

Platinum and Other Heavy Metal Compounds in Cancer Chemotherapy

Andrea Bonetti • Roberto Leone
Franco M. Muggia • Stephen B. Howell
Editors

Platinum and Other Heavy Metal Compounds in Cancer Chemotherapy

Molecular Mechanisms
and Clinical Applications

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Editors

Andrea Bonetti
Department of Oncology
Mater Salutis Hospital
Legnago
Italy
andrea.bonetti@aulsslegnago.it

Franco M. Muggia
Division of Medical Oncology
New York University School of Medicine
and the NYU Cancer Institute
New York, NY, USA
france.muggia@nyumc.org

Roberto Leone
University of Verona
Institute of Pharmacology
Verona, Italy
rleone@sfm.univr.it

Stephen B. Howell
Department of Medicine
and the Moores Cancer Center
University of California, San Diego
La Jolla, CA
USA
showell@ucsd.edu

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This book is dedicated to the memory of Lloyd R. Kelland, Ph.D., a generous and thoughtful colleague whose careful investigating of the mechanisms by which the platinum-containing drugs kill tumor cells provided valuable insights into how to improve their use in the management of cancer.

Preface

Cisplatin, the first member of the family of platinum-containing chemotherapeutic agents, was discovered by Barnett Rosenberg in 1965 and approved by the FDA for marketing in 1978. After 30 years of use in the clinic, cisplatin remains a central element of many treatment regimens. Cisplatin is still an irreplaceable component of a regimen that produces high cure rates in even advanced nonseminomatous germ-cell cancers, and is widely used in the treatment of ovarian cancers and other gynecologic cancers, head and neck, and numerous other tumor types. The development of carboplatin has reduced some of the adverse events associated with cisplatin treatment, and the introduction of the DACH platinum compound oxaliplatin has broadened the spectrum of activity of the platinum compounds to include gastro-intestinal cancers, especially colorectal cancer. The clinical importance of this family of drugs continues to drive investigation into how these drugs work and how to improve their efficacy and reduce their toxicity.

The papers in this volume were presented in Verona, Italy, during the tenth International Symposium on Platinum Coordination Compounds in Cancer Chemotherapy. The symposium was jointly organized by the Department of Oncology of the Mater Salutaris Hospital – Azienda Sanitaria Locale 21 of the Veneto Region – and by the Department of Medicine and Public Health, Section of Pharmacology, the University of Verona. They reflect the vitality of this field and the increasing use of new molecular and cell biologic, genetic, and biochemical tools to identify approaches to further improve their use.

Legnago, Italy
La Jolla, California, USA
Verona, Italy
New York, New York, USA

Andrea Bonetti
Stephen B. Howell
Roberto Leone
Franco M. Muggia

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Contributors

Brooke J. Andrews

Department of Medicine, Indiana University School of Medicine,
Indianapolis, IN, USA;
Biomedical Science Graduate Program, Wright State University, Dayton,
OH, USA

Daniela Antonucci

Department of Biotechnology and Environmental Science, University of Salento,
Lecce, Italy

Lea Baer

Department of Radiation Oncology, New York University School of Medicine,
New York, NY, USA;
NYU Cancer Institute, New York, NY, USA

Giacomo Baldi

Division of Medical Oncology, Azienda USL 6, Istituto Toscano Tumori,
Livorno, Italy

Enzo Banelli

Department of Radiation Oncology, University “Sapienza,” Rome, Italy

Philip Beale

Sydney Cancer Centre, Concord Repatriation General Hospital, Concord,
Australia

Michele Benedetti

Department of Biotechnology and Environmental Science, University of Salento,
Lecce, Italy

Valentina Benedetti

Department of Experimental Oncology, Fondazione IRCCS Istituto Nazionale
Tumori, Milan, Italy;
Department of Experimental Oncology and Laboratories, Preclinical
Chemotherapy and Pharmacology Unit, Istituto Nazionale per lo Studio e la Cura
dei Tumori, Milan, Italy

Alberta Bergamo

Callerio Foundation Onlus, Trieste, Italy

Roberta Bertani

Department of Chemical Processes of Engineering, University of Padova, Padova, Italy

Debadeep Bhattacharyya

Department of Biochemistry and Biophysics, School of Medicine, University of North Carolina, Chapel Hill, NC, USA

