International Journal of Medical Physics, Clinical Engineering and Radiation Oncology, 2015, 4, 300-307
Published Online November 2015 in SciRes. http://www.scirp.org/journal/ijmpcero
http://dx.doi.org/10.4236/ijmpcero.2015.44036

Comparative Study of Experimental Enhancement in Free Radical Generation against Monte Carlo Modeled Enhancement in Radiation Dose Deposition Due to the Presence of High Z Materials during Irradiation of Aqueous Media

Nava Paudel[1,2], Diana Shvydka[1], E. Ishmael Parsai[1]

[1]Department of Radiation Oncology, The University of Toledo Medical Center, Toledo, OH, USA
[2]Department of Radiation Oncology, University of Arkansas for Medical Sciences, Little Rock, AR, USA
Email: e.parsai@utoledo.edu

Received 3 July 2015; accepted 7 November 2015; published 10 November 2015

Abstract

Purpose: To investigate conflicting results demonstrating higher cell-kill by irradiated high atomic number (Z) material, gold (Au) in tumor compared to Monte Carlo (MC) modeled enhancement in radiation dose deposition, and to compare the difference between radiosensitizing effects of gold and platinum. Methods and Materials: Since a majority of cell kill due to radiation is mediated by free radicals, evaluation of radicals generated from radiolysis of an aqueous medium can provide some insight into cell-kill. Here, free radicals generated due to the radiolysis of water by a clinical Iridium-192 (Ir-192) brachytherapy source in the presence and absence of thin and pure gold or platinum wires were quantified with electron paramagnetic/spin resonance (EPR/ESR) spectrometry and enhancements in free radical generation due to the presence of the wires during radiolysis were calculated. Those enhancements were compared against MC modeled enhancement in radiation dose deposition obtained from the geometry replicating the experimental setup. Results: Enhancements in free radical generation due to 100 and 127 μm diameter gold wires, and 127 μm diameter platinum wire were more than two times higher than the corresponding MC modeled enhancements in radiation dose deposition. Enhancement in hydroxyl free radical (OH•) generation due to thicker wires of gold and platinum was close to the enhancements in radiation dose deposition. The effects were similar for gold and platinum wires of equal diameter. Conclusions: Higher enhancement in radical generation compared to MC modeled enhancement in radiation dose deposition due to micron-size pure gold and platinum wires demonstrates that the surfaces

How to cite this paper: Paudel, N., Shvydka, D. and Parsai, E.I. (2015) Comparative Study of Experimental Enhancement in Free Radical Generation against Monte Carlo Modeled Enhancement in Radiation Dose Deposition Due to the Presence of High Z Materials during Irradiation of Aqueous Media. *International Journal of Medical Physics, Clinical Engineering and Radiation Oncology*, **4**, 300-307. http://dx.doi.org/10.4236/ijmpcero.2015.44036

of high Z materials in aqueous media become a secondary source of radicals under radiation field. High surface-to-volume ratio of nanoparticles can make this effect more pronounced, leading to higher cell kill than the predictions based on pure dose enhancement.

Keywords

Hydroxyl Radical, EPR/ESR Spectrometry, Monte Carlo, Ir-192, Nanoparticles

1. Introduction

Indirectly ionizing radiation produces most of the biological damage in tumors through the action of free radicals, especially hydroxyl [1]. Radiation induced cell damage can be enhanced by utilizing biologically compatible high Z materials such as gold [2]-[4]. Studies show that free radicals are responsible for most of the cell damage even in the presence of high Z materials [5] [6]. The effect of high Z materials, extensively studied through MC simulations as well as experiments clearly show significant enhancement in radiation dose deposition in the photoelectric effect dominant low energy range [7] [8]. This effect is mediated by increased production of low energy secondary electrons at their interfaces [9] [10].

