

PLATINUM COORDINATION COMPLEXES IN CANCER CHEMOTHERAPY

**Miles P. Hacker,
Evan B. Douple,
and Irwin H. Krakoff (editors)**

PLATINUM COORDINATION COMPLEXES IN CANCER CHEMOTHERAPY

*Proceedings of the Fourth International Symposium on
Platinum Coordination Complexes in Cancer Chemotherapy
convened in Burlington, Vermont by the Vermont Regional
Cancer Center and the Norris Cotton Cancer Center, June 22-24, 1983.*

edited by

Miles P. Hacker
Evan B. Douple
Irwin H. Krakoff



Martinus Nijhoff Publishing
A member of the Kluwer Academic Publishers Group
Boston/The Hague/Dordrecht/Lancaster

Distributors for North America:
Kluwer Academic Publishers
190 Old Derby Street
Hingham, MA 02043

Distributors outside North America:
Kluwer Academic Publishers Group
Distribution Centre
P.O. Box 322
3300 AH Dordrecht
The Netherlands

Library of Congress Cataloging in Publication Data

**International Symposium on Platinum Coordination
Complexes in Cancer Chemotherapy (4th : 1983 : Burlington, Vt.)
Platinum coordination complexes in cancer chemotherapy.**

(Developments in oncology)

Sponsored by Bristol-Myers Company and others.

Includes indexes.

1. Cisplatin—Congresses.
 2. Cancer—Chemotherapy—Congresses.
 3. Platinum compounds—Therapeutic use—Testing—Congresses.
 4. Coordination compounds—Therapeutic use—Testing—Congresses.
 5. Complex compounds—Therapeutic use—Testing—Congresses.
 - I. Hacker, Miles P. II. Douple, Evan B. III. Krakoff, Irwin H. IV. Vermont
Regional Cancer Center. V. Norris Cotton Cancer Center. VI. Bristol-
Myers Company. VII. Title. VIII. Series.
- RCZ71.C55158 1983 616.99'4061 83-23722
ISBN 0-89838-619-5

Copyright 1984 © by Martinus Nijhoff Publishing, Boston

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, photocopying, recording, or otherwise, without written permission of the publisher, Martinus Nijhoff Publishing, 190 Old Derby Street, Hingham, Massachusetts 02043.

Printed in the United States of America

PLATINUM COORDINATION COMPLEXES IN CANCER CHEMOTHERAPY

Other books in this series:

F.J. Cleton and J.W.I.M. Simons, eds., Genetic Origins of Tumor Cells

ISBN 90-247-2272-1

J. Aisner and P. Chang, eds., Cancer Treatment Research

ISBN 90-247-2358-2

B.W. Ongerboer de Visser, D.A. Bosch and W.M.H. van Woerkom-Eykenboom, eds., Neuro-Oncology: Clinical and Experimental Aspects

ISBN 90-247-2421-X

K. Hellmann, P. Hilgard and S. Eccles, eds., Metastasis: Clinical and Experimental Aspects

ISBN 90-247-2424-4

H.F. Seigler, ed., Clinical Management of Melanoma

ISBN 90-247-2584-4

P. Correa and W. Haenszel, eds., Epidemiology of Cancer of the Digestive Tract

ISBN 90-247-2601-8

L.A. Liotta and J.R. Hart, eds., Tumor Invasion and Metastasis

ISBN 90-247-2611-5

J. Banoczy, ed., Oral Leukoplakia

ISBN 90-247-2655-7

C. Tjissen, M. Halprin and L. Endtz, eds., Familial Brain Tumours

ISBN 90-247-2691-3

E.M. Muggia, C.W. Young and S.K. Carter, eds., Anthracycline Antibiotics in Cancer

