Using Nanomedicine to Potentiate the Effects of Hypofractionation

Robert J. Griffin, PhD – UAMS; Azemat Jamshidi-Parsian, MS – UAMS; Ruud Dings, PhD – UAMS; Samir Jenkins, PhD – UAMS

Objectives: We are studying the potential of radiotherapy to generate electrons from a nanoparticle to activate a photosensitizer coated on the particle surface, leading to potent free radical-induced cellular damage and cytotoxicity. The particle/photosensitizer hybrid can be directly inoculated into the tumor volume before radiation exposure. Photodynamic therapy uses light to activate a photosensitizer molecule to generate reactive oxygen species, particularly singlet oxygen, and destroy tissue in the region. Enhanced therapeutic effects have been seen when nanoparticles have been used to deliver the photosensitizer to the tumor, but the major limiting factor in photodynamic therapy is the penetration depth of the activating light. Recent work in the literature has shown the potential of combining radiation with photodynamic therapy, using light emitting particles that contain lanthanide salts, yet these have toxicity concerns. Therefore, we are working to avoid using toxic materials and instead exploit the free radical generation and energy transfer from gold particles. The underlying hypothesis of this project is that by virtue of conformal treatment planning to the tumor volume, radiation dose to the targeted tissue can be enhanced while sparing the surrounding normal tissue, which will result in increased therapeutic index. Adjacent normal tissue is spared through the combination of standard treatment planning and a radiation activated therapeutic. We are testing this system initially in head and neck, lung, and pancreatic tumor models, as these lesions are frequently treated with radiotherapy.

Methods: The SCCVII murine head and neck carcinoma was used to study clonogenic response in vitro and test the combined anti-tumor effects of radiation and particle direct injection in vivo. The particle was synthesized by coating commercially available gold nanospheres of ~50 nm average diameter, or custom-made gold nanocages of ~70 nm average diameter with the FDA-approved photosensitizer Chlorin e6. The photosensitizer was covalently bound to the gold particle surface by using thiolation chemistry and stability was verified using spectrophotometry. The particles were injected in 50 pM aliquots directly into the center of tumor 2 h before radiation exposures began. Radiation was delivered by an XRad 320 kV irradiation chamber to the tumor region of mice otherwise shielded by custom made lead barriers at 20 Gy single dose or 2 x 10 Gy daily or 4 X 5 Gy daily.

Results: Our initial results indicated significant reduction at 6 Gy in clonogenic survival in tumor cells exposed to the hybrid particle compared to any single modality. In addition, tumor growth delay was slightly increased when the particles were injected intratumorally followed by localized high single dose radiotherapy and markedly increased when daily fractions of 5 Gy are administered after a single particle injection. In the combined treatment group 4 out of 6 tumors have not regrown after 30 days. Approaches to further improve the photosensitizer coating and particle used for delivery and the rationale for use of hypofractionated radiotherapy to maximize anti tumor effect will be highlighted.

Conclusion(s): Our patented combination nanoparticle approach has the potential to significantly enhance the effect of radiation therapy delivered to 3D treatment volumes at high doses per fraction. This may translate to dose reduction, and sparing normal tissue by virtue of less particle uptake in non-cancerous tissue and sub-activation radiation doses outside of the planned treatment volume. The substantial increase in tumor response when fractionated radiation is applied after tumor injection of the hybrid particle suggests realistic clinical potential and possible long term immune activation.