Andrea Bonetti

Department of Oncology, Mater Salutis Hospital, Legnago, Italy

Ovidio Bussolati

Unit of General and Clinical Pathology, Department of Experimental Medicine, University of Parma, Parma, Italy

Sharon Campbell

Department of Biochemistry and Biophysics, School of Medicine, University of North Carolina, Chapel Hill, NC, USA

Guido Cavaletti

Department of Neurosciences and Biomedical Technologies, University of Milan “Bicocca,” Monza, Italy

Stephen G. Chaney

Department of Biochemistry and Biophysics, School of Medicine, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA

Etienne Chatelut

EA3035, Institut Claudius Regaud, Toulouse, France
Paul Sabatier University, University of Toulouse, Toulouse, France

Christine Chevreau

EA3035, Institut Claudius-Regaud, Toulouse, France

Giuliano Ciarimboli

Universitätsklinikum Münster, Medizinische Klinik und Poliklinik D, Experimentelle Nephrologie, Münster, Germany

Giovanni Codacci-Pisanelli

Department of Experimental Medicine and Pathology, University “Sapienza,” Rome, Italy

Samanta Cupini

Division of Medical Oncology, Azienda USL 6, Istituto Toscano Tumori, Livorno, Italy

Esteban Cvitkovic

AAIOncology, Kremlin-Bicêtre, France

Ross Davey

Bill Walsh Cancer Research Laboratories, Department of Medical Oncology,
Royal North Shore Hospital, Sydney, Australia;
The University of Sydney, Lidcombe, NSW, Australia

Anton I.P.M. de Kroon

Biochemistry of Membranes, Bijvoet Institute and Institute of Biomembranes,
Utrecht University, Utrecht, The Netherlands

Angelo De Milito

Department of Therapeutic Research and Medicines Evaluation, Unit of Antitumor
Drugs, Drug Resistance and Experimental Therapeutic, Istituto Superiore
di Sanità, Rome, Italy

Shanta Dhar

Department of Chemistry, Massachusetts Institute of Technology, Cambridge,
MA, USA

Francesco Dionisi

Department of Radiation Oncology, University “Sapienza,” Rome, Italy

Nikolay V. Dokholyan

Department of Biochemistry and Biophysics, School of Medicine, Lineberger
Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC,
USA

Fabrizio Drudi

Department of Oncology and Oncohematology, Infermi Hospital, Rimini, Italy

Cosimo Ducani

Department of Biotechnology and Environmental Science, University of Salento,
Lecce, Italy

Stefano Fais

Department of Therapeutic Research and Medicines Evaluation, Unit of Antitumor
Drugs, Drug Resistance and Experimental Therapeutic, Istituto Superiore
di Sanità, Rome, Italy

Sandrine Faivre

RayLab and Department of Medical Oncology, Beaujon University Hospital,
Clichy, France

Alfredo Falcone

Division of Medical Oncology, Azienda USL 6, Istituto Toscano Tumori,
Livorno, Italy;
Department of Oncology, Transplantations and New Technologies in Medicine,
University of Pisa, Italy

Francesco P. Fanizzi

Department of Biotechnology and Environmental Science, University of Salento, Lecce, Italy

Manuela Fantini

Department of Oncology and Oncohematology, Infermi Hospital, Rimini, Italy

Gwenaël Ferron

Department of Surgical Oncology, Institut Claudius Regaud, Toulouse, France

Antonio T. Fojo

Experimental Therapeutics Section, Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Lorenzo Fornaro

Division of Medical Oncology, Azienda USL 6, Istituto Toscano Tumori, Livorno, Italy

Silvia C. Formenti

Department of Radiation Oncology, New York University School of Medicine, New York, NY, USA;
NYU Cancer Institute, New York, NY, USA

Renata Franchi-Gazzola

Unit of General and Clinical Pathology, Department of Experimental Medicine, University of Parma, Parma, Italy

Lara Furini

Department of Oncology, Mater Salutis Hospital, Legnago, Italy

Elisabetta Gabano

Department of Environmental and Life Sciences, University of Piemonte Orientale "A. Avogadro," Alessandria, Italy

Valentina Gandin

Department of Pharmaceutical Sciences, University of Padova, Padova, Italy

Marzia B. Gariboldi

Department of Structural and Functional Biology, University of Insubria, Busto Arsizio, Italy;