ISBN 90-247-2711-1

B.W. Hancock, ed., Assessment of Tumour Response

ISBN 90-247-2712-X

D.E. Petersen and S.T. Sonis, eds., Oral Complications of Cancer Chemotherapy

ISBN 90-247-2786-3

R. Mastrangelo, D.G. Poplack, and R. Riccardi, eds., Central Nervous System Leukemia: Prevention and Treatment

ISBN 0-89838-570-9

A. Polliack, ed., Human Leukemias: Cytochemical and Ultrastructural Techniques in Diagnosis and Research

ISBN 0-89838-585-7

W. Davis, C. Maltoni, and S. Tanneberger, eds., The Control of Tumour Growth and its Biological Bases

ISBN 0-89838-603-9

A.P.M. Heintz, C.T. Griffiths, and J.B. Trimbo, eds., Surgery in Gynecological Oncology

ISBN 0-89838-604-7

DEDICATION

DAVID B. BROWN

1943-1983

*Professor of Chemistry, University of Vermont,
Member, Vermont Regional Cancer Center*

This volume is dedicated to David Brown. He was one of the leaders in conceiving and planning the Fourth International Platinum Symposium. In his research, Dave exemplified the spirit of the symposium and was an example of the intense involvement of a laboratory scientist in clinical problems leading to new insights and more rapid progress. Unfortunately, the field of cancer therapy had not advanced rapidly enough for Dave to be able to benefit directly from the effort in which he had taken such an active part. And if he would have lived to attend the symposium, we hope that he would have been proud of this volume and its intent to advance the application of metal coordination complexes in cancer therapy.

SYMPOSIUM COMMITTEES

ORGANIZING

Joseph H. Burchenal
Michael J. Cleare
Thomas A. Connors
Evan B. Douple, *Co-Chairman*
Miles P. Hacker
Irwin H. Krakoff, *Co-Chairman*
Jean-Pierre Macquet
Barnett Rosenberg

PROGRAM

David B. Brown
Joseph H. Burchenal
Michael J. Cleare
Miles P. Hacker, *Chairman*
Karin Lindquist
Stephen J. Lippard
Charles L. Litterst
Robert A. Newman
Robert C. Richmond

ARRANGEMENTS

David B. Brown
Joan MacKenzie, *Chairman*
John J. McCormack

SPONSORS

BRISTOL-MYERS COMPANY

E.I. du PONT de NEMOURS & COMPANY

ENGELHARD CORPORATION

JOHNSON MATTHEY, INC.

NORRIS COTTON CANCER CENTER

A.H. ROBINS COMPANY

SMITH KLINE & FRENCH LABORATORIES

STUART PHARMACEUTICALS

VERMONT REGIONAL CANCER CENTER

WARNER-LAMBERT

*The symposium was supported in part by Grant
#CA 34679 from the National Cancer Institute.*

CONTRIBUTORS

DONALD L. BODENNER, Department of Pharmacology and University of Rochester Cancer Center, University of Rochester, Rochester, New York, 14642, U.S.A.

RICHARD F. BORCH, Department of Pharmacology and University of Rochester Cancer Center, University of Rochester, Rochester, New York, 14642, U.S.A.

FRANCES E. BOXALL, Department of Biochemical Pharmacology, Institute of Cancer Research, Belmont, Sutton, Surrey, England.

WILLIAM T. BRADNER, Pharmaceutical Research and Development Division, Bristol-Myers Company, Syracuse, New York, 13221-4755, U.S.A.

JOSEPH BURCHENAL, Memorial Sloan-Kettering Cancer Center, New York, New York, 10021, U.S.A.

JEAN-LUC BUTOUR, Laboratoire de Pharmacologie et de Toxicologie Fondamentales du CNRS, 31400, Toulouse, France.

A. HILARY CALVERT, Department of Biochemical Pharmacology, Institute of Cancer Research, Belmont, Sutton, Surrey, England.

JOHN P. CARADONNA, Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts, 02139, U.S.A.

STEPHEN K. CARTER, Pharmaceutical Research and Development Division, Bristol-Myers Company, New York, New York, 10154, U.S.A.

