Ion Channels and Improved Radiation Therapy

James Olson, Ph.D.

All cancer treatments are designed to damage or remove tumor cells, while allowing normal tissue to survive. Radiation treatment focuses beams of high-energy particles on the tumor, with a reduced dose of radiation given to adjacent normal cells. Chemotherapy exploits slight differences in the biochemistry of normal and cancerous cells in order to selectively poison the tumor. However, normal cells are often in the path of the high-energy radiation beam or may be adversely affected by the chemotherapeutic treatment. Thus, to avoid excessive damage to normal cells, the magnitude of the therapeutic dose delivered to the patient is limited. As the dose is reduced, a larger number of viable cancerous cells will remain after the radiation or chemotherapy treatments, thus increasing the risk that the tumor will reappear.

Research at the Wallace-Kettering Neuroscience Institute (WKNI) and other centers has suggested that combining radiation and chemical treatment methods may enhance the selective killing of tumor cells, and thus provide more effective and safe cancer therapies. This interaction between therapeutic modalities is explored in detail in a basic research project headed by Drs. James Olson and Viney Jain and funded by the Wallace-Kettering Neuroscience Institute. The researchers are examining novel drug treatments that may specifically sensitize tumor cells for damage by radiation treatment or protect cells from injury.

Drs. Olson's and Jain's research builds on recently discovered information about the biochemical mechanisms of cell death. Cells injured by radiation and other causes initiate a built-in self-destruct program called apoptosis (Figure 1). During this process, the outer cell membrane opens specific ion

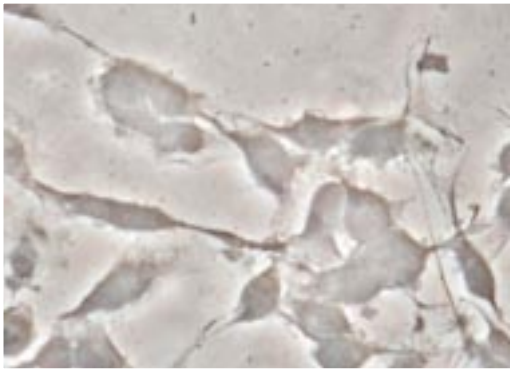

Figure 1A. Phase contrast photograph of brain cancer cells.

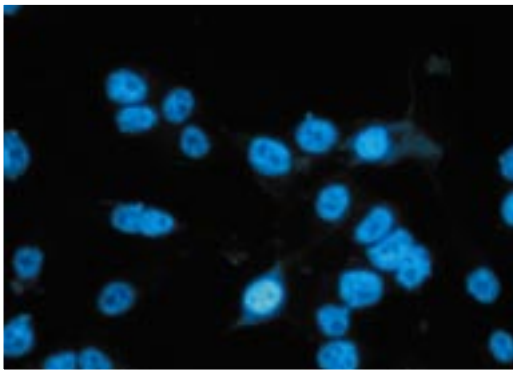

Figure 1B. The nucleus of each cell in Figure 1A is identified with a blue fluorescent stain.

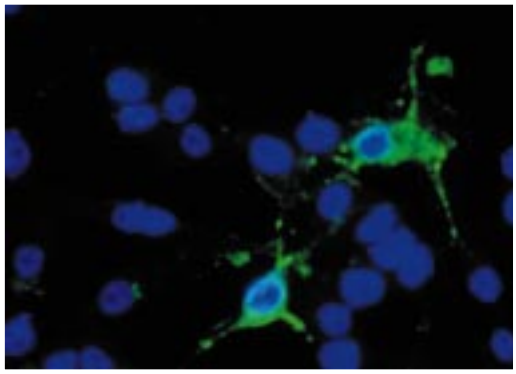

Figure 1C. Cells injured by oxidative stress (simulating damage produced by radiation) are identified by a green fluorescent stain, to indicate which cells have begun the process of programmed cell death called apoptosis.

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In addition to funding from WKNI, Dr. Olson's research is supported by two grants from the National Institutes of Health. He graduated from Cornell University with a Bachelor of Science in Engineering Physics and obtained his Ph.D. in Biophysics from the University of California at Berkeley. Following postdoctoral training at Stanford University Medical School, he took a faculty position at Tulane University Medical School. Dr. Olson moved to his present position at Wright State University in 1986.

channels. This causes the cell to lose intracellular electrolytes and shrink in size. Subsequently, the cell activates enzymes that digest its internal proteins and chop up its long DNA molecules into shorter pieces. Eventually these processes bring the metabolic machinery of the cell to a halt and the cell dies. Several researchers have shown that by inhibiting the initial opening of the membrane ion channels, the programmed progression to cell death is blocked.

To bring this new information to bear upon the treatment of patients with brain tumors, Drs. Olson and Jain are examining membrane ion channels of human cells from normal brain and from brain tumors. Their attention is focused on channels involved in cell death following radiation treatment. Because the regulation of membrane channels in normal and tumor cells is different, the researchers anticipate that drug treatments can be designed to block the function of channels in normal tissue, but not those of tumor cells. Alternatively, certain drugs may selectively increase the activation of membrane channels in irradiated tumor cells. Such treatments would protect the normal brain cells from injury, while increasing the number of tumor cells to undergo the programmed cell death of apoptosis. For example, after protecting normal cells from apoptosis with a drug treatment, the dose of radiation used to kill cancerous cells may be increased, thus causing greater damage to the tumor and reducing the risk of it reappearing. These results would directly impact patients at Kettering Medical Center Network – and throughout the world – by providing a more selective means to destroy tumor cells while maintaining the viability and function of normal brain tissue.

Ongoing WKNI Research Projects

New High Magnetic Field MRI Coming to Sycamore

Peter Roe, B.S., Mehdi Adineh, Ph.D., John German, M.D., Bilal Ezzeddine, Ph.D.

As technology races ahead, changing the world faster and faster, the world of MRI is forever changing and improving. Sycamore Hospital will be installing a new high magnetic field MRI system this summer. The new magnet will be a 1.5 Tesla short bore system, which will feel much like an open magnet but with superior imaging qualities. The opening of the magnet is flared and larger than many MRI systems and combines the accuracy of a tunnel scanner with the comfort of an open MRI. The integrated panoramic array allows simultaneous scanning with up to four coils. The advantage is revolutionary: you do not have to take the patient off the table to change coils for more than 95% of all studies. Given the improved technology in the gradient strengths and imaging coils, this magnet will provide Sycamore with state-of-the-art MRI capabilities, and high-resolution images when they are needed.

Clinically this new MRI can provide higher resolution capability with stronger and more precise images for diagnosis. It includes new arrays of neuroimaging sequences to allow greater diagnostic capability and accuracy. This more powerful system produces images faster, which adds to the comfort of the patient.