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# PROCEEDINGS OF THE XI INTERNATIONAL SYMPOSIUM OF PLATINUM COORDINATION COMPOUNDS IN CANCER CHEMOTHERAPY

*11-14 October, 2012*
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*Preface*

# Platinum and Other Heavy Metal Coordinating Compounds in Cancer Chemotherapy: Overview of Verona ISPCC XI

FRANCO MUGGIA[1], ROBERTO LEONE[2], ANDREA BONETTI[3]

[1]*New York University School of Medicine and Cancer Institute, New York, NY, U.S.A.;*
[2]*Pharmacology Unit, Department of Public Health and Community Medicine, University of Verona, Verona, Italy;*
[3]*Department of Oncology, Mater Salutis Hospital-ASL 21 della Regione Veneto, Legnago (VR), Italy*

ISPCC X took place in Verona, Italy in 2007, and its deliberations were followed by a volume published by Humana Press (1) and by an overview of such a meeting in Gynecologic Oncology (2). Subsequently, a planned meeting ran into economic woes and compounded by logistical issues, prompting a rescue effort by a large cadre of enthusiastic past participants, and by the hosts of the preceding meeting. This gave rise to ISPCC XI that was held in October 11-14, 2012, and covering themes that are represented in updated form within this issue of Anticancer Research. We thank the publisher, John Delinasios for invaluable editorial assistance in these submissions.

Since the outset of ISPCC meetings, chemists continue to explore novel structures and ligands that modify platinum chemistry, and the same goes on to a lesser scale with other heavy metals. The inspiration behind these pursuits is, of course, the discovery of the anticancer actions of cisplatin by Barnett Rosenberg in 1965 – as further detailed in this issue by James Hoeschle who became one of his students at Michigan States Department of Microbiology. At the 2012 meeting, and exemplified by structures that have been recently introduced, several new compounds are being studied to explore aspects of their biological activity that may differ from the parent compounds. Dicycloplatin, phenanthriplatin, phosplatin, and liposomal formulations are under development, as are new studies with gold and ruthenium compounds. Competing market priorities make studies in this area challenging, albeit the success of the meeting is proof of continued interest in the biological activity of these agents.

Major aspects of laboratory investigations relate to DNA repair, development of resistance, implications for collateral sensitivity, and identification of toxicity protection. These areas were covered in depth at this and the preceding meeting (those not covered in this issue did appear in part in 2009, references 3-5), and are partly covered by the current articles. The clinical implications from the insight provided by these studies continue to mount: DNA repair pathways are being delineated as tumor genomes are deciphered, tumors lacking homologous recombination repair have become targets not only of cisplatin but also inhibitors of poly-ADP-ribose-polymerase (PARP), and further identification of cellular transporters are now being targeted to overcome resistance or, if specific to certain tissues – such as the cochlea or the renal tubules – to protect these cells against known clinical toxicities.

Progress in treatment with platinum compounds continues to take place, as these drugs often occupy center stage in the management of germ cell tumors and cancers of gynecological, urogenital, aerodigestive and respiratory tracts. Understanding what contributes to neurotoxicity, a major dose-limiting toxicity of cisplatin and oxaliplatin, is the focus of a continued review in this volume, and new areas include prevention of hypersensitivity reactions and depression associated with cumulative use of platinums. As an example, their evolving role in ovarian cancer and in colorectal cancers is described.

Technology has simplified communications and discovery. However, much of medical progress builds on past knowledge and on constructive discussion by committed researchers, and we hope that disseminating these recordings may prove useful in cementing these achievements.

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*F. Muggia, R. Leone, A. Bonetti*

# Biography of Professor Barnett Rosenberg: A Tribute to His Life and His Achievements

JAMES D. HOESCHELE

*Department of Chemistry, Eastern Michigan University, Ypsilanti, MI, U.S.A.*

This biography pays tribute to Professor Barnett Rosenberg (Figure 1), a personal friend, mentor, and a brilliant and creative scientist, whose "curiosity, imagination and persistence led to the discovery and development of the globally important antitumor drug, cisplatin" (1). This tribute to Professor Rosenberg is especially fitting since 2012 represents the 50th Anniversary of the start of his research at Michigan State University (MSU) that led to the discovery of cisplatin.

