J Nanomed Nanotechnol 2013, 4:6
http://dx.doi.org/10.4172/2157-7439.S1.015

OMICS Group Conferences
Accelerating Scientific Discovery

3rd International Conference on
Nanotek & Expo

December 02-04, 2013 Hampton Inn Tropicana, Las Vegas, NV, USA

Engineering PEGylated gold nanoparticles for tumor target drug delivery

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One of the most effective treatments for solid organ malignancies is a surgical procedure known as isolated limb and organ perfusion (ILP) in which a vascular disrupting agent, such as Tumor Necrosis Factor Alpha (TNF) and chemotherapy are perfused through a tumor-bearing limb. A single treatment with this combination, albeit delivered through heroic surgical perfusion, results in 60-85% response rates in cancer patients that are refractory to conventional therapies. Key to the success of ILP is not only the semi-targeted delivery of TNF and chemotherapy, achieved by the surgical perfusion, but the temporal sequence in which these active pharmaceutical ingredients (APIs) are administered.

Briefly, the preclinical data reveal that the delivery of TNF must precede that of the chemotherapy, as its initial delivery induces near instantaneous vascular leak within the tumor vasculature and a concomitant reduction in the interstitial fluid pressure (IFP) within the tumor. The elimination of the IFP gradient enhances uptake and efficacy of the follow-on chemotherapy. Nevertheless, as promising as ILP appears it only represents a regional solution for treating solid tumors without broad application to disseminated disease.

In an effort to achieve results similar to ILP CytImmune Sciences has, over the past decade, engineered 27 nm particles of PEGylated colloidal gold, into a family of tumor targeting nanomedicines. Each nanomedicine is designed to address specific barriers of drug delivery in the treatment of solid tumors.

The first of these nanodrugs is termed CYT-6091 targets the delivery of TNF as a single agent to solid tumors. To date the sum of our preclinical data show that CYT-6091, by targeting the TNF to the site of disease, induces progressive disruption of the tumor neovasculature resulting in potent anti-tumor responses. Furthermore, in our recently completed phase I clinical trial we report that CYT-6091, when administered intravenously, is well tolerated, traffics to solid tumors, and increases overall exposure to TNF without inducing the dose-limiting toxicity of the cytokine, hypotension. With CYT-6091 we are generating clinical proof of concept for the use of colloidal gold nanoparticles for the development of systemically administrable

Building on the early success of CYT-6091 our second-generation nanomedicine, CYT-20000, is engineered to deliver not only TNF but also chemotherapy to solid tumor. Our preclinical data support CYT-20000 may fully replicate the ILP paradigm as the TNF mediated targeting, afforded by the particle bound TNF, precedes the release of the of active chemotherapy from the particle.

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