Laura Gatti

Department of Experimental Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy;
Department of Experimental Oncology and Laboratories, Preclinical Chemotherapy and Pharmacology Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy

Amélie Gesson-Paute

Department of Surgical Oncology, Institut Claudius Regaud, Toulouse, France

Aïda Ghoul

RayLab and Department of Medical Oncology, Beaujon University Hospital, Clichy, France

Giuseppe Giaccone

Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Lorenzo Gianni

Department of Oncology and Oncohematology, Infermi Hospital, Rimini, Italy

Alessandra Gilardini

Department of Neurosciences and Biomedical Technologies, University of Milan “Bicocca,” Monza, Italy

Laurence Gladiëff

Department of Medical Oncology, Institut Claudius Regaud, Toulouse, France

Michael M. Gottesman

Laboratory of Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Ying Guo

Department of Biochemistry, School of Medicine, Morgantown, WV, USA
Mary Babb Randolph Cancer Center, Robert C. Byrd Health Sciences Center, West Virginia University, Morgantown, WV, USA

Martin Gutierrez

Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Matthew D. Hall

Laboratory of Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Irene H.L. Hamelers

Biochemistry of Membranes, Bijvoet Institute and Institute of Biomembranes, Utrecht University, Utrecht, The Netherlands

Qi He

Department of Biochemistry, School of Medicine, Morgantown, WV, USA;
Mary Babb Randolph Cancer Center, Robert C. Byrd Health Sciences Center, West Virginia University, Morgantown, WV, USA

Paul J. Hoskins

British Columbia Cancer Agency, Vancouver, BC, Canada

Stephen B. Howell

Department of Medicine and the Moores Cancer Center, University of California, San Diego, La Jolla, CA, USA

Fazlul Huq

Discipline of Biomedical Sciences, Cumberland Campus, The University of Sydney, Lidcombe, NSW, Australia

Manuela Imola

Department of Oncology and Oncohematology, Infermi Hospital, Rimini, Italy

Claudio Isella

Division of Molecular Oncology, Institute for Cancer Research and Treatment, Candiolo, Torino, Italy

Ulrich Jaehde

Department of Clinical Pharmacy, Institute of Pharmacy, University of Bonn, Bonn, Germany

Dirk Jäger

National Center for Tumor Diseases, Department of Medical Oncology, University of Heidelberg, Heidelberg, Germany

Ganna V. Kalayda

Department of Clinical Pharmacy, Institute of Pharmacy, University of Bonn, Bonn, Germany

Maurizio Lanfranchi

Department of General and Inorganic, Analytical, and Physical Chemistry, University of Parma, Parma, Italy

Cinzia Lanzi

Department of Experimental Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy;

Department of Experimental Oncology and Laboratories, Preclinical Chemotherapy and Pharmacology Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy

Armelle Laurand

Institut Bergonié, Université Victor Segalen, Bordeaux, France

Michele Laus

Department of Environmental and Life Sciences, University of Piemonte Orientale "A. Avogadro," Alessandria, Italy

Valérie Le Morvan

Institut Bergonié, Université Victor Segalen, Bordeaux, France

Xiaobing Liang

Department of Biochemistry, School of Medicine, Morgantown, WV, USA; Mary Babb Randolph Cancer Center, Robert C. Byrd Health Sciences Center, West Virginia University, Morgantown, WV, USA

Xing-Jie Liang

Laboratory of Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA;

Division of Nanomedicine and Nanobiology, National Center of Nanoscience and Technology of China, Zhongguancun, Beijing, China

Stephen J. Lippard

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA, USA

François Lokiec

Rene Huguenin Cancer Center, Saint-Cloud, France

Florian Lordick

National Center for Tumor Diseases, Department of Medical Oncology, University of Heidelberg, Heidelberg, Germany

Fotios Loupakis

Division of Medical Oncology, Azienda USL 6, Istituto Toscano Tumori, Livorno, Italy;

Department of Oncology, Transplantations and New Technologies in Medicine, University of Pisa, Italy

Francesca Luciani

Department of Therapeutic Research and Medicines Evaluation, Unit of Antitumor Drugs, Drug Resistance and Experimental Therapeutic, Istituto Superiore di Sanità, Rome, Italy