Dr. Rosenberg, a former Professor at MSU and co-discoverer, with Loretta Van Camp, and developer of cisplatin, died at his home on August 8, 2009 at the age of 82, following a long and debilitating illness. Dr. Rosenberg is survived by a very accomplished family: his wife, Ritta; daughter, Tina (winner of the prestigious McArthur Award and the Pulitzer Prize in Journalism); son, Paul (Ph.D., Philosophy), three grandchildren and his son-in-law, Rob (a humanitarian lawyer).

## Education and Early Professional Experience

Barney, as we all called him, was born in New York City in 1926 and at an early age knew that he wanted to become a scientist. He enrolled in Brooklyn College, NY, but left college to join the Army when he turned 18, and was stationed in the Philippine Islands for the next 19 months working as a pharmacist until WWII ended. He returned to Brooklyn College and graduated in 1948 with a BS Degree in Physics. He spent the next year in Zurich, Switzerland, at the Federal Institute of Technology as a so-called "wanderjahr", but ostensibly as a graduate student. Little did he realize that in 1973 (and again in 1982), he would propose establishing a "Metals in Medicine Institute at MSU" with a field laboratory in Zurich, because, to Barney, Zurich symbolized just how international in scope the Pt field had become by 1973, with over 150 laboratories doing work in the Pt or metals field.

Following his stint in Zurich, Barney entered the graduate school at New York University (NYU) where he obtained his MS (1950) and Ph.D. (1955) in Physics. His Ph.D. mentor studied under Albert Einstein and, needless to say, Barney was proud to be the 'academic grandson' of Einstein, whom he regarded as…the "Ultimate Thinker".

After completing his Ph.D., he accepted a Post-doctoral Fellowship at NYU, in the Institute of Mathematical Sciences from 1955-56. He then accepted an industrial position at Westinghouse Electric Corp. (1956-58) as a Senior Research Physicist.

He returned to NYU as a Research Scientist–Project Director from 1958-61. It was at NYU that Barney started doing biophysical studies with his own government grant and where he conceived the idea to study the effect of an electric field on cell division in mammalian cells. From inception, this idea was a cancer-oriented study. Shortly thereafter, however, he started looking for a permanent position at a University in the US.

## Dr. Rosenberg – The Professor

Dr. Rosenberg Joined MSU in 1961 and co-founded the Biophysics Department with Dr. Leroy Augenstein. His research in the Biophysics Department focused initially on vision and then predominantly on Platinum Cancer Chemotherapy (1962-1982). He was a Professor in the Biophysics Dept. (1961-1979) and in the Chemistry Department (1980-1997). In 1982, he founded Barros Research Institute in Holt, MI, where he directed a diverse range of non-Pt-related research projects until 2009. He officially retired from MSU on January 1, 1997.

## Dr. Rosenberg – The Person

Dr. Rosenberg was a kind, gentle and non-pretentious person who, despite his stature, showed respect to everyone. He especially valued and encouraged thinking. Anyone who interacted with Barney knew that he was passionate about his work but, at the same time, he avidly promoted the work of young scientists and women. As an example, in lieu of a traditional retiree symposium held for Barney (1997), Barney insisted that the work of MSU's bright young scientists be

highlighted rather than reviewing highlights of his own career. Thus, six young MSU faculty members, representing a variety of academic disciplines, were featured at 'his retirement' festivities. "Let's invest in brains", Rosenberg insisted. "Let's have enough sense, where we already see promise shown, to give them the money and let them run free with it, at least for a sufficiently long period of time. Let them make their contributions to the University and the world. Most of them may not make great contributions, but some might. And that will more than repay our system."

Barney was the quintessential idea person. At meetings, he challenged his colleagues to think about the many ideas/hypotheses that he and others proposed.

Working in Barney's lab was indeed an enriching experience. It presented the opportunity to become involved in the new and exciting field of using metal complexes in medicine, to travel abroad to present papers at international meetings, and to meet internationally-known scientists in the field.

Barney did not micro-manage his students, who were mainly post-doctoral students. Rather, he trusted in their abilities and provided them with a maximum amount of freedom to do their research.

A hallmark of Barney's personal research philosophy was that he only did research that no one else was doing and only research that would benefit mankind.

Figure 1. *Dr. Barnett Rosenberg, Professor, Michigan State University, circa 1970.*

## Dr. Rosenberg – Communicator Extraordinaire

Barney was indeed an extraordinary communicator. His personal connections and frequent contacts with the NCI, drug and Pt companies, and clinicians, communicating timely information, immensely expedited the development, approval, and licensing of cisplatin. Clearly, he was the primary developer of cisplatin.

