A tribute by Enrico Mihich, MD, FAACR

Maire T. Hakala (Hakala-Zakrzewski) was an internationally recognized leader among scientists studying the biochemical pharmacology of anticancer drugs. She was born in Helsinki, Finland, and by age 15 she was working as a laboratory technician. From 1939 to 1944 she was on the staff of the Orion Company with Nobel laureate A.I. Virtanen and continued to work with him until 1949, when she emigrated to the United States. In 1944, her family home in Finland had been destroyed by Soviet fire bombs.

She did research at Roswell Park Cancer Institute from 1956 to her retirement in 1987. Dr. Hakala’s 1957 paper in Science showed that the toxicity of methotrexate and aminopterin for mammalian cells in culture is prevented by the products of C-1 transfer reactions. This finding provided the basis for the HAT medium, which is of critical value in molecular biology. Her other studies showed the importance of extracellular environmental factors in altering drug sensitivity in cell culture. Dr. Hakala’s research clarified the mechanisms of resistance to antifolates. She found that dihydrofolate reductase is induced by methotrexate and that methotrexate-resistant tumor cells have enormous amounts of dihydrofolate reductase. Robert Schmike used such cells for developing the concept of gene amplification.

Other investigations elucidated the molecular mechanisms of cellular uptake of methotrexate. The fact that the incorporation of bromodeoxyuridine into DNA in place of thymidine caused imbalanced growth provided an early example of this type of mechanism of growth inhibition. Of major importance was her finding that the effect of 5-fluorouracil in human cells is greatly increased by leucovorin, leading to the development of widely used protocols of 5-fluorouracil and leucovorin for treating colorectal cancer. A symposium on the expanding role of folates and fluoropyrimidines in cancer chemotherapy was held in her honor at Roswell Park in 1988. The organizers noted that it was Dr. Hakala’s seminal research on these drugs that provided the basis for clinical trials at Roswell Park and elsewhere.

Dr. Hakala was an outstanding teacher and mentor as well as a long-time member of the AACR and of other societies such as the American Society of Biological Chemistry. In her retirement years, she was active in the League of Women Voters in Buffalo. After her husband’s death in 2005, she moved to Watertown, N.Y., and often wrote letters to the editors of the Buffalo Evening News and the Watertown Daily Times.

Survivors include her daughter, Dr. Kristina Harff, son-in-law Chris Ritcey, three grandchildren, and two sisters. Dr. Hakala will be greatly missed by colleagues and friends for her warm personality; she was always ready to help others and give them the benefit of her friendship and her wisdom in science and life.