Cancer Research

Barnett Rosenberg: In Memoriam (1924–2009)

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Dr. Barnett Rosenberg. This image is being published with the kind permission of Michigan State University.

Dr. Barnett Rosenberg, a professor of chemistry and biophysics at Michigan State University since 1961, passed away on August 8, 2009 after a brief illness. Although he was not a cancer researcher by training or by departmental ties, Dr. Rosenberg made a fundamental observation: Platinum salts could exert potent antiproliferative effects on living organisms. His work led to the development of the immensely important array of platinum analogues that are today the backbone of solid tumor therapy. These drugs are responsible for saving the lives of untold numbers of patients with testicular cancer and other, more common tumors. The discovery and development of these therapies represent the collaborative work of animal researchers, biologists, and clinical trialists inspired by Dr. Rosenberg's idea that metals could have a therapeutic role in the treatment of cancer.

Metals have attracted attention in the past for cancer treatment. Various types of arsenicals had been the mainstay of folk therapies for leukemia for centuries, although their place in the treatment of acute promyelocytic leukemia as an intravenous preparation was not recognized until 10 years ago, due to seminal work with arsenic trioxide in China (1). None of the other heavy metals proved to be tolerable or effective in early experiments with rodent models. Gallium evoked interest but, while taken up by tumors as a scanning agent, had significant nephrotoxicity and minimal antitumor activity in humans (2).

Dr. Rosenberg graduated from Brooklyn College with a bachelor of science in physics in 1948 and received his doctorate in physics from New York University in 1956. Following his work as a senior research scientist at Westinghouse Electric Corp. (1956–1958) and a research scientist at New York University (1959–1961), Dr. Rosenberg joined the biophysics faculty at Michigan State University and conducted experiments with bacteria placed in a solution with platinum electrodes. When a current was passed through the solution, elongated bacterial forms emerged, the product of futile attempts to proliferate. He found that these effects could be reproduced by medium previously exposed to an electric current and were caused by the platinum chloride salts found in solution (3). The *cis*-diamminedichloride platinum salt (cisplatin; Fig. 1) was particularly potent. Under contract with the National Cancer Institute (NCI), Dr. Rosenberg discovered that the cisplatin salt produced potent antitumor activity against sarcoma 180 and leukemia L1210, and the drug won a place in the NCI pipeline (the linear array) in the early 1970s. Despite significant nephrotoxicity, cisplatin entered the clinic in 1972, and in its initial tests at Memorial Sloan-Kettering, produced remarkable responses in drug-refractory cancers (4). However, the enthusiasm for cisplatin was tempered by significant renal dysfunction in 30% of patients treated with 50 to 75 mg/m^2 doses. Other toxicities, including hearing loss, magnesium wasting, and neuropathy, became apparent in patients receiving longer-term treatment. Renal tubular toxicity posed the major obstacle to the further development of cisplatin, but the Memorial Sloan-Kettering group, and particularly, Dr. Esteban (Steve) Cvitkovic, a research fellow from Croatia, discovered a way to avoid this toxic response: Chloride diuresis maintained the platinum salt in its inactive dichloride state and prevented the aquation reaction necessary for adduct formation (5). It is notable that Dr. Cvitkovic was later the lead clinical investigator responsible for the development of oxaliplatin, a drug with slightly different pharmacologic properties and a different spectrum of toxicities than cisplatin and with significant activity in colon cancer.

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The further clinical development of cisplatinum is well known in the oncology field. Six years after the initiation of clinical testing, it was approved by the Food and Drug Administration in 1978 for the treatment of testicular cancer, largely based on the work of Dr. Larry Einhorn and colleagues at Indiana University (6). Subsequent refinements of its use in this disease have led to the cure of more than 90% of these patients. The joint investment of NCI and Bristol-Myers Squibb (to whom cisplatinum was licensed by NCI) further extended the range of uses for this drug. Cisplatinum became the backbone of combination therapy for testicular, bladder, lung, ovarian, head and neck, and gastric cancers, and most recently, for triple negative breast cancer and a number of other less common tumors. Cisplatinum analogues, carboplatin and oxaliplatin, have further extended this range of benefit. The patients cured by these regimens and those that have benefited from this therapy number in the millions. As a radiation sensitizer, it is commonly used in locally aggressive esophageal, cervical, and endometrial cancers. Its exquisite biology as a DNA adduct–forming agent has led to discoveries of new classes of proteins that protect DNA, repair DNA damage, and mediate cell death. It would be frightening to imagine the current status of cancer treatment without this essential drug. The discovery of cisplatinum brought great recognition to Dr. Rosenberg, and royalties stemming from its patents have funded extensive biomedical research programs at Michigan State University over the past 25 years.

Dr. Rosenberg continued his interest in cancer pharmacology through his work in biophysics at Michigan State University and later through his foundation, the Barros Research Institute. Dr. Rosenberg was the recipient of many honors during his lifetime, including the Bruce F. Cain Award from AACR in 1983, the Charles F. Kettering Prize of the General Motors Cancer Research Foundation in 1984, and the Harvey Prize from the Technion-Israel Institute of Technology in 1985. His work stands as a testament to the importance of keen observation and imagination in following the leads to basic research.

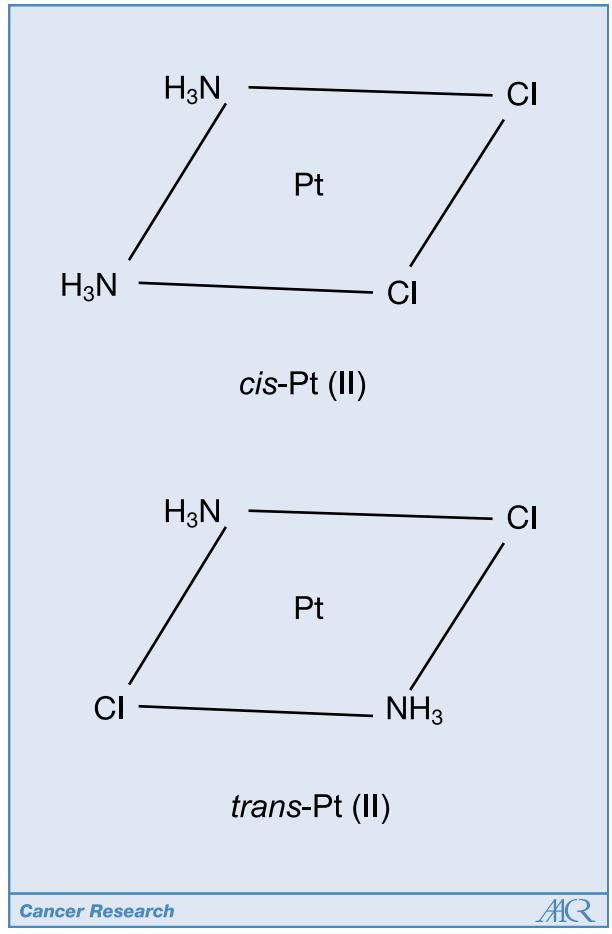

Figure 1. The structure of *cis*-diamminedichloroplatinum and its inactive *trans* isomer.

Dr. Rosenberg is survived by his wife, Ritta, and two children.

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