

Energy Dependence of Biological Systems Under Radiation Exposure

Rachel Black
Paper G29.00006

Ariano Munden
Paper G29.00007

Yuriy Prilepskiy
Paper G29.00009

Energy Dependence of
Cancer Cell
Irradiation

Calibration Of A System For
Energy Dependence Study Of
Cancer Cell Irradiation

Radiation Damage From Mono-
energetic Electrons Up to 200 keV
On Biological System

Tuesday, March 14
09:24 AM–09:36 AM
Rm 326

Tuesday, March 14
09:36 AM–09:48 AM
Rm 326

Tuesday, March 14
10:24 AM–10:36 AM
Rm 326

PI
Co-PI
Collaborators

Paul Guèye¹, Ph.D. (gueye@ilab.org)
Richard Britten², Ph.D.
David Hamlette³, Angela Johnson², Ph.D., Cynthia Keppel^{1,3}, Ph.D.,
Christopher Sinesi⁴, MD

Students
Institutions

Rachel Black¹, Michael Epps^{1,3}, Ariano Munden¹, Yuriy Prilepskiy¹
¹Hampton University, Hampton, VA
²Eastern Virginia Medical School, Norfolk, VA
³Thomas Jefferson National Accelerator Facility, Newport News, VA
⁴Bon Secours DePaul Hospital, Norfolk, VA

Author Summary of Paper Z26.6
Friday, March 17, 2006, Room 323
2006 APS March Meeting, Baltimore, MD

Research Description

Improvement and optimization of conventional cancer treatment is one of the goals for the next generation of treatment modalities. Potential improvements include the development of target specific nuclear medicine agents, advanced molecular imaging, and leveraging biological response to radiation or drugs. The biological effects of radiation result principally from damage to DNA through a breakage of chemical bonds. Depending on the severity of the damage, the reconstruction of the process can result in serious illnesses (i.e., cancer). These effects can be produced by very high energy particles (greater than a few tens of MeV to TeV, similar to the ones created at or near an accelerator site), or a high concentration of (relatively) low energetic-radioactive material (less than a few MeV, similar to those found in radioactive sources used for medical treatments). In the case of radioactive materials, typical energies range from a few keV to a few MeV. To date, there is no data that address which (if any) energy regime is particularly responsible for the DNA breakdown.

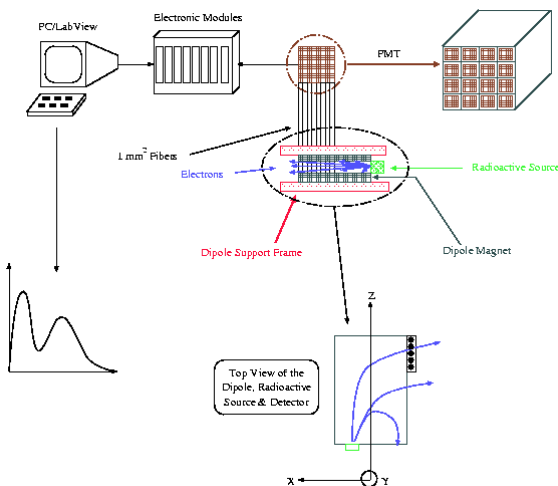
The Brachytherapy Research Group at the Center for Advanced Medical Instrumentation at Hampton University (Hampton, VA) performed a “*proof-of-principle*” study in 2005 of the energy damage of electrons incident on cancer cells. Survival studies have been done in the past but this is the first such work at the protein level. The new work is the first of its kind to span up to the MeV range. Preliminary results suggest a strong difference in the energy response of the

expression of the proteins (proteome) within the cancer cells. These initial findings have inspired a planned program led by Hampton University and the Eastern Virginia Medical School to thoroughly investigate tumor cell response to mono-energetic beams. For energies below 200 keV, the high quality mono-energetic beam of the Continuous Electron Beam Accelerator Facility at the Thomas Jefferson National Accelerator Facility will be used. For energies above 6 MeV, the electron beam will originate from a linear accelerator located at the Bon Secours DePaul Hospital. A radioactive source will generate electrons with energies between 200 keV and 3 MeV. If confirmed, this research will have broad implications for determining the reaction mechanisms of cancer cell death and cancer genome identification. This could result in isolating individual energies to optimize radiation treatment for given tumors and minimize side effects, as well as increasing the efficiency in finding pathways of their biological processes.