Irradiated gold nanoparticles (AuNPs) with some coating or in some chemical environments play a catalytic role in producing reactive species [11]-[13] and hence in radiosensitizing cells. Radiosensitizing effects of AuNPs have also been attributed to low energy Auger electrons for irradiating photon energy below k-edge of gold [14], and to dose inhomogeneity surrounding the AuNPs [15]. However photoelectrons are attributed to this effect for irradiation energy greater than k-edge energy of gold [14]. Analogous to the results with low energy radiation, biological experiments with megavoltage (MV) beam also show higher radiosensitization of high Z nanoparticles compared to MC modeled dose enhancement [16]-[18]. These results suggest some effects other than pure physical dose deposition.

While MC modeling is an established standard for solving radiation transport problems in materials, EPR spectrometry is a standard technique of free radical measurement. Hence these two techniques can provide complementary information on the overall radiation effect in an aqueous medium. We examine the conflicting results of radiosensitization and radiation dose enhancement by measuring the intensity of radiolysis induced OH• radical signal with EPR spectrometry and comparing enhancement in OH• radical generation due to micron thick pure gold and platinum wires against corresponding MC modeled enhancement in radiation dose deposition in aqueous media under Ir-192 high dose rate (HDR) brachytherapy source irradiation. While most of the studies on radiosensitization use nanoparticles with some coating in order to prevent clustering, the unknown roles of the coatings make the analysis complicated. So we use pure gold and platinum micro-wires with no coating and study their role in a bulk volume of aqueous solution.

Platinum and gold have similar Z values. Platinum and platinum based chemotherapeutic agents sensitize tumor cells to radiation [19]-[21]. Comparing the effect of these two materials on enhancing radical generation under irradiation is another objective of this study.

2. Methods and Materials

EPR spectrometry is a standard technique of free radical measurement which uses spin properties of unpaired electrons of free radicals [22]. In this study, a Bruker ESP300E ESR Spectrometer was used to measure free radicals generated in water due to its radiolysis by a clinical Ir-192 (complex spectrum with average energy ~380 keV) HDR source (Varian, VariSource afterloader). Free radicals generated due to radiolysis are highly reactive and have a very short life time (~10^{-6} - 10^{-9} s). This time is too short for any accurate experimental measurement. However they can be trapped long enough (for measurement) with trapping agents to form intermediate molecules called spin adducts and their properties can be preserved for hours to months depending on the temperature [23].

2.1. Experimental Study

Spin trap agent 5,5-dimethyl-1-pyrroline N-oxide (DMPO from Enzo Life Sciences, purity > 97%) was mixed

with deionized water to make 500 mM solution and the solution was injected into a set of 1.2 mm inner (1.5 mm outer) diameter (smallest commercially available dimension) Pyrex glass capillaries. Gold or platinum wires (Alfa Aesar, purity > 99.95%, no coating) were placed longitudinally to fully submerge in the DMPO solution in few capillaries. Capillaries filled with the solution with and without wire were inserted through a hole, 2 mm below the top of a Teflon holder and irradiated to an equal dose by a line source created by multiple dwell positions of the clinical HDR source under identical conditions. The source was set on top of the Teflon holder parallel to the capillary The choice of radiation source and dimensions of wires and capillaries had a two-fold objective: a) maximize surface to volume ratio of wires; b) achieve radiation dose enhancement detectable with our EPR spectrometer in terms of enhancement in free radical generation.

Experimental geometry of irradiation was replicated for a MC study with Monte Carlo N Particle Version (MCNP5). The model is depicted in **Figure 1**.

A number of sample sets were prepared on different days. Each set of samples was divided into three groups: a) group containing DMPO-water only samples; b) group containing 1 or 2 gold wires in each sample (diameter: 100, 127, 250 and 500 μm) and c) group containing 1 platinum wire in each sample (diameter: 127, 250 and 500 μm). Each set contained at least 3 DMPO-water only samples. The number of samples containing gold or platinum wire of a diameter was also at least 3 in each set but not necessarily all diameters were included in a single set as the measurement would take a very long time. So this experiment was conducted with a number of sets prepared on different days and signals were compared among the samples belonging to the same set.