Maurizio Marangolo

Department of Oncology, Santa Maria Delle Croci Hospital, Ravenna, Italy

Luciano Marchiò

Department of General and Inorganic, Analytical, and Physical Chemistry, University of Parma, Parma, Italy

Cristina Marzano

Department of Pharmaceutical Sciences, University of Padova, Padova, Italy

Gianluca Masi

Division of Medical Oncology, Azienda USL 6, Istituto Toscano Tumori, Livorno, Italy

Silvia Mazzega Sbovata

Department of Chemical Processes of Engineering, University of Padova, Padova, Italy

Enzo Medico

Division of Molecular Oncology, Institute for Cancer Research and Treatment, Candiolo, Torino, Italy

Delphine Meynard

Institut Bergonié, Université Victor Segalen, Bordeaux, France

Rino A. Michelin

Department of Chemical Processes of Engineering, University of Padova, Padova, Italy

Danilo Migoni

Department of Biotechnology and Environmental Science, University of Salento, Lecce, Italy

Roberta Molteni

Department of Structural and Functional Biology, University of Insubria, Busto Arsizio, Italy

Elena Monti

Department of Structural and Functional Biology, University of Insubria, Busto Arsizio, Italy

Michael D. Mueller

Department of Biochemistry, School of Medicine, Morgantown, WV, USA; Mary Babb Randolph Cancer Center, Robert C. Byrd Health Sciences Center, West Virginia University, Morgantown, WV, USA

Franco M. Muggia

Division of Medical Oncology, New York University School of Medicine, New York, NY, USA; NYU Cancer Institute, New York, NY, USA

Daniela Musio

Department of Radiation Oncology, University “Sapienza,” Rome, Italy

Stefania V.L. Nicoletti

Department of Oncology and Oncohematology, Infermi Hospital, Rimini, Italy

David Nowotnik

Access Pharmaceuticals Inc., Dallas, TX, USA

Domenico Osella

Department of Environmental and Life Sciences, University of Piemonte Orientale “A. Avogadro,” Alessandria, Italy

Ilaria Panzini

Department of Oncology and Oncohematology, Infermi Hospital, Rimini, Italy

Maximilian Papi

Department of Oncology and Oncohematology, Infermi Hospital, Rimini, Italy

Giuseppe Parisi

Department of Radiation Oncology, University “Sapienza,” Rome, Italy

Enzo Pasquini

Department of Oncology, Cervesi Hospital, Cattolica, Italy

Nick Pavlakis

Bill Walsh Cancer Research Laboratories, Department of Medical Oncology,
Royal North Shore Hospital, Sydney, Australia;
The University of Sydney, Lidcombe, NSW, Australia

Anna F.A. Peacock

Department of Chemistry, University of Warwick, Coventry, UK

Paola Perego

Department of Experimental Oncology, Fondazione IRCCS Istituto Nazionale
Tumori, Milan, Italy;
Department of Experimental Oncology and Laboratories, Preclinical
Chemotherapy and Pharmacology Unit, Istituto Nazionale per lo Studio e la Cura
dei Tumori, Milan, Italy

Aurélie Pétain

EA3035, Institut Claudius-Regaud, Toulouse, France

Cinzia Possenti

Department of Oncology and Oncohematology, Infermi Hospital, Rimini, Italy

Denis Querleu

Department of Surgical Oncology, Institut Claudius Regaud, Toulouse, France
Paul Sabatier University, University of Toulouse; Toulouse, France

Nicola Raffetto

Department of Radiation Oncology, University “Sapienza,” Rome, Italy

Srinivas Ramachandran

Department of Biochemistry and Biophysics, School of Medicine, Lineberger
Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC,
USA

Alberto Ravaioli

Department of Oncology and Oncohematology, Infermi Hospital, Rimini, Italy

Raffaella Ravizza

Department of Structural and Functional Biology, University of Insubria, Busto
Arsizio, Italy

Eric Raymond

RayLab and Department of Medical Oncology, Beaujon University Hospital,
Clichy, France

Eddie Reed

Division of Cancer Prevention and Control, National Center for Chronic Disease
Prevention and Health Promotion, Centers for Disease Control and Prevention,
Atlanta, GA, USA

Keyvan Rezaï

Rene Huguenin Cancer Center, Saint-Cloud, France

Riccardo Riccardi

Division of Pediatric Oncology, Department of Pediatric Sciences, Catholic University of Rome, Rome, Italy