MICHAEL J. CLEARE, Johnson Matthey Research Center, Blunt's Court, Sonning Common, Reading RG4-9N4 England

JERRY COLLINS, Clinical Pharmacology Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland, 20205, U.S.A.

BRIAN J. CORDEN, Clinical Pharmacology Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland, 20205, U.S.A.

J. WAYNE COWENS, Department of Clinical Pharmacology and Therapeutics and Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York, 14263, U.S.A.

PATRICK J. CREAVER, Department of Clinical Pharmacology and Therapeutics, Roswell Park Memorial Institute, Buffalo, New York, 14263, U.S.A.

JEROEN H. DEN HARTOG, Department of Chemistry, State University Leiden, 2300 RA Leiden, The Netherlands.

LEIGH A. FERREN, Environmental Sciences, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 37830, U.S.A.

ANNE MARIE J. FICHTINGER-SCHEPMAN, Department of Chemistry, State University Leiden, 2300 RA Leiden, The Netherlands.

ALEXANDER P. FLORCZYK, Pharmaceutical Research and Development Division, Bristol-Myers Company, Syracuse, New York, 13221-4755, U.S.A.

DEVINDER S. GILL, Department of Biological Sciences, Carnegie-Mellon University, Pittsburgh, Pennsylvania, 15213, U.S.A.

MILES P. HACKER, Vermont Regional Cancer Center and Department of Pharmacology, University of Vermont, Burlington, Vermont, 05401, U.S.A.

STEPHEN J. HARLAND, Department of Biochemical Pharmacology, Institute of Cancer Research, Belmont, Sutton, Surrey, England.

KENNETH R. HARRAP, Department of Biochemical Pharmacology, Institute of Cancer Research, Belmont, Sutton, Surrey, England.

K. J. HIMMELSTEIN, Inter Research Corporation, Lawrence, Kansas, 66044, U.S.A.

JAMES D. HOESCHELE, Warner-Lambert/Parke-Davis Pharmaceutical Research Division, Ann Arbor, Michigan, 48105, U.S.A.

WILLIAM J. M. HRUSHESKY, Department of Medicine, University of Minnesota, Minneapolis, Minnesota, 55455, U.S.A.

PAUL C. HYDES, Johnson Matthey Research Centre, Sonning Common, Reading RG4 9NH, England.

NEIL P. JOHNSON, Laboratoire de Pharmacologie et de Toxicologie Fondamentales du CNRS, 31400, Toulouse, France.

MERVYN JONES, Department of Biochemical Pharmacology, Institute of Cancer Research, Belmont, Sutton, Surrey, England.

JANET C. KATZ, Department of Pharmacology and University of Rochester Cancer Center, University of Rochester, Rochester, New York, 14642, U.S.A.

DAVID P. KELSEN, Memorial Sloan-Kettering Cancer Center, New York, New York, 10021, U.S.A.

HARTMUT KÖPF, Institute für Anorganische und Analytische der Technischen Universität Berlin, D-1000 Berlin 12, West Germany.

PETRA KÖPF-MAIER, Institute für Anatomie der Freien Universität Berlin, D-1000 Berlin 33, West Germany.

STEPHEN J. LIPPARD, Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts, 02139, U.S.A.

CHARLES L. LITTERST, Laboratory of Medicinal Chemistry and Pharmacology, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland, 20205, U.S.A.

PHUONG VAN T. LUC, Vincent T. Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, D.C., 20007, U.S.A.

JEAN-PIERRE MACQUET, Laboratoire de Pharmacologie et de Toxicologie Fondamentales du CNRS, 31400, Toulouse, France.

STEFAN MADAJEWICZ, Department of Clinical Pharmacology and Therapeutics, Roswell Park Memorial Institute, Buffalo, New York, 14263, U.S.A.

ANTONIUS T. M. MARCELIS, Department of Chemistry, State University Leiden, 2300 RA Leiden, The Netherlands.