The wires were taken out of capillaries immediately following irradiation to minimize any post-irradiation interaction with radicals and to avoid heating during EPR scanning. Capillaries with irradiated solution were placed in dry ice (temperature: −79˚C) to slow down the decay rate of free radicals. For the measurement of convenience, each sample in a set was brought to room temperature five minutes before EPR spectrometry and scanned with the spectrometer under identical conditions including constant frequency microwave (9.68 GHz), constant microwave power (12.5 mW) and variable magnetic field (3440 - 3520 Gauss). Intensities of free radicals generated by irradiating 500 mM DMPO water in the presence of high purity gold or platinum wires were compared with those from the capillaries without wires (from the same set) to obtain enhancement in free radical generation. Average percentage enhancement in free radical generation was obtained from a number of sample sets and compared against corresponding MC modeled percentage enhancement in dose deposition in water. However the presence of DMPO was ignored in MC modeling as its effects at the concentration used in this experiment were negligible.

2.2. Monte Carlo Study

For the MC study, a clinical Ir-192 source spectrum was modeled, 10^7 particles were run with both photon and electron cutoff energies set to 10 keV and a detailed secondary electron transport model was utilized to account for all possible interactions. Energy deposited in water in the presence and absence of wires was tallied and error in each simulation was kept below 1%. [24] Dose enhanced by the wires in water was calculated from the tallied energy deposited obtained from the simulation.

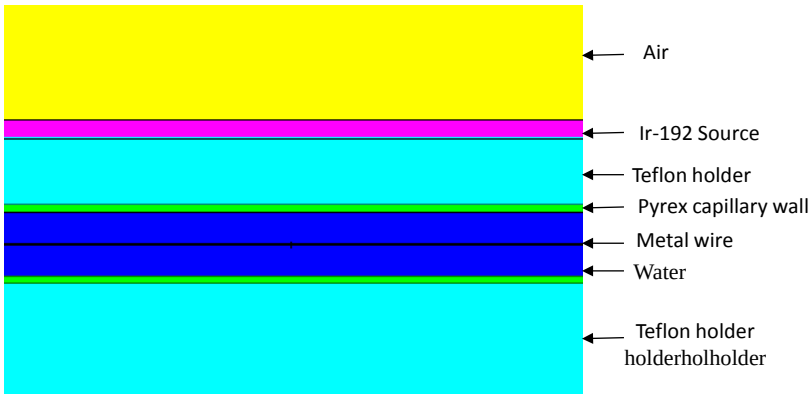

Figure 1. Geometry of sample irradiation with Ir-192 source; also used for MC study of dose enhancement.

3. Results

A number of empty capillaries were irradiated to 50 Gy and scanned with EPR spectrometer to check any impurity in the capillaries and no evidence of inherent radical was found.

In our experiment, free radicals generated during radiolysis of water were captured with DMPO to form spin adducts.

$$\mathrm{DMPO} + \mathrm{OH}\bullet \rightarrow \mathrm{DMPO} - \mathrm{OH}\bullet \quad (1)$$

Equation (1) represents the capture of OH• by DMPO to form a spin adduct DMPO-OH• [25]. Similarly DMPO can capture hydrogen radical (H•) to form DMPO-H•. Both of these adducts can be identified with their unique spectra and detected with EPR spectrometry but DMPO-H• was excluded in our study as its spectra from few samples were noisy. A typical DMPO-OH• spectrum obtained experimentally with EPR spectrometer is presented in **Figure 2**.

The four tallest peaks in **Figure 2** belong to DMPO-OH• and the 3 peaks in between them belong to DMPO-H• [26]. Intensity ratio of the peaks in the DMPO-OH• spectrum is 1:2:2:1 and the adjacent peaks are separated by 14.9 Gauss due to equal hyperfine structure constants of nitrogen and hydrogen ($a_N = a_H = 14.9$ Gauss) [25]. EPR spectra, represented as first derivatives of intensity were double integrated to obtain the corresponding signal intensity of radicals [22]. Intensity of radicals generated due to radiolysis depends on the absorbed dose. The dose dependence was verified by plotting radical intensity against dose delivered as shown in **Figure 3**.

