MALLINCKRODT FELLOWSHIP

USING ANTI-SENSE TO PREDICT CHEMOTHERAPY RESISTANCE OF TUMORS

DESPITE AN ONSLAUGHT OF successive generations of radiotherapy, surgical, and chemical weapons against cancer, physicians in the last 25 years have scarcely made a dent in the overall mortality from the affliction, especially in patients with tumors that have reemerged after treatment. One reason: primary tumors frequently give rise to secondary malignancies that withstand even the most potent cancer drugs.

A plucky proposal to use anti-sense oligonucleotides as radiopharmaceuticals to diagnose a baffling form of chemotherapy resistance has won Daniel Williamson, MD, PhD The Society of Nuclear Medicine's 1993 Mallinckrodt Fellowship. Dr. Williamson is a radiology resident at Brigham and Women's Hospital and clinical fellow in radiology at the Harvard Medical School, Boston. The $30,000 grant funded by Mallinckrodt Medical Inc. will be awarded to Dr. Williamson at the SNM Annual Meeting in June.

Of the identified chemotherapy resistance mechanisms, a form traced to a specific gene called MDR1, for multidrug resistance, has been shown to defeat the broadest spectrum of toxins used in cancer therapy. When activated, the gene orchestrates the synthesis of a glycoprotein that spans the plasma membrane and selectively pumps out drugs, lowering the concentration to harmless levels. Since healthy cells lining the intestines, kidney tubules, and in liver and adrenal tissues produce the MDR1 glycoprotein, scientists suspect that it may have evolved by serving a useful purpose protecting the body against circulating toxins.

Studies with patients whose tumors produce high levels of the MDR1 glycoprotein show that malignant tissues somehow activate the gene.

"The development of a noninvasive diagnostic imaging technique to screen for the expression of the multidrug resistance P-glycoprotein in tumors in vivo would be a significant advance for cancer chemotherapy," says David Piwnica-Worms, MD, PhD, director of the laboratory of molecular radiopharmacology at Brigham and Women's Hospital in Boston where Dr. Williamson will continue efforts to develop useful anti-sense imaging agents. An anti-sense oligonucleotide is a single strand of DNA made-to-order with a sequence of bases that is complementary to a specific mRNA target to which it binds. An effective anti-sense agent would enable patients to be tested for MDR before undergoing chemotherapy so they could get alternate treatments that would avoid pointless and severe side effects, says Dr. Piwnica-Worms. "It's kind of a high risk project, but high pay-off if it works."

Most cancer investigators have focused on radiolabeled peptides and antibodies for imaging molecular interactions inside the human body. "Surprisingly, no one has really pursued the use of anti-sense methodology for imaging molecular biology," says Dr. Williamson. Oligonucleotides pose the advantage of access to molecular targets inside the cell and nucleus which are largely off-limits to antibodies and other proteins.

The goal of most experiments with anti-sense DNA has been treatment based on thwarting the synthesis of specific proteins by jamming the translation of messenger RNA with a swarm of anti-sense oligonucleotides. The success of Dr. Williamson's approach hinges on achieving highly selective binding. He has designed an anti-sense DNA oligonucleotide complementary to the start codon of the mRNA encoded by the MDR1 gene. The radiolabeled compound should accumulate in tumors producing large amounts of the mRNA, which in theory would be discernable in SPECT images.

Dr. Williamson has demonstrated the accumulation of the anti-sense strands within cancer cell cultures that express the MDR glycoprotein, but he is not sure whether binding of the radiolabeled probe will be specific enough to obtain good images in whole animals.

If this long-shot approach works, Dr. Williamson hopes it might eventually be used by clinicians to assess the course of chemotherapy and by researchers to screen new MDR reversing agents.The basic anti-sense imaging technique could also be adapted for diagnostic imaging of other conditions. Parathyroid adenomas, for example, often only 1-2 mm across, usually are too small to show up in computed tomography or magnetic resonance scans. But such cancer cells are virtual factories of parathyroid hormone and are laden with mRNA.

Dr. Williamson, a radiologist who describes himself as "an NMR spectroscopist by trade," worked as a research chemist in molecular biology investigations before his clinical residency. Born in Lincoln, Nebraska, he went on to attend college and medical school at the University of Nebraska. He was recently married to Margaret Phillips, MD, also a radiologist at Brigham and Women's Hospital. Of the fellowship award, the research-oriented Dr. Williamson happily says, "This means I won't have to be a chest radiologist—this will allow me to be in the lab all the time."

J. Rojas-Burke