Jacques Robert

Institut Bergonié, Université Victor Segalen, Bordeaux, France

Alessandro Romano

Department of Biotechnology and Environmental Science, University of Salento, Lecce, Italy

Britt Rudnas

Department of Oncology and Oncohematology, Infermi Hospital, Rimini, Italy

Antonio Ruggiero

Division of Pediatric Oncology, Department of Pediatric Sciences, Catholic University of Rome, Rome, Italy

Peter J. Sadler

Department of Chemistry, University of Warwick, Coventry, UK

Roohangiz Safaei

Department of Medicine and the Moores Cancer Center, University of California, San Diego, La Jolla, CA, USA

Lisa Salvatore

Division of Medical Oncology, Azienda USL 6, Istituto Toscano Tumori, Livorno, Italy

Gianni Sava

Department of Biomedical Sciences, University of Trieste and Callerio Foundation Onlus, Trieste, Italy

Antonin Schmitt

EA3035, Institut Claudius-Regaud, Toulouse, France

Maria Serova

RayLab and Department of Medical Oncology, Beaujon University Hospital, Clichy, France

Shantanu Sharma

Department of Biochemistry and Biophysics, School of Medicine, University of North Carolina, Chapel Hill, NC, USA

Ding-Wu Shen

Laboratory of Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Emily A. Short

Department of Medicine, Indiana University School of Medicine,
Indianapolis, IN, USA

Sarah C. Shuck

Department of Biochemistry and Molecular Biology, Indiana University
School of Medicine, Indianapolis, IN, USA

Katia Sparnacci

Department of Environmental and Life Sciences, University of Piemonte
Orientale “A. Avogadro,” Alessandria, Italy

Gian Paolo Spinelli

Department of Experimental Medicine and Pathology, University “Sapienza,”
Rome, Italy

Irene Stasi

Division of Medical Oncology, Azienda USL 6, Istituto Toscano Tumori,
Livorno, Italy

Britta Stordal

Bill Walsh Cancer Research Laboratories, Department of Medical Oncology,
Royal North Shore Hospital, Sydney, Australia
The University of Sydney, Lidcombe, NSW, Australia

Emiliano Tamburini

Department of Oncology and Oncohematology, Infermi Hospital, Rimini, Italy

Saverio Tardito

Unit of General and Clinical Pathology, Department of Experimental Medicine,
University of Parma, Parma, Italy

Kevin Tay

Medical Oncology Branch, National Cancer Institute, National Institutes
of Health, Bethesda, MD, USA

Brenda Temple

Department of Biochemistry and Biophysics, School of Medicine, University
of North Carolina, Chapel Hill, NC, USA

Fabienne Thomas

EA3035, Institut Claudius Regaud, Toulouse, France
Paul Sabatier University, University of Toulouse, Toulouse, France

Ryan C. Todd

Department of Chemistry, Massachusetts Institute of Technology, Cambridge,
MA, USA

John J. Turchi

Department of Medicine and Department of Biochemistry and Molecular Biology,
Indiana University School of Medicine, Indianapolis, IN, USA

Sabine H. van Rijt

Department of Chemistry, University of Warwick, Coventry, UK

Enrico Vasile

Division of Medical Oncology, Azienda USL 6, Istituto Toscano Tumori,
Livorno, Italy;

Department of Oncology, Transplantations and New Technologies in Medicine,
University of Pisa, Italy

Vita M. Vecchio

Department of Biotechnology and Environmental Science, University of Salento,
Lecce, Italy

Tiziano Verri

Department of Biotechnology and Environmental Science, University of Salento,
Lecce, Italy

Yibing Wu

Department of Biochemistry and Biophysics, School of Medicine,
University of North Carolina, Chapel Hill, NC, USA

Qing-Wu Yan

Department of Biochemistry, School of Medicine, Morgantown, WV, USA
Mary Babb Randolph Cancer Center, Robert C. Byrd Health Sciences Center,
West Virginia University, Morgantown, WV, USA

Jing Jie Yu

Department of Biochemistry, School of Medicine, Morgantown, WV, USA
Mary Babb Randolph Cancer Center, Robert C. Byrd Health Sciences Center,
West Virginia University, Morgantown, WV, USA