Figure 3 demonstrates that the radical generation in water increases with the increase in absorbed radiation dose. It increases linearly at lower dose and saturates at higher dose. Based on this calibration curve, 10 Gy from the linear region was chosen for the comparative study of the enhancement in free radical generation.

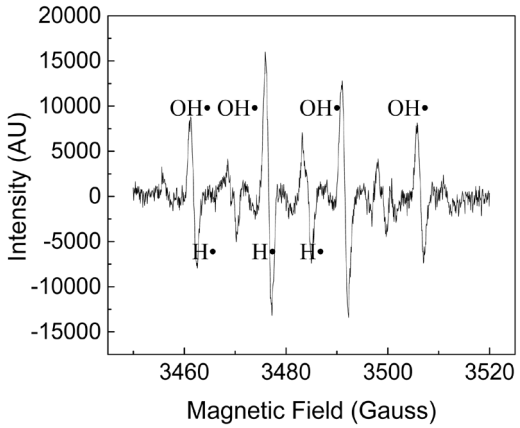

Figure 2. Typical EPR spectrum of DMPO-OH• and DMPO-H• obtained with Bruker ESP300E ESR Spectrometer.

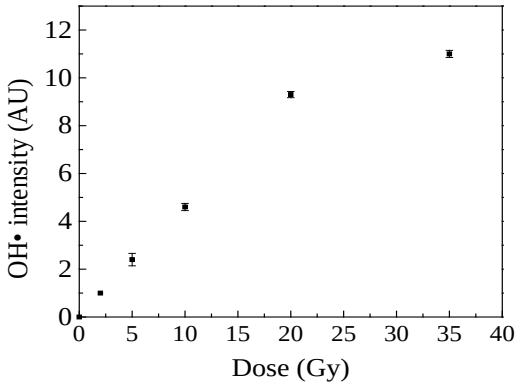

Figure 3. Dose dependence of OH• radical generation (with error bars) due to radiolysis of water by Ir-192 source.

As radicals undergo various reactions, their concentration and the corresponding EPR signal intensity decays with time [25]. The decay rate is slow at lower temperatures [27]. Therefore, the samples were stored at dry ice after irradiation.

For identical conditions of irradiation, storage and scan, hydroxyl intensities obtained from 500 mM DMPO water samples irradiated in the presence of metal wires were higher than the ones obtained from the samples irradiated in the absence of the wires. A typical comparison of two spectra is presented in **Figure 4**.

A comparison of the intensities of hydroxyl radicals, from a representative set of samples prepared, irradiated and scanned under identical conditions, is presented in **Figure 5**.

Average experimental enhancement in hydroxyl radical generation and MC modeled enhancement in radiation dose deposition due to the presence of metal wires during radiolysis are plotted in **Figure 6**. Averaged values and uncertainties in enhancement in radical generation were obtained from a number sample sets totaling 5 - 8 samples for each diameter of wire. Since the wires used in this experiment were thin and non-rigid their positions in the capillaries were not reproducible. Hence central as well as four extreme positions: top, bottom, right and left of the wires were considered for MC modeling and mean and standard deviation in MC modeled dose enhancement in water were obtained. This resulted in error bars ranging from 3% to 7% in MC modeled mean dose enhancement despite keeping uncertainties in each MC simulation less than a percent. Condensed history algorithm used by MCNP5 approximates the cumulative effect of multiple collisions of electrons in a single step. This has a negligible impact in our simulated results for the cut-off energy set and the dimensions used. The cut-off energy selected for MC simulation in this study is well within a safe limit for the dimensions used in the experiment.