KEVIN G. MC GHEE, Department of Biochemical Pharmacology, Institute of Cancer Research, Belmont, Sutton, Surrey, England.

J. GORDON MC VIE, Department of Oncology, Netherlands Cancer Institute and Free University Hospital, 1007 MB Amsterdam, The Netherlands.

VEN L. NARAYANAN, Drug Synthesis and Chemistry Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland, 20205, U.S.A.

MOHAMED NASR, Starks C.P., Inc., Silver Spring, Maryland, 20910, U.S.A.

DAVID R. NEWELL, Department of Biochemical Pharmacology, Institute of Cancer Research, Belmont, Sutton, Surrey, England.

ROBERT F. OZOLS, Medicine Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland, 20205, U.S.A.

T. F. PATTON, Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, Kansas, 66045, U.S.A.

LAKSHMI PENDYALA, Department of Clinical Pharmacology and Therapeutics, Roswell Park Memorial Institute, Buffalo, New York, 14263, U.S.A.

HERBERT M. PINEDO, Department of Oncology, Free University Hospital, 1007 MB Amsterdam, The Netherlands.

VICTOR M. PRIEGO, Vincent T. Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, D.C., 20007, U.S.A.

AQUILUR RAHMAN, Vincent T. Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, D.C., 20007, U.S.A.

HONORAT RAZAKA, Laboratoire de Pharmacologie et de Toxicologie Fondamentales du CNRS, 31400, Toulouse, France.

JAN REEDIJK, Department of Chemistry, State University Leiden, 2300 RA Leiden, The Netherlands.

A. J. REPTA, Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, Kansas, 66045, U.S.A.

JOHN A. ROBERTS, Health and Safety Research Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 37830, U.S.A.

WILLIAM C. ROSE, Pharmaceutical Research and Development Division, Bristol-Myers Company, Syracuse, New York, 13221-4755, U.S.A.

BARNETT ROSENBERG, Barros Research Institute, Holt, Michigan, U.S.A.

PETER J. SADLER, Department of Chemistry, Birkbeck College, University of London, London, WC1E 7HX England.

BERNARD SALLES, Laboratoire de Pharmacologie et de Toxicologie Fondamentales du CNRS, 31400, Toulouse, France.

PHILIP S. SCHEIN, Vincent T. Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, D.C., 20007, U.S.A.

HOWARD I. SCHER, Memorial Sloan-Kettering Cancer Center, New York, New York, 10021, U.S.A.

JOHN E. SCHURIG, Pharmaceutical Research and Development Division, Bristol-Myers Company, Syracuse, New York, 13221-4755, U.S.A.

H. SHIH, Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, Kansas, 66045, U.S.A.

ZAHD H. SIDDIK, Department of Biochemical Pharmacology, Institute of Cancer Research, Belmont, Sutton, Surrey, England.

IAN E. SMITH, Department of Biochemical Pharmacology, Institute of Cancer Research, Belmont, Sutton, Surrey, England.

- LARRY A. STERNSON, Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, Kansas, 66045, U.S.A.
- W. W. TEN BOKKEL HUININK, Department of Oncology, Netherlands Cancer Institute and Free University Hospital, 1007 MB Amsterdam, The Netherlands.
- W.J.F. VAN DER VIJGH, Department of Oncology, Netherlands Cancer Institute and Free University Hospital, 1007 MB Amsterdam, The Netherlands.
- J.B. VERMORKEN, Department of Oncology, Netherlands Cancer Institute and Free University Hospital, 1007 MB Amsterdam, The Netherlands.
- CLAUDE VIEUSSENS, Laboratoire de Pharmacologie et de Toxicologie Fondamentales du CNRS, 31400, Toulouse, France.
- L. R. WHITFIELD, Warner-Lambert/Parke-Davis Pharmaceutical Research Division, Ann Arbor, Michigan, 48105, U.S.A.
- EVE WILTSHAW, Department of Biochemical Pharmacology, Institute of Cancer Research, Belmont, Sutton, Surrey, England.
- PAUL V. WOOLLEY, Vincent T. Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, D.C., 20007, U.S.A.
- MICHEL WRIGHT, Laboratoire de Pharmacologie et de Toxicologie Fondamentales du CNRS, 1400, Toulouse, France.
- ROBERT C. YOUNG, Medicine Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland, 20205, U.S.A.

