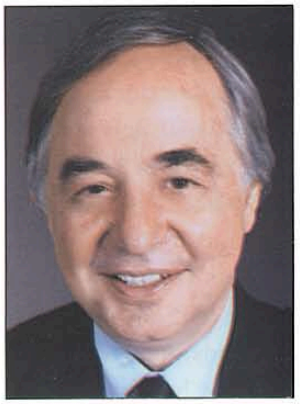
Cover legend: **Basil Rigas;** a member of The Editorial Academy of The International Journal of Oncology



Basil Rigas was born in Greece, in the ancient town of Nafpaktos, west of Delphi. After finishing high school in Athens, he entered Athens University Medical School, graduating *summa cum laude* in 1972. Three years later he obtained his DSc degree from the same school with highest honors. In 1974 he started his three-year residency in internal medicine at Brown University. After two and a half years of service in the Greek Army (which for Rigas included a year in an elite paratroopers unit) he did a fellowship in the Graduate Department of Biochemistry at Brandeis University, where William P. Jencks, a physician himself, offered an innovative (and rigorous) program for physicians planning to pursue a career at the interface between clinical medicine and science. This included, among others, advanced courses and rotations through enzymology and physical biochemistry.

At Brandeis, Rigas, who had by then decided to pursue gastroenterology as a medical subspecialty, worked for over a year with Lawrence Levine, a pioneer in the development of prostaglandin (PG) assays. Together they identified the major eicosanoids in saliva, demonstrated that their levels were independent of saliva's flow rate, documented their circadian variation, and demonstrated increased PGE_2 levels in the saliva of cystic fibrosis patients. Although the significance of the latter finding was not then fully appreciated, it is clear now that it was an observation ahead of its time.

Following Brandeis, Rigas went to Yale for a fellowship in Gastroenterology. After a busy clinical year, he joined the laboratory of Sherman Weissman in Human Genetics. While trying to isolate an HLA gene using the conventional arduous methodology, Rigas started developing a novel method to screen cDNA libraries. The idea was to exploit the ability of RecA protein to catalyze homologous recombination. The probe coated with RecA would search for the target sequence in a library whose DNA was now in solution and not in plated *E. coli* colonies. Target isolation would be accomplished by biotinylating the probe and isolating the intertwined probe and target through a streptavidin column. What was planned to be a few months of digression from the main project required nearly two years to complete. The method fully developed (and patented) is now widely used, available as a kit from various companies. Several RecA-based approaches have been developed as extensions of this idea.

In 1986 Rigas moved to Cornell Medical College, for his first faculty appointment in the Division of Digestive Diseases, where he initially studied the role of HLA in cancer. After carefully mapping HLA expression in human colon cancer, Rigas and his team demonstrated that PGE_2 downregulated transcriptionally HLA expression in colonocytes. Prompted by the first epidemiological report that NSAIDs lower the incidence of colon cancer, and using carefully collected surgical samples, they demonstrated that PGE_2 levels are elevated in human colon cancer. This critical observation was followed by the first demonstration that NSAIDs inhibit colon cancer cell proliferation, induce apoptosis and change the distribution of cells in the cell cycle; they also showed that aspirin induces an unusual form of apoptosis. Rigas' team, having as a key collaborator Steve Shiff at Rockefeller University, literally across the street from Cornell, also studied in detail the effects of various PGs and leukotrienes on colon cancer cell growth.

