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A New Simplified System for the Evaluation of BNCT Pharmaceuticals

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DISCLAIMER

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A system for testing potential BNCT pharmaceuticals in cell cultures has been developed with the cooperation of Oak Ridge National Laboratory (ORNL), the University of Tennessee Chemistry Department and the University of Tennessee Nuclear Engineering Department. A BNCT test model has been established with the use of the human lung cancer cell line A 549. These cells were maintained in standard laboratory facilities and subjected to boronated chemicals. Following toxicity studies the human lung cancer cells were exposed to ^{252}Cf neutron sources provided by the Radiochemical Engineering Development Center (REDC) at ORNL. The isotope ^{252}Cf performs effectively for BNCT applications. The neutron spectrum is similar to that of a reactor fission source with an average energy of 2.1 MeV. A 50 mg source of ^{252}Cf moderated by water provides a source on the order of 1×10^9 thermal neutrons/cm^2/sec at a distance of 3 cm. The half-life of ^{252}Cf is 2.65 years, and thus may provide a simple and reliable source of neutrons for BNCT in locations without suitable nuclear reactors. The REDC of ORNL stores and processes the U.S. stockpile of ^{252}Cf.

The compounds examined were boron-containing nucleosides and boron-containing amino acids (Figure 1). Chemical analysis for the measurement of total cellular boron was conducted at ORNL using inductively

coupled plasma mass spectroscopy. Boron concentrations were measured against a calibration curve generated with a series of NIST standards. In nitric acid solutions containing boron, the detection limit was 0.4 ppb. In similar solutions containing cellular debris the boron detection limit was determined to be 1.0 ppb.

Calculations of cellular dosimetry in human lung cancer cells from sources of ^{252}Cf and intracellular ^{10}B concentrations have been made (Table 1). All experiments with thermal neutrons plus boronated pharmaceutical compounds displayed a greater cancer cell killing effect than control experiments without boronated compounds (Figure 2). Thus, a cooperative program for the future evaluation of BNCT pharmaceutical agents is now in place.

In conclusion, the following objectives of this research have been achieved:

1. The cellular toxicity of the proposed BNCT compounds has been determined . The least toxic agent of the A549 lung cancer cell is ACBC followed by LSK 1-38, CDU-4 and the most toxic agent is CN-V-264.

2. The cellular uptake of the BNCT compounds has been determined. The greatest cellular uptake of B/cell occured with ACBC at a concentration of 24.6×10^{-3} ng followed by LSK 1-38 with a concentration of 8.6×10^{-3} ng B/cell, CN-V-264 demonstrated an uptake concentration of 4.5×10^{-3} ng B/ cell and CDU-4 displayed the lowest uptake concentration of $.9 \times 10^{-3}$ ng B/cell.

3. A 30 mg source of ^{252}Cf moderated by 2.5 cm of water and polyethylene produced a thermal neutron flux of approximately 2 x 10^8 neutrons/cm^2/sec. The REDC source allowed for the development of cellular survival curves in A549 lung cancer cells.

4. A system for testing potential BNCT pharmaceuticals in cell cultures has been developed with the cooperation of ORNL, the UTK Chemistry Department and the UTK Nuclear Engineering Department.

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Figure 1 The boronated chemicals used in this experiment.

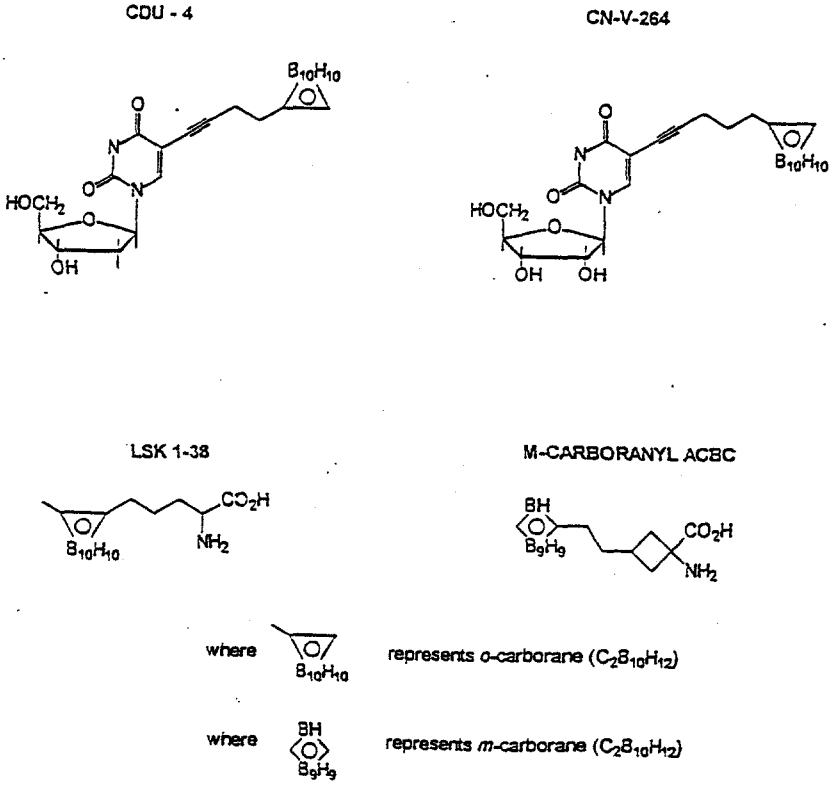

Table 1

Uptake of boronated compounds by A549 lung cancer cells and calculated number of thermal neutron interactions per cell at four minute exposure.

Compound	Boron in cell (ng B/cell)	Atoms of ^{10}B (atoms ^{10}B/cell)	Average Number of interactions per cell
ACBC	24.6×10^{-3}	274×10^{9}	5.0
LSK 1-38	8.6×10^{-3}	96×10^{9}	1.7
CN-V-264	4.5×10^{-3}	50×10^{9}	0.9
CDU-4	$.9 \times 10^{-3}$	10×10^{9}	.18

Figure 2 Bar graph of effective kill constants with various boron containing compounds versus controls.