***In Vivo* Toxicity Study of Gold Composite Nanodevices for use in Imaging and Radiotherapy.**

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Composite nanodevices (CNDs), with PAMAM dendrimer and inorganic metal components, are currently being developed as an exciting nanoplatform for several types of molecularly targeted cancer therapy and imaging (Khan, Nigavekar et al. 2005; Balogh and Khan 2007; Khan, Minc et al. 2008). We utilize gold composite nanodevices (Au-CND), as ^{198}Au has already been used in radiotherapy. Due to the unique chemical structure of dendrimers, one can attach chemical moieties of interest on the surface and/or incorporate metal atoms or therapeutic compounds inside the dendrimer molecules to form composite nanodevices with specific use(Balogh and Khan 2007; Tomalia, Reyna et al. 2007).

We previously reported on the *in vitro* toxicity assessment of differently charged dendrimer-gold nano-composites on normal cells (human endothelial cells) and prostate cancer cells (Khan, Kariapper et al. 2008). In this study we evaluate the *in vivo* toxicity of differently charged dendrimer-gold composite nanodevices in mice. *In vivo* clinical toxicity study includes daily observation and behavior of mice, weight, Hematologic assessment of blood, serum clinical chemistry analysis, and histological examination of organs that are collected after periods of 2 weeks (acute toxicity) and 3 months (late toxicity).

Little data exists regarding the toxicity of nanoparticles, and very little on nanocomposites. Prior to any human use, these devices need to be evaluated for *in vivo* toxicity. This study demonstrates the extent of in vivo safety (lack of toxicity) of these gold-dendrimer composite nanodevices. We have shown that even though certain nanodevices appeared to have the potential for toxicity in vitro, they do not appear to show any measurable

toxicity *in vivo*. It is critical to carry out detailed *in vivo* toxicity studies (early and late) and to develop better in vitro assays of toxicity.

Keywords: PAMAM composite nanodevice, *in vivo* toxicity, cancer therapy.

ACKNOWLEDGMENTS

We acknowledge Dr. Peter Kanter of Roswell Park Cancer Institute for all his help in toxicological evaluation, mouse autopsies and analysis during this study. This research was partially funded with Federal Funds from the Department of Defense grant (DAMD17-03-1-0018) and the National Institutes of Health (NIH)/National Cancer Institute (R01-CA-104479-01).

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