The Experiments

A three phase program was established for this study. Phase 1 focused on a “*proof-of-principle*” experiment that was completed in the summer 2005; phase 2 will use higher energy beams (above 500 keV); and phase 3 lower energy beams (below 500 keV). The last two phases are ongoing experiments currently being conducted in parallel, and include collaborators from Bon Secours DePaul Hospital (for phase 2), Jefferson Lab (for phase 3), EVMS and HU. The experimental procedure for phase 1 consisted of a three step process: (1) a calibration of the detector and radioactive source used; (2) the irradiation of the cell lines; and (3) proteomic evaluation of cell death.

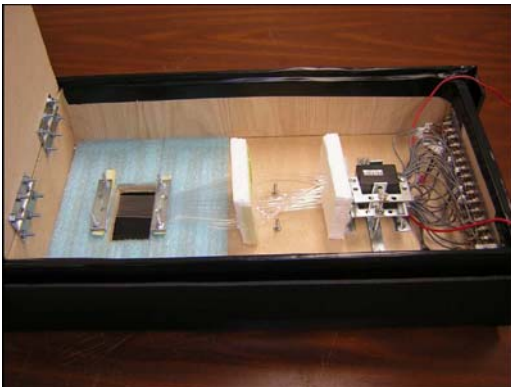
Detector calibration



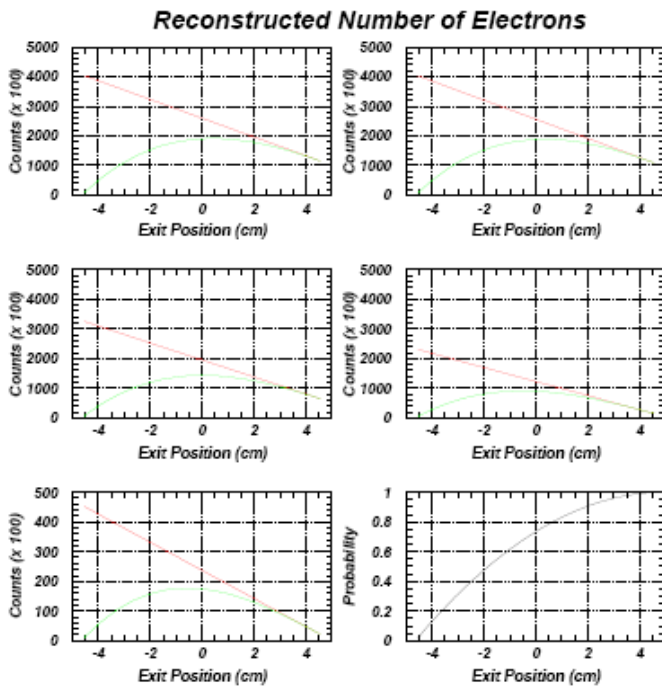
The electron source consisted of a $^{90}\text{Sr}/^{90}\text{Y}$ radioactive source with activity of 25 μCi , a maximum energy of 2.28 MeV, about 0.7 Gy/h at the target, and a cylindrical geometry (8 mm in diameter and 1 cm thick). The corresponding angular acceptance is: (Θ -horizontal, Φ -vertical) = (180° , 360°). Electrons were collimated (1 cm^2 opening) and deflected by a dipole magnetic field onto an array of scintillating fibers. The photons emitted within the fibers were then collected on a photo-multiplier tube and the corresponding signals sent to a LabView based CAMAC data acquisition system.



The permanent dipole magnet was constructed from two $5.08 \times 5.08 \times 2.54$ cm³ blocks of Neodymium Iron Boron (NdFeB) encased within an iron support frame. Two stainless steel plates defined a fixed 2 cm gap between the two blocks. The dipole was mapped using a portable Gaussmeter. The errors associated with the measurements were estimated to be 0.1 G and 1 mm for the magnetic field and location of the probe, respectively.



The detector consisted of an array of 12 fibers placed perpendicular to the exit of the dispersive plane of the dipole magnet. The fibers were 31 cm long with a rectangular cross section of 1 mm² and were connected to one of the 16 available channels of a multi-anode photomultiplier tube (Hamamatsu H6568).