Dr. Rosenberg established a Pt Cancer Research Information Center at MSU (1970). This center promoted interaction and collaboration among researchers and periodically distributed an up-to-date comprehensive bibliography of all papers published in the Pt field to all interested researchers.

He communicated with a diverse group of people, including scientists, professionals, lay people, family members/relatives wishing to acquire the 'wonder drug' or in need of a referral (physician/hospital), and cancer patients who offered to participate in clinical trials because they thought Barney was an oncologist.

Dr. Rosenberg was indeed a prolific writer and the weight of his written correspondence, stored in five file cabinet drawers, is approximately 300 lbs. Today, all of Dr. Rosenberg's correspondence and documents have been archived for public access by the MSU Archives located on the campus of MSU.

## Discovery of Cisplatin

Unquestionably, the discovery and development of cisplatin is the most significant achievement in Dr. Rosenberg's career and, arguably, in the entire research history at MSU. The discovery was indeed a team effort and in addition to the outstanding work of Loretta Van Camp, it should be recognized that Tom Krigas, Eugene Grimley, and especially Andrew Thomson, contributed significantly to the discovery. It is an inspiring and complex three-part story covering a five-year effort and includes: the discovery that cell division in bacteria was inhibited but not cell growth; an intensive and relentless search for the causative agent; and the eventual 'back-door' discovery of cisplatin.

## Inhibition of Cell Division of *Escherichia coli*

The story began with the serendipitous discovery that when normal *E. coli* B (Figure 2, left panel) were exposed to an electrical field (generated using Pt electrodes in a continuous-flow bacterial cell), cell division was inhibited but not cell growth (2), leading to the formation of long filamentous strands (Figure 2, right panel), 200- to 300-fold their normal length. What was not serendipitous, however, was Barney's ability (*i.e.* his 'Prepared Mind') to

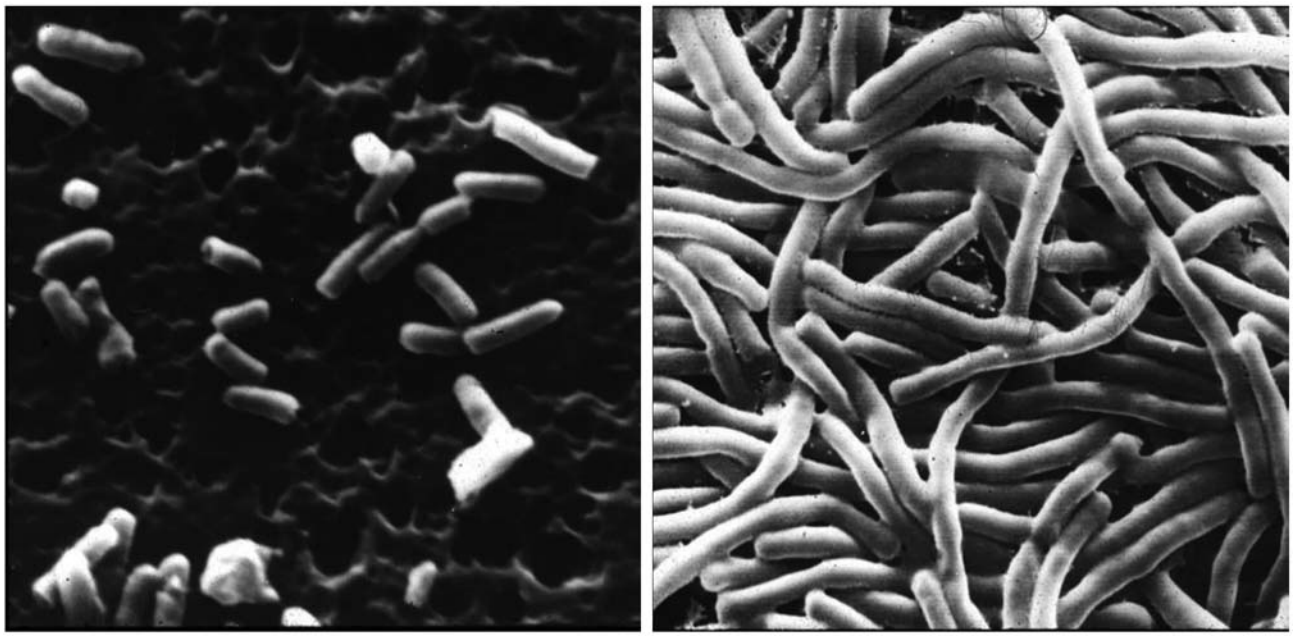

Figure 2. *Normal (left panel) and filamentous (right panel) forms of E. coli bacteria.*

immediately recognize and understand the potential of the discovery: that the agent causing the effect might indeed have utility in treating cancer. Thus, an intensive search for the causative agent began and ended in identifying cisplatin as a potent antitumor agent.

