleukin-2 showed significant toxicity with only modest efficacy, with few notable exceptions, e.g. CML, hairy cell leukemia and occasional patients with melanoma and renal cell carcinoma. Nearly all therapeutic cancer vaccines failed in pivotal phase III trials, even when the data from early clinical trials seemed quite promising.

The tide has started to turn over the last decade with several successes in late stage trials and with numerous new promising approaches in early development. Interestingly, a variety of diverse immunological approaches appear to be succeeding at the same time. Several monoclonal antibodies have been on the market for a decade to treat common tumors. While several of these inhibit signal transduction, there is clear and convincing evidence for the contribution of immune effector mechanism to the observed clinical efficacy of others, e.g. Rituxan/Mabthera. This has led to exploration of a variety of antibody engineering strategies to enhance their anti-cancer effects. Among the most promising approaches are those being pursued by Glycart and Micromet. A glycoengineered CD20 antibody optimized for ADCC and apoptosis has shown promising results in patients groups not expected to generally respond to rituximab. This is now in phase III trials. Bispecific T-cell engaging antibodies have been shown to be among the most potent anticancer agents in clinical development today and the first drug candidate from this platform has moved to pivotal trials.

Recently, the first therapeutic cancer vaccine has successfully completed phase III trials. Provenge (sipuleucel) demonstrated a 4 months improvement in survival in patients with castration refractory prostate cancer. An alternative proof of principle for breaking the tolerance of immune system to cancer has been provided by the survival benefit observed in patients with melanoma treated with iplimumab, an anti-CTLA4 antibody. Promising early results have also been observed with an anti-PD1 antibody.

Oncolytic viruses provide an innovative approach to achieve direct killing of antitumor cells with concomitant induction of anti-tumor immunity. A number of viral constructs are in development. The most advanced among these is Oncovex. This is a modified HSV that led to a 28% response rate in patients with metastatic melanoma. Importantly, the durable response rate was 20%. Even more significant was the observation of shrinkage of distant uninjected lesions in several patients, including those with deep seated lesions. This is presently in phase III trials with initial results expected in 2011.

The momentum provided by these successes has led to a resurgence of interest in exploring a diversity of next generation approaches. It is now realistic to expect that a number of immunotherapies with make it to routine clinical use to treat a variety of cancers in the near future.