Final progress report:

Our proposal hypothesized that thermosensitive liposomes (TSLs) laden with gold nanoparticles (GNPs) that accumulate within cancers via their leaky vasculature will release their payloads when stimulated extrinsically with focused ultrasound (FUS) to generate mild hyperthermia. This, in turn, leads to radiosensitization that is independent of the effect of hyperthermia on radiosensitization, but is mediated by deep-penetrating GNPs and the radiation dose enhancement by secondary photo- and Auger electrons. Towards this end, we had proposed three specific aims, namely:

1. To determine the mechanism of radiosensitization by GNP-laden TSLs activated by FUS-mediated hyperthermia with a particular emphasis on defining the quantity of gold within tumors and its intratumoral biodistribution in fibrogenic tumors.
2. To distinguish between radiosensitization due to hyperthermia and that due to triggered release of GNPs by using non-thermosensitive liposomes *in vivo*.
3. To define optimal parameters for maximal synergy between radiation and released GNPs.

As outlined in the 6-month progress report, we have tested three strategies to evaluate penetration of nanoparticles within tumors. First, we compared tumor core and tumor periphery concentrations of gold in mice systemically administered with TSLs and then subjected to FUS hyperthermia or not. In the first approach, we looked at ICP-MS of tumor core and periphery. There was greater accumulation in the tumor core after hyperthermia than without hyperthermia. This was corroborated by TEM where there were more GNPs in the tumor core after hyperthermia than without hyperthermia. Lastly, when TSLs were constructed with rhodamine-PE in their lipid bilayer, there was greater fluorescence deep within tumor cores after hyperthermia than without. Collectively, these observations lend credence to the notion that hyperthermia results in deep penetration of GNPs within tumors.

We have then performed a radiosensitization study with multiple controls to establish whether deep penetration contributes to the radiosensitization of tumors treated with GNPs in TSLs deployed by hyperthermia and then irradiated. Our results suggest that hyperthermia contributes to radiosensitization but the deep penetration of nanoparticles amplifies this radiosensization.

Future plans – While deep penetration results in radiosensitization with small quantities of gold, we predict that cellular internalization may enhance this effect even further. We therefore plan to load peptide-conjugated GNPs within the liposomes so that once deployed and free to penetrate deep within tumors, the conjugated GNPs will get internalized and secondary electron showers from internalized GNPs will be closer to DNA and cause greater radiosensitization. Another possibility is that chemotherapy can be embedded within the liposome as well.

Publications:
None

Presentations:
Focused Ultrasound Opportunities in Radiation Oncology – Society for Thermal Medicine, May 2014, Minneapolis, MN.

Grants:
Submitted a proposal as one of the main projects in a U54 Nano-Center grant submitted to NCI

Figures:

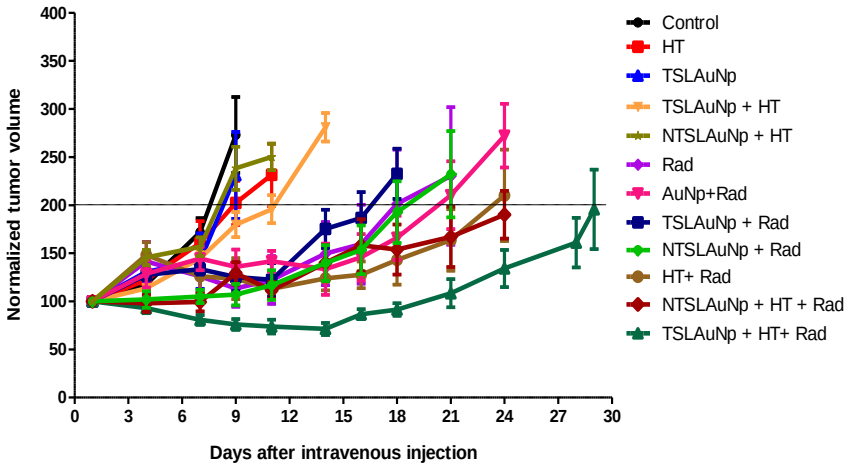

Fig. 1 Tumor regrowth delay curves showing potent radiosensitization