As evident from **Figure 6**, our experimentally determined enhancements in hydroxyl radical generation in the presence of 100 and 127 μm diameter gold and 127 μm diameter platinum wires during radiolysis are approxi-

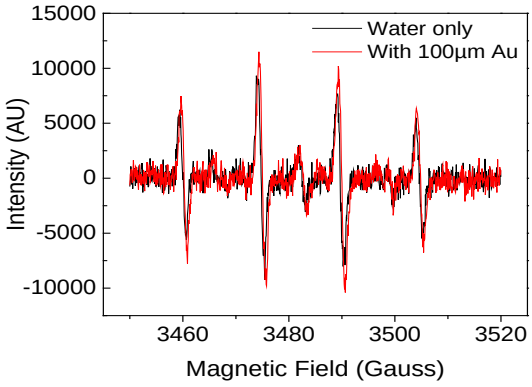

Figure 4. OH• spectra from a sample irradiated in the presence of 100 μm diameter gold wire vs. DMPO water only sample irradiated to the same dose (10 Gy).

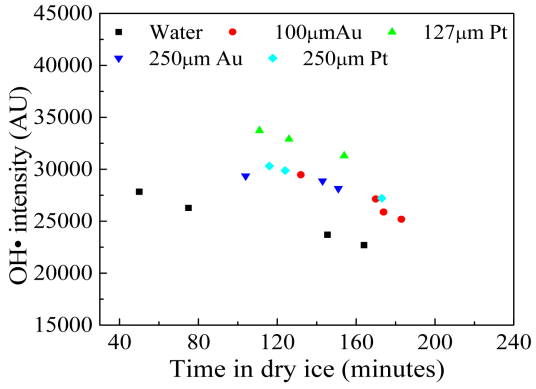

Figure 5. A representative set of samples exhibiting the effect of gold and platinum wires in hydroxyl radical generation.

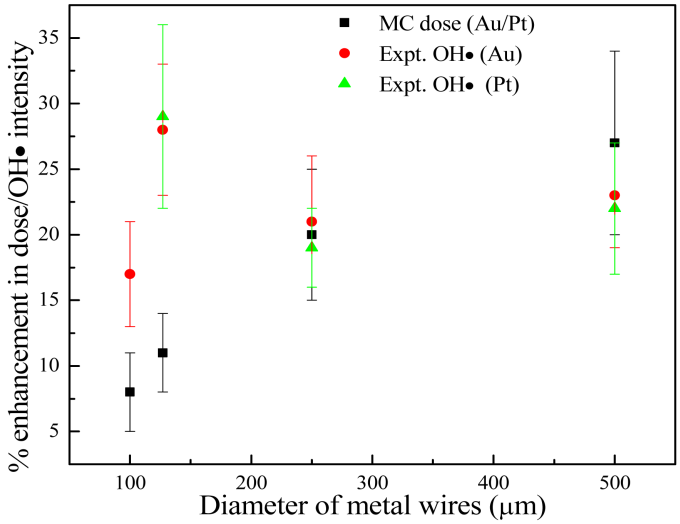

Figure 6. Summary of enhancement in OH• radical generation (±standard deviation, σ) for 10 Gy dose and MC modeled enhancement in radiation dose deposition (±σ) in the presence of gold and platinum micro-wires.

mately two times higher than the dose enhancements based on Monte Carlo modeling. The biggest variation in radiation effects measured in our experiment came from the uncertainty in wire positioning in the capillaries. These results provide direct experimental proof that the high Z materials in aqueous media play a role of secondary source of free radicals under irradiation. [28]. However, hydroxyl radical generation enhancement due to 250 or 500 μm diameter gold or platinum wires were not higher than the MC modeled dose enhancement. Also the MC modeled dose enhancement (16% ± 4%) and experimental enhancement in OH• generation (21% ± 4%) for two 100 μm gold wires were similar. Absence of increased radical generation for thicker wires points towards the importance of the surface to volume ratio of high Z materials.

4. Discussion

A number of factors can play a role in lowering enhancement in radical generation due to thick wires. We know that reaction cross section depends on the surface area. Increased surface area (proportional to diameter) of the thicker wires can result in a higher absorption of the radicals. Dose enhancement due to micron size gold under Ir-192 source decays exponentially with distance and extends over a very short distance of water equivalent material [29] [30]. Enhancement in radical generation in water due to wires increases with their thicknesses due to increased enhancement in radiation dose deposition. But the thickness of water in between wire and capillary wall gets narrower for thicker wires. This results in a higher concentration of radicals in water leading to a greater chance of their recombination. These factors lead to an apparently lower enhancement (measured) in radical generation for thicker wires.

