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Novel Cancer Treatment Using Targeted Delivery of Short-Lived Radiologically Activated Nanoparticles

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Abstract: The goal of our preliminary study is to show that a minimal of overall body toxicity while maximizing the cancer tumor treatment may be achieved in a novel approach where minute amounts of coated nanoparticles may be radiologically activated prior to treatment and "coerce" tumor cells into readily absorb these nanoparticles. This targeted intracytoplasmic delivery of short-lived radiologically activated nanoparticles could provide less "whole-body" radiation dose while delivering a short lived potent tumor localized dose, along with their low toxicity may prove to be another tool in the treatment of diverse cancers.

Key words: Nanoparticles, neutron activation, irradiation, cancer, metabolism, Warburg effect, glutamine, glucose.

1. Introduction

Many research programs over the last decades dealt with in vitro and in vivo applications of inorganic nanoparticles (NPs) in radiation therapy [1-5]. Most current radiosensitization strategies rely on the combination of drugs and activation of NPs by external X-ray beam radiation therapy, thus exposing the patient to large amounts of radiation. Photosensitization generally acts by absorbing ultraviolet or visible region of electromagnetic radiation and transferring it to adjacent molecules; nevertheless, it requires complex surgical procedures for possible treatment of other than cutaneous tumors. Photocatalytic chemistry has shown to be efficient in the treatment of cervical carcinoma but also has its limitations in the treatment of intra-organ tissue. Intercalation of chemotherapeutic agents has limitations in such as blood-brain barrier posing a difficult obstacle to deliver chemotherapy to the brain and through blood vessels. Given that radiation therapy is not a selective antitumor treatment, the main challenge for radiation oncologists, medical physicists and radiobiologists is to increase its therapeutic efficacy without increasing damage to the surrounding healthy tissues.

Multiple approaches have been used to enhance the efficacy of target cancer tissue tumor treatments while reducing overall toxicity [1]. Nanoparticles are promising in the development of cancer treatments and have been studied in radiosensitization [2], photosensitization [3], photocatalytic chemistry [4], intercalation of chemotherapeutic agents [5], among others. Though nanoparticles are promising in the development of cancer drug delivery, their toxicity remains an issue due to the amount of these nanoparticles necessary for such procedures [6]. High-energy ionizing radiations such as gamma rays or X-rays; as well as particulate radiation, such as alpha, beta particles, electron, proton [7, 8], and neutron beams [9] are used in certain specific cases to target cancer tissue tumor.

Contrary to current neutron capture therapy (NCT), where the patient is radiated with epithermal neutrons receiving a typical dose ranging from 60 to 80 Gy, the treatment proposed here suggests that minute amounts of glucose coated nanoparticles (GNP) that have been radiologically activated by neutron capture be injected

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onto the tumor thus minimizing radiological exposure to prospect patients.

Also known as the Warburg effect, aerobic glycolysis is defined as a high rate of glucose utilization and lactate production despite the presence of sufficient oxygen to oxidize glucose carbon in the mitochondria [10]. Since glucose metabolism is a primary source of energy and biomaterials for the maintenance of life. To first order, glucose is transported across the plasma membrane by the glucose transporter (Glut) down its concentration gradient. At the mitochondria level, Hexokinase (HK) then phosphorylates glucose to glucose-6-phosphate (G6P). The product generally enters the glycolytic pathway, generating NADH, ATP, and pyruvate, or the pentose phosphate pathway (PPP). In the presence of sufficient oxygen, pyruvate from glycolysis can be fed into mitochondria and fully oxidized to produce more ATP. When oxygen is limited, however, pyruvate is disposed in the form of lactate and glycolysis becomes the main source for ATP production [11]. PPP plays an important role in the synthesis of nucleic acids for DNA and RNA, as well as generation of NADPH for the synthesis of lipids and maintenance of intracellular redox homeostasis.

The goal of our preliminary study is to show that a minimal of overall body toxicity while maximizing the cancer tumor treatment may be achieved in a novel approach where minute amounts of coated nanoparticles may be radiologically activated prior to treatment and "coerce" tumor cells into readily absorb these nanoparticles utilizing the own cancerous cell elevated metabolic rate to readily absorb the glucose coated activated NPs. This targeted intracytoplasmic delivery of short-lived radiologically activated nanoparticles, along with their low toxicity may prove to be another tool in the treatment of diverse cancers.