PREFACE

The idea for convening a Fourth International Symposium on Platinum Coordination Complexes in Cancer Chemotherapy was born in an assembly of researchers from the Vermont Regional Cancer Center and the Norris Cotton Cancer Center who shared a common interest in metal complexes. It was agreed by those assembled that sufficient time had passed since the Third International Symposium on Platinum Coordination Complexes in Cancer Chemotherapy held in 1976 at the Wadley Institutes of Molecular Medicine in Dallas, Texas, during which several advances in the chemistry, biochemistry, pharmacology and clinical use of platinum complexes had occurred, to warrant a fourth symposium. Furthermore, intensive investigations in progress were bringing sophisticated methodologies to bear on the problems in the field, clinical trials were yielding interesting results, and unique approaches to cancer therapy were being designed. Therefore, an organizing committee was formed and planning culminated in the symposium which was held in Burlington, Vermont, June 22-24, 1983.

This volume includes the manuscripts of the invited speakers from each of the six sessions representing key aspects relevant to the use of platinum and other metals as chemotherapeutic agents. These speakers and session leaders were charged to review recent developments and to highlight some of the new areas of focus and promise. The abstracts of the scientific posters which were presented appear in their respective sections. In order to keep the size of the proceedings to one volume the authors were unfortunately limited. The questions and discussions generated by active participation by the attendees are not transcribed and it is therefore impossible to capture the excitement and cross-disciplinary interaction which was present among the 180 participants throughout the symposium.

The editors wish to thank the contributors for delivering the manuscripts on schedule, and the session leaders for their assistance with the editing and refereeing of the manuscripts. Financial assistance in support of the symposium was provided by several sources as acknowledged elsewhere in this volume, and this support is gratefully appreciated. We also thank the other members of the organizing committee. The program committee deserves the credit for assembling speakers and special thanks is reserved for Joan MacKenzie, who along with staff of the Vermont Regional Cancer Center, provided the local arrangements which contributed to the effective exchange of ideas and the success of the symposium.

Miles P. Hacker, Evan B. Douple and Irwin H. Krakoff
August, 1983

TABLE OF CONTENTS

Dedication	v
Sponsors	vi
Contributors	vii
Preface	xi

Nomenclature

Nomenclature for Platinum Antitumor Compounds	3
J. Reedijk	

Section I: Biochemistry of Platinum Coordination Complexes in Cancer Chemotherapy

Overview	11
S. J. Lippard	
Chemical and Biological Studies of <i>cis</i> -Diamminedichloroplatinum (II) Binding to DNA	14
J. P. Caradonna and S. J. Lippard	
Is DNA the Real Target of Antitumor Platinum Compounds?	27
J. P. Macquet, J. L. Butour, N. P. Johnson, H. Razaka, B. Salles, C. Vieussens and M. Wright	
Specific Binding of <i>cis</i> -Platinum Compounds to DNA and DNA Fragments	39
J. Reedijk, J.H.J. den Hartog, A.M.J. Fichtinger-Schepman and A.T.M. Marcelis	
Poster Presentations	51

Section II: Pharmacology and Pharmacodynamics of Platinum Coordination Complexes in Cancer Chemotherapy