Increased surface area to volume ratio and size quantization effect can make nanoparticles more catalytic for radical generation [31]. Hence the radiosensitizing effects observed by various authors including Jain *et al*. [17], Lechtman *et al.* [14] and McMahon *et al* [15] should be contributed by free radicals. Even though there could be a role of chemical remnants as the authors mention, Sicard-Roselli *et al*. [13] describes the importance and mechanism of free radicals very well. To avoid the effect of any chemical suspects, pure and uncoated wires of gold and platinum were used in our experiment. Also each water sample was treated as a bulk and the phenomenon of radiosensitization due to micron-thick wires under irradiation was studied in terms of one of the most reactive free radicals (OH•). Measured radical intensity of a particular type depends on a number of parameters including absorbed dose and efficiency of the spin trap [25]. Chemical yield of radicals was not assessed since it is out of scope of this study.

5. Conclusions

A higher enhancement in radiation induced free radical generation compared to the MC modeled radiation dose

enhancement by gold or platinum wires in aqueous medium provides an experimental proof that the irradiated metal surfaces can act as a secondary source of radicals. We think that the effect is governed by surface plasmon [32], possible interactions between the charge on the metal surface and water dipole [13] as well as the surface-to-volume ratio parameter of high Z material. These can lead to higher radical generation in nano-particle geometry. The extra radicals generated can lead to higher radiosensitization and higher cell kill than the predictions based on MC modeled enhancement in physical dose deposition.

Gold and platinum have close Z and similar radiation properties but different electronic configuration and hence different chemical properties. However, our experimental measurement did not show any difference in the enhancement in free radical generation due to the two different metals [28]. Even though enhancement in radiation dose deposition due to high Z nanoparticles in tumor under high energy radiation is low, significantly higher enhancement in radical generation can make nanoparticle-aided radiation therapy a possible arena for radiation therapy applications.

Acknowledgements

The authors would like to acknowledge the help and support provided by Dr. Victor Karpov, Department of Physics and Astronomy, The University of Toledo and Dr. Eric Findsen, Department of Chemistry, The University of Toledo on the project.

References

[1] Hall, E.J. and Giaccia, A.J. (2006) Radiobiology for the Radiologist. 6th Edition, Lippincott Williams and Wilkins, Philadelphia.

[2] Hainfeld, J.F., Slatkin, D.N. and Smilowitz, H.M. (2004) The Use of Gold Nanoparticles to Enhance Radiotherapy in Mice. *Physics in Medicine and Biology*, **49**, N309-N315. http://dx.doi.org/10.1088/0031-9155/49/18/n03

[3] Herold, D.M., Das, I.J., Stobbe, C.C., *et al*. (2000) Gold Microspheres: A Selective Technique for Producing Biologically Effective Dose Enhancement. *International Journal of Radiation Biology*, **76**, 1357-1364. http://dx.doi.org/10.1080/09553000050151637

[4] Detappe, A., Tsiamas, P., Ngwa, W., *et al*. (2013) The Effect of Flattening Filter Delivery on Endothelial Dose Enhancement with Gold Nanoparticles. *Medical Physics*, **40**, (031706-1)-(031706-4).

[5] Sech, C.L., Kobayashi, K., Ushami, N., *et al*. (2012) Comment on Therapeutic Application of Metallic Nanoparticles Combined with Particle Induced X-Ray Induced X-Ray Emission Effect. *Nanotechnology*, **23**, 78001. http://dx.doi.org/10.1088/0957-4484/23/7/078001

[6] Carter, J.D., Cheng, N.N., Qu, Y., *et al*. (2007) Nanoscale Energy Deposition by X-Ray Absorbing Nanostructures. *Journal of Physical Chemistry B*, **111**, 11622-11625. http://dx.doi.org/10.1021/jp075253u