Their working hypothesis was that NSAIDs prevent colon cancer through their effect on PG synthesis. However, remembering that fetal calf serum, which is added to culture media, contains high PG concentrations, Rigas realized that NSAIDs must inhibit cancer cell growth independently of their effect on COX. Screening several colon cancer lines for their ability to produce PGs revealed that HCT-15 did not produce any, even under exogenous stimulation. As predicted, these COX-null cells responded to NSAIDs just the same as COX-expressing cells. The manuscript describing these unconventional data was rejected by several prominent journals, finding finally a home in Biochemical Pharmacology, when an astute reviewer pointed out its mechanistic importance. Several investigators have since confirmed this finding and an array of COX-independent effects of NSAIDs and COX-2 specific inhibitors has been identified. This observation has provided an altogether different evaluation of these compounds and their effects on cancer, discrediting the tendency to

explain NSAID/coxib effects through the 'one-way street' of COX inhibition. Furthermore, this key finding explains the differential effects on cancer of various COX-2 inhibitors and also suggests that, contrary to the still common belief, COX-2 overexpression may not play a dominant role in carcinogenesis, being a rather minor target for cancer control.

In parallel with the work on NSAIDs, Rigas worked on infrared spectroscopy (IRS) and cancer. During a lecture by P. Wong on the IRS study of phospholipids in liposomes *in vitro*, Rigas had the inspirational idea that IRS could uncover novel changes in cancer. Collaborating closely with an initially reluctant Wong, they reported in 1990 a series of IRS changes associated with colon cancer, essentially opening up a new line of scientific inquiry. Their paper on IRS patterns in cervical cancer, which followed in a year, was sensational, becoming a news story around the world, especially after The New York Times devoted to this discovery nearly half a page of its Science Section. A series of studies established that cancer is associated with distinct spectral patterns, including those due to reduced cellular levels of glycogen and changes in DNA hydrogen bonding. Rigas observed that pellets of exfoliated cervical cells had abnormal IR spectra even though they often contained <1% cancer cells. To solve this paradox, Rigas, now based at The Rockefeller University, collaborated with Menashi Cohenford from Digilab in Boston. Using Coheford's IR microscope (very simple by today's standards) they studied over 1,500 individual cervical cells. This labor-intensive study revealed IR spectral abnormalities even in the normal cells of neoplastic smears. Their joint 1998 paper claimed the identification of the pre-pre-cancerous cell, defined by chemical criteria. This work was probably the first to apply principal component analysis on such a problem and to study individual cells in monolayers. The full potential of the IRS work has not yet been realized, due mainly to limitations in data acquisition and processing. These IRS discoveries are covered by several patents, including one for the first ever application of IRS to the study of cells and tissues. Rigas is considering picking this theme up again, employing currently available powerful computing.

Since 2000, with his lab relocated to the Institute for Cancer Prevention, his work shifted to nitric oxide-donating NSAIDs (NO-NSAIDs), novel compounds with superior features compared to conventional NSAIDs. He and his team are leading the effort to understand these promising compounds. For example, in less than 5 years they took nitroaspirin from an untested (for cancer) powder to its first cancer prevention clinical trial, now underway at Stony Brook University where they moved in 2004. At Stony Brook Rigas is the Chief of the Divisions of Cancer Prevention and of Gastroenterology, and also directs the Center for Cancer Prevention Using Wireless Technology. The NO-NSAID work, besides evaluating in detail and from diverse angles a set of promising compounds, has generated data of broader importance. These include highlighting the role of positional isomerism in drug action; identifying novel mechanisms for the inhibition of Wnt and NF-κB signaling; detecting a novel variant of cell death; and pointing out the importance of reactive oxygen species in the chemoprevention of cancer.

Rigas has remained clinically active throughout his career. In 1995 he published a textbook on gastroenterology, co-authored with the legendary Howard Spiro, his Yale teacher. Their book, succinct, up-to-date and user-friendly, has had a successful career around the world, with an international English edition and also Spanish, Portuguese and Italian translations. Rigas also enjoys his hobbies in history and art. Recently, he resurrected the forgotten work of John Lykoudis, an early discoverer of the microbial etiology of peptic ulcer; and in collaboration with two gifted nuns, one a painter and the other a chemist, he studied by IRS and 'restored' a 1290 AD Byzantine fresco by the great master Panselinos.

Rigas is continuing his work on cancer prevention, employing a multidisciplinary approach that encompasses a wide range of methodologies that extend from synthetic chemistry and nanoscience to human clinical trials.