(1) Comparison of the integral of the reconstructed energy spectrum to the projected number of electrons can be achieved by taking into account the acceptance of the spectrometer. The agreement is within a factor of 2.5. Note that a simple acceptance correction was made: source collimation by the dipole physical geometry and only one side of the dipole is “active” (where the detector is located). In addition, no correction from multiple scattering in air was taken into account, as well as the production of secondary particles and phase space. These contributions are being investigated with a Geant4 Monte Carlo simulation.

(2) Shown on the left are the 5 different positions of our detector with the top being the closest to the source, and the bottom the farthest. The bottom right panel is the cumulative probability distribution of finding an electron at a


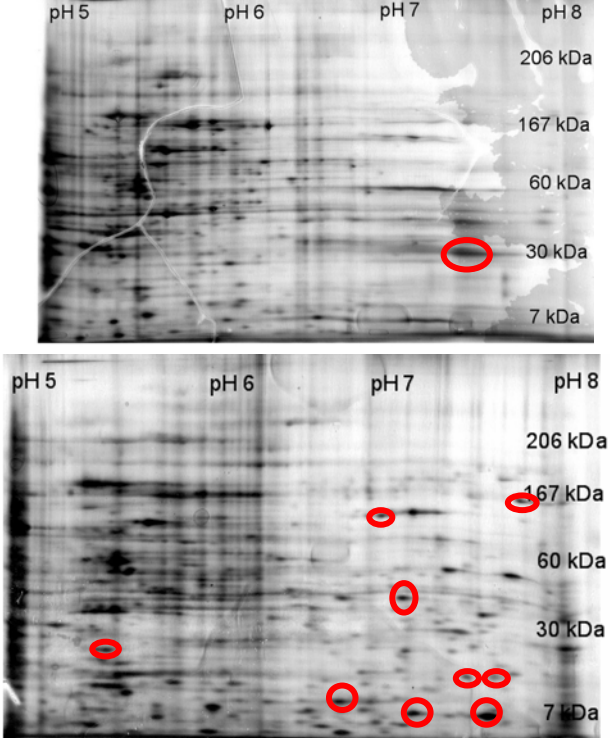
given exit position.

(3) After correction, the reconstructed average energy was found to be around 950 MeV (2.2% from the nominal 930 keV value).

(4) The energy resolution (for 1 mm² fibers) was found to be 1.38%.

Cell irradiation

Step two of our experiment consisted of the irradiation of human fibroblast cell lines using the above described radioactive source and dipole magnet (for electron energy separation and calibration).

	<p>(1) 30 samples of a normal human fibroblast cell lines were irradiated for 24 hours in a room maintained at constant temperature of 37 °C. The equivalent radiation exposure was about 3.5 Gy.</p> <p>(2) The samples were placed in plastic containers housing 4 compartments with individual volumes of 1x1x0.8 cm³. The base of the container was placed perpendicular to the dispersive plane of the dipole magnet.</p>
	<p>(1) After 24 hours of exposure, the radiation induced changes in the cellular proteome were established using 2D gel electrophoresis.</p> <p>(2) Examination of the Relative Biological Effectiveness of the various electron beam energies on human cell lines indicates an energy dependence of the radiation induced changes in the proteome. The top figure shows the response of the samples for kinetic energies below 1 MeV, the bottom one above.</p> <p>Some of the differentially expressed proteins have been highlighted in red circles and are currently undergoing further characterization and identification.</p>

Future experiments

Ongoing studies are being conducted to specifically establish the impact that a standard dose (~2 Gy) of each energetic bandwidth has on clonogenic survival (reproductive capacity), DNA double strand break (DSB) induction and the cellular proteome. Post irradiation changes in DSB levels will be established using a previously published PFGE technique (Britten *et al*, 1999). A modified version of this technique will be used to also monitor radiation-induced DNA single strand breaks. Radiation induced changes in the cellular proteome will be established using 2D gel electrophoresis, coupled with mass spectroscopic identification of candidate proteins. These studies will first be confined to 4 normal human fibroblast cell lines: AGO1521, AGO1522, GM06419 and WI-38.