Jun Qing Yu

Discipline of Biomedical Sciences, Cumberland Campus, The University
of Sydney, Lidcombe, NSW, Australia

Wainer Zoli

The Scientific Institute of Romagna for the Study and Treatment of Cancer,
Meldola, Forlì-Cesena, Italy

Franco Zunino

Department of Experimental Oncology, Fondazione IRCCS Istituto Nazionale
Tumori, Milan, Italy;

Department of Experimental Oncology and Laboratories, Preclinical
Chemotherapy and Pharmacology Unit, Istituto Nazionale per lo Studio e
la Cura dei Tumori, Milan, Italy

Platinum Compounds: The Culmination of the Era of Cancer Chemotherapy

Franco M. Muggia

Abstract The history of cancer chemotherapy is considered part of a chapter of empiricism that is coming to a close. However, the effect of cisplatin on germ cell tumors and, to a lesser extent, on epithelial ovarian cancer has captivated scientists and oncologists, and continues to expand its therapeutic horizons as more is learned. This is the Tenth Symposium on Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy, and its highlights provide further confirmation of the value of scientific investment in this area of therapeutic research.

Keywords Chemotherapy; Cisplatin; Carboplatin; Germ cell and testicular tumors; Ovarian cancer

Various reviews have recounted the history of cancer chemotherapy, and its dawn at the beginning of the twentieth century with the introduction of “the magic bullet” concept against infectious pathogens and tumors by the brilliant German pathologist, Paul Ehrlich. The introduction of sulfonamides against bacteria and the effects of hormones against certain tumors constituted early validation of this concept. Modern chemotherapy, however, is usually traced to the sensational 2 December 1943 incident (1, 2) that occurred at the harbor of Bari, Italy. An air raid destroyed 17 allied ships, including one containing mustard “bombs” (being stored as possible retaliation to the threat of chemical warfare); exposed personnel experienced the marrow hypoplasia and involution of lymphoid tissue previously reported with sulfur mustard gas during World War I (3–5). In fact, the medicinal studies of the related nitrogen mustard by the U.S. governmental agencies, in concert with biomedical researchers at academic institutions such as Yale, had already started in 1942 (6). Fleming’s unique discovery of penicillin in 1928 – a powerful stimulus for drug development – was followed by the search for drugs effective against

F.M. Muggia

Division of Medical Oncology, New York University School of Medicine
and NYU Cancer Institute, NY, USA

e-mail: Franco.Muggia@nyumc.org

tuberculosis. This constellation of events led to the creation of the U.S. National Institutes of Health and the National Cancer Institute (NCI), which were to play a pivotal role in launching the era of anticancer chemotherapy. These government entities had the ability to sponsor scientific exchanges with other national and international institutions functioning largely unencumbered by profit motives. They succeeded as a clearing house of ideas to combat cancer, despite the rather primitive understanding of neoplastic cell and molecular biology.

The Initial Phases of Systematic Anticancer Drug Discovery

With the support of Congress and as a part of the U.S. government's Public Health Service, the NCI organized itself to utilize evolving knowledge of tumor biology for the bold idea of identifying drugs for cancer treatment. Activity against carcinogen-induced L1210 and P388 leukemias in mice became a criterion for selectivity of a drug against these rapidly dividing tumor cells, without irreparably harming the host (7). A number of drugs related to nitrogen mustard and biochemically designed antimetabolites were established to have clinical activity and, in spite of the shortcomings of random screening, successes could be claimed against some human malignancies (8). Collaboration with other governmental agencies (e.g., the Department of Agriculture) and the pharmaceutical industry also led to the selection of useful natural products such as the vincas, camptothecins, and taxanes – the vincas mostly developed by industry, and camptothecins, and taxanes through the perseverance of NCI-sponsored investigations. Another landmark achievement was the identification, by Heidelberger and colleagues, of 5-fluorouracil and its eventual potential in the treatment of breast and gastrointestinal cancers (9).

Clinical Investigators

It was important to link such therapeutic drug discovery efforts with physicians skilled in diagnosis, and eventually with experience in dealing with supportive care and management of complications of malignancies and drug treatments. It is not a coincidence that early pioneers in cancer treatment focused either on hematologic diseases (following their training in internal medicine), or on certain solid tumors (following their training in surgery and its specialties). In either case, these physicians considered clinical investigation the final common pathway for anticancer drug development and, in the course of patient care, began to apply them systematically in situations that, until that time, had been considered hopeless. Documentation of their success in clinical trials became a major important step in these efforts (reviewed by DeVita and Chu) (10).

