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GADOLINIUM AS AN ELEMENT FOR NEUTRON CAPTURE THERAPY

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Gadolinium is being studied as an alternate active element to B for Neutron Capture Therapy (NCT). The advantages of Gd-157 as compared to B-10 are that Gd-157 has a very large thermal neutron cross section (455,000 b), and Gd containing compounds that target to tumors are being developed as MRI contrast agents. A disadvantage is that the products of the Gd + n reaction, gamma rays and Auger electrons, do not appear to be as well suited to NCT as the products of the B + n reaction, but these still may be effective in destroying tumors. Because of the advantages of Gd, an investigation of Gd as an element for NCT is proceeding at BNL¹.

The one Gd loaded MRI contrast agent, Gd-DTPA, that is now accepted for imaging does target brain tumors and will not be toxic at the levels of injection that will be needed for GdNCT¹. Calculations and measurements of the physical dose show that with 150 ppm in a 50 cc tumor and a source of 5×10^{12} neutrons, greater than 30 Gy of dose from the prompt gamma rays will be delivered to the tumor². The dose drops off rapidly away from the tumor similar to the dose distribution in brachytherapy. Measurements of this dose with a biological dosimeter agree with calculations. In addition, the biological dosimeter shows that the dose can be enhanced with the addition of IdUrd to the treatment. Thus far, for the compounds tried, the biological effect observed from Auger electrons has been modest. In another study, a different delivery system was examined. Calculations show that Gd metal seeds can be used with GdNCT in a combination of brachytherapy and NCT³.

At BNL, preparations are being made to test *in vitro* compounds containing Gd and compare their response to the response of Gd-DTPA to determine if one or several compounds can be located that enter the cells and enhance the Auger effect. Figure 1 shows the shape of the two similar rotators with positions for cell vials that have been constructed for these tests. The first rotator is made of only paraffin which simulates healthy tissue and provides control curves. The second rotator has 135 ppm of Gd-157 in the paraffin to simulate a Gd loaded tumor. Cells are irradiated in vials in the paraffin rotator and in the Gd-paraffin rotator at the epithermal beam of the Brookhaven Medical Research Reactor (BMRR). This produces an irradiation similar to what a patient would receive in an actual treatment. A combination of irradiations are made with both rotators; with no Gd compound or IdUrd in the cell media, with only Gd compound in the cell media and with both Gd compound and IdUrd in the cell media. The first set shows the effects of gamma rays from the H(n,gamma) reaction and the prompt gamma rays from capture of neutrons by Gd. The second set shows if there is any effect of Gd being in the cell media or inside the cells, i.e., an Auger effect. The third set shows the effect of enhancement by the IdUrd produced by the gamma rays from neutrons captured by either H or Gd. The fourth set combines all of the reactions and enhancements. Preliminary calculations and physical measurements of the doses that the cells will receive in these rotators have been made. Figure 2 shows preliminary cell survival measurements and Table 1 lists both measurements and calculated results.

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Table 1. Calculated and Measured Doses per MW-min in the Rotators.

Source	Calculation		Measured	
	Physical	Biological	Physical	Biological
Paraffin Rotator				
D_γ	2.6 cGy	2.6 RBEcGy	2.2	
D_{N-14}	0.7 cGy	3.3 RBEcGy		
D_{fast}	0.5 cGy	2.4 RBEcGy		
Φ_{th} (n/cm ² /s)	7.1×10^8		6.6×10^8	
τ -radiation to reach 10% cell survival (MW-min)		86.0	91.0	78 +/- 9
Gd Rotator				
D_γ	16.0	16.0	12.0	
D_{N-14}	0.4	1.8		
D_{fast}	0.5	2.4		
Φ_{th} (n/cm ² /s)	4.0×10^8		4.1×10^8	
Irradiation to reach 10% cell survival (MW-min)		35.9	44.8	39