## Search for The Causative Agent and The Discovery of Cisplatin

The Rosenberg team systematically evaluated the role of many experimental variables as possible causative agents. Eventually, it was hypothesized that $(NH_4)_2PtCl_6$, produced by electrolysis under the experimental conditions, was the causative agent (3). In another surprising discovery, Loretta Van Camp observed that stock solutions of $(NH_4)_2PtCl_6$ prepared for *in vitro* experiments to duplicate the inhibitory effects observed under electrical field conditions underwent photochemical change in the bacterial medium and the medium became more potent (3). It was shown that the species responsible for the increased potency was cis-$[Pt(NH_3)_2Cl_4]$, produced in the photochemical process, which was identified by isolating it from the medium, and by independently synthesizing it using *cis*-$[Pt(NH_3)_2Cl_2]$ as the synthetic precursor. Both *cis*-$[Pt(NH_3)_2Cl_4]$ and cis-$[Pt(NH_3)_2Cl_2]$ inhibited cell division *in vitro* and were subsequently tested *in vivo* for antitumor activity. Both complexes were found to be active, but *cis*-$[Pt(NH_3)_2Cl_2]$ demonstrated superior antitumor activity. Thus, it was at this final stage of the investigation that cisplatin was discovered. To date, it is still not known whether cisplatin was produced in the bacterial cell under the electrical field conditions.

## Regression of Advanced Solid Sarcoma 180 Tumors by Cisplatin

Figure 3 shows the historic results of the antitumor tests of cisplatin on mice bearing S180s tumors which had been allowed to grow to day 8 and were then treated with a single dose of cisplatin at 8.0 mg/kg body weight (4).

The top panel shows the fate of the untreated controls: 100% lethality by day 20/21. The bottom panel shows the progressive and successful regression of the large S180s tumors (~0.5-1 g on day 8). In subsequent tests conducted at the NCI and a host of other labs, cisplatin was found to be effective against a wide variety of tumors.

Cisplatin entered clinical trials in 1972 in the USA and was approved by the FDA in 1978.

## Impact – Discovery, Development, and FDA Approval of Cisplatin

The impact of the discovery, development, and FDA approval of cisplatin was profound. It generated enormous interest and research in metal-based drugs in universities, government, and commercial entities. It opened-up sources of grant support for their study, brought about a renaissance in bioinorganic chemistry, and stimulated interest in anticancer drugs in the pharmaceutical industry in general.