Often unrecognized is one such pioneer: Ezra Greenspan (1919–2004), best known for developing the foundations of combination chemotherapy against advanced breast and ovarian cancers (11, 12). His optimistic outlook – as stated

in the autobiographical notes he left to his colleagues – derived from having survived pneumonia while attending college at Cornell, because his physician opted to treat him with the recently obtained Prontosyl (a classmate who had preceded him in the hospital died without such intervention). Subsequently, upon finishing his medical studies at NYU, he was exposed to his first clinical trial under the mentorship of Isidore Snapper: the use of urethane (ethyl carbamate) in multiple myeloma (5) that included attempts to correlate clinical benefit with serial bone marrow examinations. When recruited into the Army in 1947, he became a physician at the Tumor Service at Walter Reed, where he describes adding the first available drugs (nitrogen mustard, triethylene melamine, and methotrexate) to radiation therapy for the treatment of testicular cancers and Hodgkin's disease. As the NCI opened its first clinical unit, Greenspan became the first clinical investigator in this fledgling program, and teamed up with the preclinical scientist, Abraham Goldin, who was to develop many of the principles of chemotherapy based on optimizing dose-scheduling of a drug in mouse leukemia models (13, 14). This experience with new therapeutic agents provided Greenspan with the unwavering optimism he demonstrated in facing the challenges of his long career as a clinical oncologist at Mount Sinai Hospital in New York.

Greenspan was the first to exploit the antitumor effects of methotrexate for the treatment of solid tumors, and document positive results in combination with alkylating agents (11, 12). In the 1950s and 1960s, a number of other physicians in academic centers began to develop clinical units devoted to the treatment of cancer, but met with resistance and disdain, particularly from Departments of Medicine that were skeptical of investing human resources in coupling the semi-empirical identification of anticancer drugs with the science of clinical trials (10). Despite this, clinical oncology began to flourish in the 1950s under the leadership of Alfred Gellhorn at Columbia and David Karnofsky at Memorial Sloan-Kettering, to be followed in the 1960s by a number of prominent specialists in hematology, general internal medicine, and surgery that were to become the key developers of Medical Oncology, followed by other oncologic specialties (10).

In the meantime, the NCI with its Chemotherapy Program led by C. Gordon Zubrod (himself a product of pharmacology research first devoted to antituberculous drugs), and its Medicine Branch staffed with clinical investigators such as Emil Frei and Emil (Jay) Freireich, concentrated its efforts on finding therapeutic regimens useful against leukemias (15). These efforts were later expanded to the treatment of Hodgkin's and other lymphomas, and subsequently to breast and ovarian cancers, with investigators such as Vincent DeVita, Paul Carbone, George Canellos, Robert Young, Philip Schein, and Bruce Chabner (10, 16–19). The success of the NCI intramural programs, coupled with a dramatic extramural expansion via cooperative groups (initially under the leadership of James Holland, Bernard Fisher, and John Durant, among others) and its phase I/II working groups, led to widening of the clinical testing of anticancer drugs, thereby accelerating changes in cancer treatment worldwide. The investment of the pharmaceutical industries in this area, long considered a risky proposition, grew rapidly in the 1970s, with substantial

programs being developed in the U.S. by Bristol Myers, in Europe by Burroughs Wellcome, Farmitalia, Rhone Poulenc, Roche, and Sandoz, and in Japan.