Overview	67
C.L. Litterst	
Plasma Pharmacokinetics, Urinary Excretion, and Tissue Distribution of Platinum Following IV Administration of Cyclobutanedicarboxylatoplatinum-II and <i>cis</i> -Platinum to Rabbits	71
C.L. Litterst	
Clinical Pharmacokinetics of Diammine [1,1-Cyclobutanedicarboxylato- (2-)-0,0'-Platinum (CBDCA)	82
P.V. Woolley, V.M. Priego, P.V.T. Luc, A. Rahman and P.S. Schein	
Biliary Excretion, Renal Handling and Red Cell Uptake of Cisplatin and CBDCA in Animals	90
Z.H. Siddik, D.R. Newell, F.E. Boxall, M. Jones, K.G. McGhee and K.R. Harrap	
Biodistribution and Pharmacokinetics of ^{195m} Pt-Labeled <i>cis</i> -Dichloro- <i>trans</i> -Dihydroxo-bis(Isopropylamine)- Platinum(IV), CHIP, in the Normal Female Fischer 344 Rat	103
J.D. Hoeschele, L.A. Ferren, J.A. Roberts and L.R. Whitfield	

Clinical Pharmacokinetics of <i>cis</i>-Dichloro-<i>trans</i>-Dihydroxobis(Isopropylamine)Platinum(IV)	114
L. Pendyala, J.W. Cowens, S. Madajewicz and P.J. Creaven	
Disposition of Cisplatin vs Total Platinum in Animals and Man	126
L.A. Sternson, A.J. Repta, H. Shih, K.J. Himmelstein and T.F. Patton	
Poster Presentations	138

Section III: Toxicology of Platinum Coordination Complexes in Cancer Chemotherapy

Overview	151
M.P. Hacker	
Diethyldithiocarbamate and <i>cis</i>-Platinum Toxicity	154
R.F. Borch, D.L. Bodenner and J.C. Katz	
Selected Aspects of Cisplatin Nephrotoxicity in the Rat and Man	165
W.J.M. Hrushesky	
Evaluation of Platinum Complexes for Emetic Potential	187
J.E. Schurig, A.P. Florczyk and W.T. Bradner	
Poster Presentations	200

Section IV: Development of New Platinum Coordination Complexes

Overview	213
M.J. Cleare	
Synthesis and Testing of Platinum Analogues — An Overview	216
P.C. Hydes	
Experimental Antitumor Activity of Platinum Coordination Complexes	228
W.C. Rose and W.T. Bradner	
JM8 Development and Clinical Projects	240
A.H. Calvert, S.J. Harland, K.R. Harrap, E. Wiltshaw and I.E. Smith	
Poster Presentations	253

Section V: Non-Platinum Metal Complexes As Antitumor Agents

Structure Activity Relationship of Antitumor Palladium Complexes	267
D.S. Gill	
The Metallocene Dihalides — A Class of Organometallic Early Transition Metal Complexes as Antitumor Agents	279
P. Köpf-Maier and H. Köpf	
The Design of Metal Complexes as Anticancer Drugs	290
P.J. Sadler, M. Nasr, and V.L. Narayanan	

Section VI: Unique Therapeutic Approaches Using Platinum Coordination Complexes

Overview	307
J. Burchenal	
Phase I and Early Phase II Trials of 4' Carboxyphthalato (1,2 Diaminocyclohexane) Platinum (II)	310
D.P. Kelsen, H. Scher and J. Burchenal	
High Dose Cisplatin in Hypertonic Saline: Renal Effects and Pharmacokinetics of a 40 MG/M² QD x 5 Schedule	321
R.F. Ozols, B.J. Corden, J. Collins and R.C. Young	

Clinical Experience with 1,1-Diaminomethylcyclohexane (Sulphato) Platinum (II) (TNO-6)	330
J.B. Vermorken, W.W. ten Bokkel Huinink, J.G. McVie, W.J.F. van der Vijgh and H.M. Pinedo	
Poster Presentations	344
David B. Brown Memorial Lecture	
Cisplatin — Past, Present and Future	359
S.K. Carter	
Author Index	377
Subject Index	381

NOMENCLATURE