2. Preliminary Results

Three commercially available transition metal oxide NPs: TiO_2 (10-30 nm), ZnO (10-30 nm), and Fe_3O_4 (20-30 nm); were chosen for their well understood biocompatibility, relatively short radiological activation half-life, and biological toxicology. These NPs were activated at the NIST Reactor Instrumental Neutron Activation Analysis (INAA) facility. Each sample was irradiated and the elements comprising each sample undergo neutron capture resulting in the formation of radioactive product nuclides. The energy of the radiation emitted from the most significant product nuclei during radioactive decay is indicated in Table 1 along with calculated values and calculated mean energy from beta particles, conversion electrons, Auger electrons, and the average radial range normalized by tissue density (ρ_T).

Considering the ability of tumor cells to metabolize sugar up to 19 times faster than normal cells, the energy of the radiation emitted from the most

Table 1 Calculated and measured energies of activation for the different GCNPs. Also, it is shown the average radial range normalized by tissue density (ρ_T).

Activation Data			Energy per distingeration (MeV/dist.)						Mean energy per distingeration		Wt Avg. Energy per dist. (MeV)	Range (g/cm^2)		D_{Max} (cm)
NP	Offical NuclideName	Total Activity @ end of irradiation (Bq)	Gamma rays	X rays	β +	β -	IC electrons	Auger electrons	Gamma rays	X rays	β +/- IC electrons and Auger Electrons	β_{Avg}	β_{Max}	(Range/ρT)
ZnO	Zn-65	1.59E+08	5.65E-01	3.11E-03	2.00E-03		1.02E-04	4.78E-03	1.12E+00	5.98E-04	5.88E-02	0.02103	0.08502	0.08502
	Cu-64	1.09E+07	6.37E-03	1.20E-03	4.84E-02	7.43E-02	7.73E-07	2.05E-03	1.35E+00	5.00E-04	2.40E-01	0.0453	0.2286	0.2286
	Cu-66	5.07E+05	9.78E-02	9.63E-08		1.07E+00	2.65E-05	1.30E-07	1.04E+00	7.23E-04	1.07E+00	0.02103	0.08502	0.08502
	Cu-67	6.94E+03	1.15E-01	5.55E-04		1.36E-01	1.37E-02	7.51E-04	1.57E-01	7.16E-04	1.31E-01	0.02103	0.2032	0.2032
	Zn-69m	2.24E+09	4.16E-01	1.89E-04		9.58E-05	2.23E-02	2.55E-04	4.39E-01	7.15E-04	4.25E-01	0.06433	0.2805	0.2805
	Zn-69	1.38E+11	6.00E-06	2.06E-10		3.22E-01	1.55E-08	2.47E-10	4.14E-01	6.37E-04	3.22E-01	0.08502	0.387	0.387
	Zn-71	3.56E+08	3.15E-01	7.68E-06		1.05E+00	4.29E-04	9.21E-06	5.94E-01	6.36E-04	1.05E+00	0.441	1.26	1.26
TiO_2	Sc-46	7.28E+03	2.01E+00	2.40E-07		1.12E-01	2.47E-04	9.25E-07	1.01E+00	1.26E-04	1.14E-01	0.01444	0.5774	0.5774
	Sc-47	2.39E+05	1.09E-01	2.90E-06		1.62E-01	4.76E-04	1.12E-05	1.59E-01	1.26E-04	1.62E-01	0.02844	0.2286	0.2286
	Sc-48	9.61E+04	3.35E+00	5.99E-07		2.21E-01	3.79E-04	2.31E-06	1.09E+00	1.26E-04	2.22E-01	0.0453	0.2286	0.2286
Fe_3O_4	Fe-55	1.56E+07	1.61E-10	1.67E-03			2.52E-12	4.17E-03	1.26E-01	2.63E-04	8.25E-04	0.01444	N/A	N/A
	Mn-54	7.06E+03	8.35E-01	1.36E-03	1.02E-09	8.42E-07	2.03E-04	4.00E-03	8.35E-01	2.04E-04	4.08E-02	0.06433	0.2286	0.2286
	Mn-56	2.26E+06	1.69E+00	6.39E-07		8.30E-01	2.83E-04	1.40E-06	1.19E+00	3.36E-04	8.30E-01	0.3334	1.26	1.26
	Fe-59	1.59E+08	1.19E+00	1.43E-06		1.18E-01	2.48E-04	2.76E-06	1.14E+00	4.16E-04	1.18E-01	0.01444	0.7145	0.7145

significant product nuclei during radioactive decay can be injected directly into a tumor. Since these particles are coated in a glucose (or polysaccharide) shell, the tumor cells have a potential to phagotize these radiologically activated nanoparticles, thus containing the activated nanoparticles within the constraints of the tumor area.

The dose rate is given by:

$$\dot{D}(t) = \dot{D}e^{-(\lambda_{NP}+\lambda_B)t}$$

And the total absorbed dose $\bar{D}$

$$\bar{D} = \int \dot{D}(t)dt$$

in Grays per hour (Gy/hr).