The RBES used; gamma rays = 1, fast neutrons = 4.5, N(n,p) = 4.5

An MRI scan and a SPECT scan for DTPA of a boy with a brain tumor indicated that Gd-DTPA concentrates in a brain tumor while very little goes to brain, but that some Gd goes to the scalp³. Calculations have been made to see the effects of neutrons captured by the Gd in the skin. A tumor was placed about 1.25 cm below the surface on the side of a head phantom. The skull and the brain have typical skull and brain tissues. Guided by the SPECT scans, 188 ppm of Gd-157 were put in the tumor and 63 ppm in the skull and then the head was irradiated from the side with an epithermal beam representing the one at the BMRR. The dose components along the line through the center of the tumor were calculated and some of these are displayed in figure 3. The components of the background coming from capture of neutrons by tissue material are seen. In addition, the peaked dose to the tumor is seen at the location of the tumor. An additional dose, peaking at the front and back surfaces of the head, is present from neutrons captured by the Gd in the skin and producing gamma rays. However this dose is relatively small and does not exclude GdNCT as a feasible therapy. In addition, this surface effect can probably be reduced by determining the build up and wash out of the Gd in the tumor and in the scalp and selecting an optimum time after administration of the compound for irradiation.

Figure 1. The Rotators at the BMRR Epithermal Beam Port.

Table 2. Gd Brachytherapy Phantom at Li-Poly Face, at 35 mm Depth per MW-min.

	Calculated		Measured	
	Control	Seeds	Control	Seeds
$\Phi_{th} \times 10^8$ (n/cm ² /s)	7.96	6.35	---	5.89
D_{γ} (cGy)	4.22	10.37	---	8.06
D_{fast} (cGy)	0.35	0.35	---	---
D_{N-14} (cGy)	0.15	0.12	---	---

Figure 2. Preliminary Cell Survival Measurements in the Rotators.

Figure 3. The RBE Dose Rate through a Head Phantom.

One set of compounds of particular interest at this time, for not only photodynamic therapy, but also BNCT, are porphyrins⁴. It has been shown that these compounds target tumors and that they enter the cells but possibly not the nucleus of the cells. Porphyrins, since they are light sensitive, are being tested for photodynamic therapy. Porphyrins have been modified with two and four carborane cages on side chains giving porphyrin molecules with 20 and 40 B atoms per molecule of porphyrin⁵. These porphyrins are candidates for BNCT. In addition, a Gd atom can be added to the center of the ring giving one Gd in addition to the 20 or 40 atoms of B per molecule. For the 40 B atoms plus 1 Gd atom per molecule, the thermal neutron cross section/molecule is 154,000 b for the B, but 255,000 b/molecule for the Gd. The dose from the B fission is deposited at the location of the molecule with an RBE of 2.5, but the dose from the de-excitation of the Gd-158* is more broadly distributed by the gamma rays and a factor of about 0.06 must be applied for this distribution and an RBE of 1 for the gamma rays. This indicates that the B is about 25 times more effective when only the gamma rays from Gd are compared to the fission products from B. However, for porphyrins, the Gd appears to be inside the cells and an Auger effect should be significant. The Auger electrons from Gd have energies as large as 50 keV and ranges up to 30 microns. Fifty percent more of the molecules will have a reaction of neutrons with Gd than with B. The effect of the Gd through the Auger reaction could be as great as the effect from the B. *In vitro* cell survival experiments should demonstrate this effect.

Calculations have shown that Gd in the form of brachytherapy seeds and irradiated with thermal neutrons will deliver a significant dose to a tumor². Seeds have been made of Gd metal and dose measurements made in a phantom. The seeds can be made of natural Gd since the cross section is so large that any neutron reaching the surface of a seed is captured. The magnitude of the dose produced is proportional to the surface area of the seeds and not their volume. The calculated and measured dose rates that the cells will experience when this phantom is placed in the epithermal beam of the BMRR are given in table 2.

In conclusion, recent studies at BNL of Gd as an element for NCT continue to indicate that GdNCT might be successful. Rotators for irradiating cells have been made so that *in vitro* screening can be made of Gd compounds. One compound that looks particularly interesting is porphyrin with both B and Gd added.

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SHMT Survival Curve

Fig. 26

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