Curable Tumors as the “Stalking Horse” of Drug Discovery

Joseph Burchenal, who headed Developmental Therapeutics at Memorial Sloan-Kettering for approximately 40 years, starting from the 1950s (pairing up with David Karnofsky, who ran the Chemotherapy service), used the imagery of a “stalking horse” to describe Burkitt’s lymphoma as an identifier of strategies applicable to leukemia in his 1966 presidential address to the American Association for Cancer Research. Early experience in testicular cancer has similarly served to validate treatment strategies: “prophylactic” radiation to the retroperitoneal space (20), and Greenspan’s addition of alkylating agents to men he treated in 1947–1949 at Walter Reed’s tumor service. Twenty-five years after the Walter Reed experience, complete responses to cisplatin in advanced testicular cancer were documented by Higby et al. (21) in Holland’s group at Roswell Park, convincing initially skeptical investigators that it was worthy of further development. Shortly thereafter, trials performed at Memorial Sloan-Kettering (22) and at Indiana University with collaborators from the Southeastern Cancer Study Group (23) defined cisplatin-based treatments as curative. In the setting of recurrence, Einhorn and his group established the usefulness of certain anticancer drugs (e.g., etoposide and ifosfamide) (24), and also tested whether cisplatin dose-intensification would be a reasonable strategy. If such intensification did not prove useful in testicular cancer, it certainly would not be useful against cancers that are much less sensitive to platinum (25).

The impressive activity of cisplatin against germ-cell tumors, leading to cures in advanced disease conditions (exemplified by Lance Armstrong’s extraordinary saga), should continue to influence our notions on how to succeed in drug development. Although it has been fashionable to speak about “personalized therapy,” such a concept belies the fact that unparalleled successes can take place without individualized knowledge on the deranged pathways involved in tumorigenesis. Platinum contributions are not confined to this most impressive example; the extraordinary sensitivity of ovarian cancer to cisplatin and carboplatin is nothing short of remarkable, if one considers the very advanced presentations that are commonplace in this disease. In addition, the strides achieved during the past decade in the treatment of colorectal cancer owe as much to the introduction of oxaliplatin-based combinations as to the monoclonal antibodies against VEGF and EGFR (26). Emphasizing such contributions is not designed to shift the focus back to cytotoxic drug development, but to reiterate that research into mechanisms of platinum resistance and their manipulation may lead to therapeutic developments of the magnitude now preferentially expected from “targeted therapies.” In fact, in an animal model of ovarian cancer from Dinulescu’s laboratory (27), cisplatin is able to achieve cures that are beyond the reach of targeted agents directed against the targets that were

implicated in the model. Similar observations have been made in the engineered mouse model of triple negative breast cancer (28).

Platinums in the Era of “Targeted Agents”

One might ask: What is it that continues to bring together chemists, basic scientists, and oncologists to hold meetings on platinums? For those of us who have attended a number of these events, the answer appears to be that platinums represent the culmination of anticancer drug development to date, and their achievements have continued to expand over the years (see Table 1). As an example, the 2007 meeting showcased a new generation of “targeted” drugs, such as poly (ADP-ribose) polymerase-1 (PARP-1) inhibitors and the proteasome inhibitor bortezomib, which are reversing important mechanisms that mediate resistance to platinums, such as DNA-repair and intracellular transport, respectively. The involvement of chemists and experimental biologists gleaned from these publications stimulates clinical investigations, and vice versa.

For an oncologist, the overview of these meetings epitomizes the satisfaction of being part of scientific advances that have the potential of bringing about major improvements in outcomes where inexorable progression of a cancerous tumor was once the rule. The pioneers that led the field of cancer chemotherapy in the early days were undoubtedly similarly inspired. Learning more about platinum drugs continues to provide us with an expanding number of patients that can attain the most successful outcome: a cure.

Table 1 Highlights of the ten international symposia on platinum coordination compounds in cancer chemotherapy (ISPPC), from 1971 to 2007

Year	Site	Chair(s)	Highlights and/or (ref)
1971	Prague	Barnett Rosenberg	Cisplatin: discovery and preclinical activity (29)
1973	Oxford	Tom Connors and John Roberts	(30)
1976	Dallas	Joseph Hill	Phase II studies by NCI and the Wadley Institute (31, 32)
1983	Burlington	Irwin Krakoff	Carboplatin introduced (33)
1987	Padova	Mario Nicolini	(34)
1991	San Diego	Stephen Howell	(35)
1995	Amsterdam	Herbert Pinedo and Jan Schornagel	(36)
1999	Oxford	Lloyd Kelland and IR Judson	Oxaliplatin highlighted (37)
2003	New York	Nicholas Farrell and Franco Muggia	Copper transporters; clinical results in gynecologic and colorectal cancers
2007	Verona	Andrea Bonetti and Roberto Leone	Current publication

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Section A
Novel Platinum Analogues, Original
Formulations and Other Heavy Metals