The radiological effect of the ionizing radiation is given by:

$$\lambda_{eff} = \lambda_{NP} + \lambda_B$$

where, λ_{eff} is the effective half-life and takes into consideration the NP radiological activated half-life (λ_{NP}) and the NP biological half-life (λ_B) (the average time a compound takes to have half of its mass removed from the biological process)

A criterion of treatment effectiveness is the ability of the activated GCNPs to deposit the majority of its radiological energy, in a localized fashion. Once the activated nanoparticles are absorbed into the tumor cells, the effective half-life (λ_{eff}) of the activated NPs ensures that approximately 90 percent of the emitted activity would be concentrated within the tumor cells promoting cell apoptosis. This is assumed by the D_{max} range given in Table 1. Thereafter, the GCNPs have gone through a number of effective half-life λ_{eff}. Fig. 1 shows a correlation between the empirical decay and the tissue specific MIRD mean absorbed dose calculation for each activated NP. In the case for the Fe_3O_4 NPs (Fig. 1a), half of the total radiological dose contribution is released within one biological half-life (λ_B), approximately 2.5 hours after intratumoral injection within about 0.7 cm radius from the NP. And after 10 λ_B there is only a fraction of the typical neutron capture therapy (NCT) dose (less than 5%) a patient is

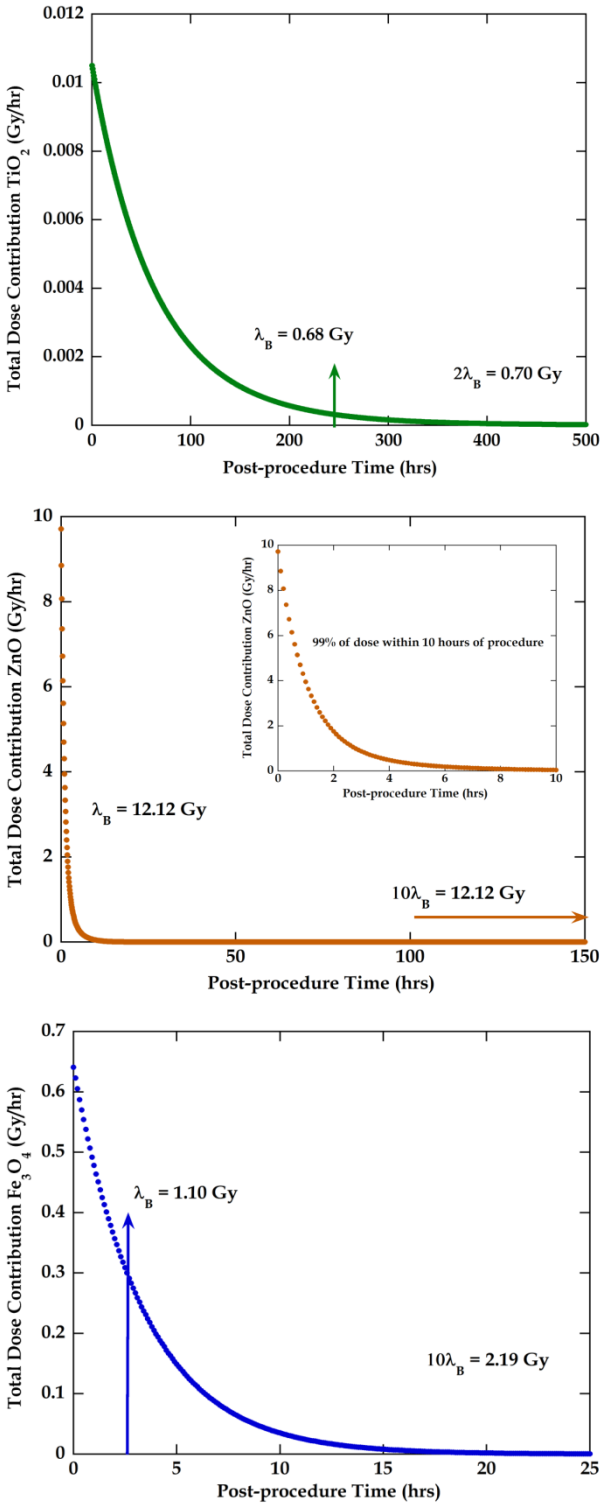

Fig. 1 Mean absorbed dose calculation for each nanoparticle: (a) Fe_3O_4; (b) ZnO; (c) TiO_2. Values here derived from observed activation decay. The vertical line represents the biological half-life (λ_B) for each NP (the average time a compound takes to have half of its mass removed from the biological process).