[7] Regulla, D.F., Hieber, L.B. and Seidenbusch, M. (1998) Physical and Biological Interface Dose Effects in Tissue Due to X-Ray-Induced Release of Secondary Radiation from Metallic Gold Interfaces. *Radiation Research*, **150**, 92-100. http://dx.doi.org/10.2307/3579649

[8] Das, I.J., Moskvin, V.P., Kassaee, A., *et al*. (2002) Dose Perturbations at High-Z Interfaces in Kilovoltage Photon Beams: Comparison with Monte Carlo Simulations and Measurements. *Radiation Physics and Chemistry*, **64**, Article ID: 1730179. http://dx.doi.org/10.1016/S0969-806X(01)00460-1

[9] Regulla, D., Schmid, E., Friedland, W., *et al*. (2002) Enhanced Values of the RBE and H Ratio for Cytogenetic Effects Induced by Secondary Electrons from an X-Irradiated Gold Surface. *Radiation Research*, **158**, 505-515. http://dx.doi.org/10.1667/0033-7587(2002)158[0505:EVOTRA]2.0.CO;2

[10] Walzlein, C., Scifoni, E., Kramer, M., *et al*. (2014) Simulations of Dose Enhancement by Heavy Atom Nanoparticles Irradiated by Protons. *Physics in Medicine and Biology*, **59**, 1441-1458. http://dx.doi.org/10.1088/0031-9155/59/6/1441

[11] Mishawa, M. and Takahashi, J. (2011) Generation of Reactive Oxygen Species Induced by Gold Nanoparticles under X-Ray and UV Irradiations. *Nanomedicine*: *Nanotechnology*, *Biology and Medicine*, **7**, 604-614. http://dx.doi.org/10.1016/j.nano.2011.01.014

[12] Cheng, N.N., Starkewolf, Z., Davidson, R.A., Sharmah, A., Lee, C., Lien, J. and Guo, T. (2012) Chemical Enhancement by Nanomaterials under Irradiation. *Journal of the American Chemical Society*, **134**, 1950-1953. http://dx.doi.org/10.1021/ja210239k

[13] Sicard-Roselli, C., Brun, E., Gilles, M., Baldacchino, G., Kelsey, C., McQuaid, H., *et al*. (2014) A New Mechanism for Hydroxyl Radical Production in Irradiated Nanoparticle Solutions. *Small*, **10**, 3338-3346.

http://dx.doi.org/10.1002/smll.201400110

[14] Lechtman, E., Chattopadhyay, N., Cai, Z., Mashouf, S., Reilly, R. and Pignol, J.P. (2011) Implications on Clinical Scenario of Gold Nanoparticle Radiosensitization in Regards to Photon Energy, Nanoparticle Size, Concentration and Location. *Physics in Medicine and Biology*, **56**, 4631-4647. http://dx.doi.org/10.1088/0031-9155/56/15/001

[15] McMahon, S.J., Hyland, E.B., Muir, M.F., Coulter, J.A., Jain, S., Butterworth, K.T., *et al*. (2011) Nanodosimetric Effects of Gold Nanoparticles in Megavoltage Adiation Therapy. *Radiotherapy and Oncology*, **100**, 412-416. http://dx.doi.org/10.1016/j.radonc.2011.08.026

[16] Jain, S., Coulter, J.A., Hounsell, A.R., Butterworth, K.T., McMahon, S.J., Hyland, W.B., *et al*. (2011) Cell Specific Radiosensitization by Gold Nanoparticles at Megavoltage Radiation Energies. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **79**, 531-539. http://dx.doi.org/10.1016/j.ijrobp.2010.08.044

[17] Liu, C.J., Wang, C.H., Chen, S.T., Chen, H.H., Leng, W.H., Chien, C.C., *et al*. (2010) Enhancement of Cell Radiation Sensitivity by Pegylated Gold Nanoparticles. *Physics in Medicine and Biology*, **55**, 931-945. http://dx.doi.org/10.1088/0031-9155/55/4/002

[18] Chithranii, D.B., Jelveh, S., Jalai, F., van Prooijen, M., Allen, C., Bristow, R.G., *et al*. (2010) Gold Nanoparticles as Radiation Sensitizers in Cancer Therapy. *Radiation Research*, **173**, 719-728. http://dx.doi.org/10.1667/RR1984.1