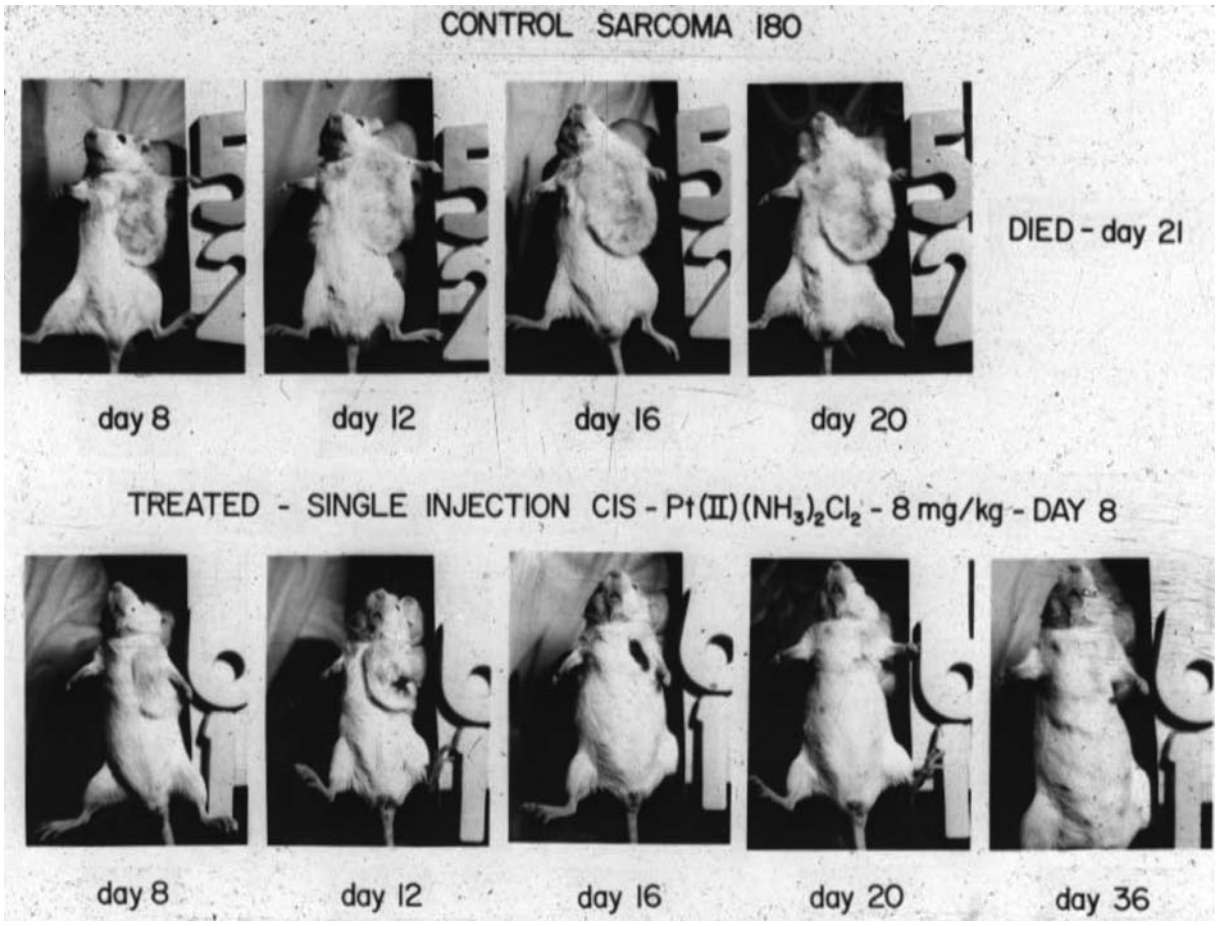


Figure 3. *Regression of Advanced Solid Sarcoma 180 Tumors by Cisplatin.*

Very importantly, it overcame the stigma that all metal-based compounds are heavy metal poisons and devoid of biological activity. And, most importantly, it made available to the world a needed and effective drug that has benefited millions of patients afflicted with solid tumors.

## Dr. Rosenberg – The Scholar/Inventor

Barney was indeed a deep thinker and a prolific writer, and much of his thinking was done to the accompaniment of the music of Dvorak, Mozart, and other classical composers. He produced 155 publications, 11 review articles (relating to Pt studies), 67 Pt-related articles, and 88 non-Pt articles covering a widely diverse range of research topics. What is remarkable about these publications is their diversity and originality, as well as the immense social good derived from them.

Dr. Rosenberg presented innumerable invited lectures and was the recipient of 22 patents. Of great significance is the fact that two out of the three FDA-approved Pt drugs to date were synthesized in his laboratory.

## Honors and Awards

Indeed, Professor Rosenberg had a long and distinguished career and was the recipient of 16 awards, including the prestigious Cain Memorial Award, American Association of Cancer Research (1983); Charles F. Kettering Prize given by the General Motors Cancer Research Foundation (1984); Galileo Galilei (Gold) Medal at the University of Padua (Italy, 1987); and the Harvey Prize, University of Israel (1985).

Although hopeful and certainly deserving, he never received what many scientists thought was his inevitable and deserved big prize–the Nobel Prize. He was recommended to the Nobel Prize Committee several times, the last time being in 2002.

## Research at the Barros Institute

The following is a partial list of Dr. Rosenberg's research interests, demonstrating the diverse nature of the projects that he directed:

- Aging
- Induction of cancer propensity from cosmic ray exposure in previous generations
- Microwave detection of brain activity (for triage on the battlefield)
- Development of a rapid, portable heart rate variability detector
- Theoretical study of the origin of the constancy of charge and mass in fundamental sub-atomic particles.
- Fish herding
- Isolation of bacteria that convert coal to methane
- Accidental discovery and development of Barrogen – a protozoan protein having anticancer/antiviral activity

The accidental discovery and development of Barrogen, an 18-kDa protozoan protein with anticancer/antiviral activity, is most noteworthy and is still being pursued. Clinical results have shown it to be very effective in vertebrates, but not in man.

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