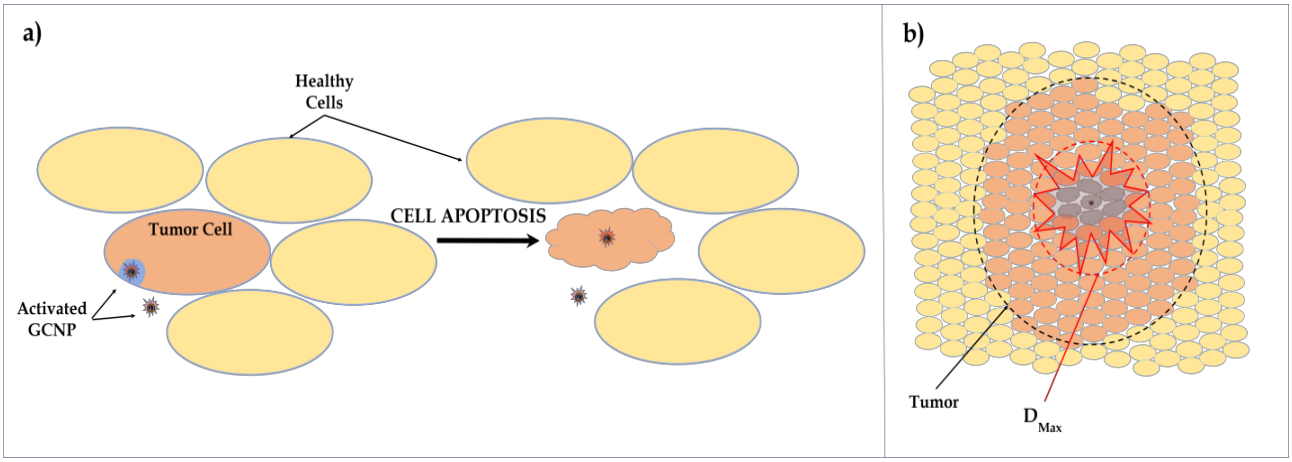

Fig. 2 (a) Schematic representation of the targeted delivery of short-lived radiologically activated nanoparticles leading to cell apoptosis; (b) The schematics shows a representation of the GCNP energy range relative to an assumed tumor size of 3 cm^3. In this case, approximately 90% of the emitted radiation would fall well within the tumor.

expected to experience. For the case of the ZnO NPs (Fig. 1b), 99% of the total radiological dose contribution is released within 10 hours of the intratumoral injection procedure (inset Fig. 1b); and quickly decaying thereafter as it is expelled from the biological process. Once again, only a fraction of the typical neutron capture therapy (NCT) dose a patient is expected to experience. And finally, it is observed that for the TiO_2 NPs (Fig. 1c), though the radiological activity saturation occurs much faster, even after an extended post-procedure time there is even less overall total radiological dose contribution for a spherical range of about 0.6 cm.

Here we have assumed an average cell size to be between 100 and 500 μmeters (liver cell); biological half-life of 240 hrs for TiO_2 [12], 144 hrs for ZnO [13] and 2.4 hrs for Fe_3O_4 [14]; a cell glucose metabolic rate of approximately 100 minutes; a spherical tumor size of 3 cm^3 and a free mean path radiation field congruent with the activated GCNP (Table 1). Once these coated NPs are within the tumor intracellular spaces, the fast glucose metabolic rate of tumor cells (in the order of 19 times that of normal cells [8]) should readily absorb the glucose coated NPs thus delivering an overall intracellular radiation dose and causing apoptotic cell death. Moreover, assume that 90% of the emitted radiation falls well within the tumor (Table 1) leading to a cascade effect as represented by schematics on Fig. 2.

3. Conclusion

A proposed combination of the well-known Warburg effect [10], and radiological activation of certain nanoparticles coated in glucose or a polysaccharide derived from algae might serve as a platform for future studies in the treatment of an estimated up to 80 percent of cancers [11]. Toxicology studies for TiO_2 showed absence of toxicological effects after intravenous injection at concentrations of 7.7 to 9.4 mg/kg [12]; and after 5 hours of thermal neutron activation for the NPs, the MIRD mean absorbed dose to an organ falls within levels viable for treatment. Though large quantities of ZnO could pose interactions in the ionic form in the body; quantities of ~10 mg/day showed no toxicological effects since the biological half-life is relatively short [13]. Fe_3O_4 NPs are currently widely used in medicine [14] and thus is also a good candidate for further studies in this proposed treatment suggesting that minute amounts of glucose coated nanoparticles (GCNP) that have been radiologically activated by neutron capture at a reactor may be injected onto the tumor in order to cause a cascade cell apoptosis effect leading to tumor reduction or eradication, and subsequent safe secretion

of treatment NPs, thus, minimizing radiological exposure to prospect patients. Further in-vivo studies are still necessary to categorize the absorption metabolic rate of GCNPs for different tissues.

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