Novel cell penetrating formulation of cytotoxic agents administered intratumorally causes complete regression of large tumors and stimulation of an adaptive immune response in BALB/c syngeneic mice inoculated subcutaneously with murine CT26 colon cancer.

Lewis H. Bender*1, Jay A. Berzofsky, M.D., Ph.D.2, Masaki Terabe, Ph.D.2

INTRODUCTION
In 2013, the NIH estimated that over 585,000 Americans died of cancer (90% from late stage). Cancer is the second most common cause of death in the US. When surgery is not possible the main treatment option is to use chemotherapy. Yet for late stage or metastatic disease long term patient survival is extremely low and treatment toxicity is high. Here we describe a new immune-based methodology; in situ chemovaccination. In this approach a novel drug product; INT230-6, (containing 0.5 mg/mL of cisplatin, 0.1 mg/mL of vinblastine formulated with an amphiphilic, cell-penetrating excipient; IT-006 at 10 mg/mL) demonstrates a local ablative effect on large murine tumors and stimulation of an adaptive immune response when dosed intratumorally (IT).

FUNDAMENTAL PROBLEMS OF CURRENT CHEMOTHERAPY EFFECTIVENESS
Cytotoxic drugs need to disperse throughout a tumor and enter the cells. Many standard agents enter cells via receptors. Cancer cells are highly resistant to drug diffusion. Often cell death requires high intracellular drug levels.

CURRENT CHEMOTHERAPY EFFECTIVENESS

Often cell death requires high intracellular drug levels.

We conducted a study in syngeneic female BALB/c mice inoculated subcutaneously (SC) with 1x10⁶ CT26 cells. Tumors grew to mean volumes of 325mm³ predose. The study comprised four groups: 1) no treatment, 2) INT230-6 given IT, 3) the drugs given intravenously (IV) alone and 4) the drugs given IT without the excipient. Animals in the IT treatment groups received 0.1 mL per 400mm² of tumor volume for 5 days. IT & IV doses were comparable. There was no adjustment for body weight. Tumor growth inhibition was best observed in the group given INT230-6.

CR animals along with naïve controls were re-inoculated SC with 1x10⁶ CT26 cells then IV. Nearly ninety percent of the CR animals were fully protected against both SC and IV re-inoculation.

DISCUSSION & CONCLUSIONS

The observed long-term protection against CT26 cancer re-inoculation may be due to an adaptive immune response induced by the dying tumor cells. Thus in situ chemovaccination using INT230-6 may be an improved method to treat late stage and metastatic cancer.