[19] Marcu, L., Doorn, T.V. and Olver, I. (2003) Cisplatin and Radiotherapy in the Treatment of Locally Advanced Head and Neck Cancer. *Acta Oncologica*, **42**, 315-325. http://dx.doi.org/10.1080/02841860310004364

[20] Perez, E.A. (2004) Carboplatin in Combination Therapy for Metastatic Breast Cancer. *Oncologist*, **9**, 518-527. http://dx.doi.org/10.1634/theoncologist.9-5-518

[21] Usami, N., Kobayashi, K., Furusawa, Y., Frohlich, H., Lacombe, S. and Le Sech, C. (2007) Irradiation of DNA Loaded with Platinum Containing Molecules by Fast Atomic Ions C^{6+} and Fe^{26+}. *International Journal of Radiation Biology*, **83**, 569-576. http://dx.doi.org/10.1080/09553000701447130

[22] Saifutdinov, R.G., Larina, L.I., Vakul'skyaya, T.I. and Voronkov, M.G. (2002) Electron Paramagnetic Resonance in Biochemistry and Medicine. Kluwer Academic Publishers, New York.

[23] Buettner, G.R. and Oberley, L.W. (1978) Considerations in the Spin Trapping of Superoxide and Hydroxyl Radical in Aqueous Systems Using 5,5-Dimethyl-1-Pyrroline-Oxide. *Biochemical and Biophysical Research Communications*, **83**, 69-74. http://dx.doi.org/10.1016/0006-291X(78)90398-4

[24] X-5 Monte Carlo Team (2004) MCNP—A General Monte Carlo N-Particle Transport Code. Version 5, Vol. 1, Los Alamos National Laboratory, Los Alamos.

[25] Carmichael, A.J., Makino, K. and Riesz, P. (1984) Quantitative Aspects of ESR and Spin Trapping of Hydroxyl Radicals and Hydrogen Atoms in Gamma-Irradiated Aqueous Solutions. *Radiation Research*, **100**, 222-234. http://dx.doi.org/10.2307/3576343

[26] Nishikawa, H. (2003) Radical Generation on Hydroxyapatite by UV Radiation. *Material Letters*, **58**, 14-16. http://dx.doi.org/10.1016/S0167-577X(03)00396-3

[27] Jackson, S.D. and Hargreaves, J.S.J. (2009) Metal Oxide Catalysis. Wiley-VCH Verlag GmbH and Co. KGaA, Weinheim.

[28] Paudel, N., Shvydka, D., Findsen, E. and Parsai, E. (2014) Experimental Evaluation of Free Radical Generation in Nanoparticle-Aided HDR Brachytherapy. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **90**, S198-S199. http://dx.doi.org/10.1016/j.ijrobp.2014.05.744

[29] Paudel, N., Shvydka, D. and Parsai, E. (2012) Micro-Dosimetry Study of the Radiation Dose Enhancement at the Gold-Tissue Interface for Nanoparticle-Aided Radiation Therapy. *Medical Physics*, **39**, 3775. http://dx.doi.org/10.1118/1.4735396

[30] Paudel, N.R. (2014) Nanoparticle-Aided Radiation Therapy: Microdosimetry and Evaluation of Mediators Producing Biological Damage. Ph.D. Dissertation, The University of Toledo, Toledo.

[31] Henglein, A. (1989) Small-Particle Research: Physiochemical Properties of Extremely Small Colloidal Metal and Semiconductor Particles. *Chemical Reviews*, **89**, 1861-1873. http://dx.doi.org/10.1021/cr00098a010

[32] Zhang, X.D., Guo, M.L., Wu, H.Y., Sun, Y.M., Ding, Y.Q., Feng, X. and Zhang, L.A. (2009) Irradiation Stability and Cytotoxicity of Gold Nanoparticles for Radiotherapy. *International Journal of Nanomedicine*, **4**, 165-173. http://dx.doi.org/10.2147/IJN.S6723