Declaration of Nicholas P. Farrell, PhD

I, Nicholas P. Farrell, PhD, hereby declare as follows:

I am a professor of inorganic chemistry and chairman of the Department of Chemistry at Virginia Commonwealth University.

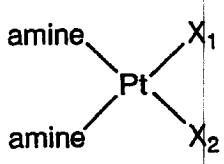
1. Background and Qualifications

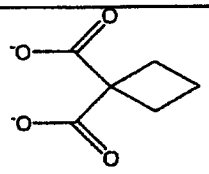
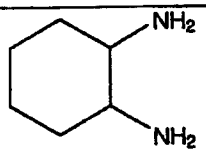
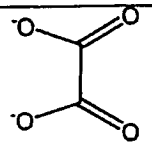
I am a graduate of University College Dublin. Afterwards, I obtained my Ph. D. from Sussex University and completed postdoctoral fellowships at The University of British Columbia. My research interests are in medicinal uses of inorganic compounds, especially platinum-based anticancer agents. In my laboratory research the fundamental molecular concepts of chemistry and DNA structures are integrated with pharmacological and cell biology parameters (mechanisms of cellular resistance, gene expression) in rational design of new medically useful agents. The first genuinely structurally novel platinum drug to enter clinical trials in thirty years has arisen from my laboratory research. With this advance, the paradigm of cisplatin-based anticancer agents has been altered.

I have written or co-edited three books in the area of platinum anticancer agents and medicinal inorganic chemistry. I have authored over 200 refereed (peer-reviewed) papers and review chapters. I have received over sixty patents world wide for my inventions. I was Chair of the first Gordon Research Conference on Metals in Medicine and, in October 2003, chaired the Ninth International Symposium on Platinum Compounds in Cancer Chemotherapy. I was recently honored as Distinguished Research Scholar of Virginia Commonwealth University for 2003-2004. A copy of my curriculum vitae and publications list is attached as Exhibit A.

2. Platinum-Based Anticancer Agents.

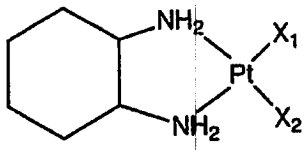
There are currently three platinum-based anticancer agents that have FDA approval for use as medicines in cancer patients: cisplatin, carboplatin and oxaliplatin. The general chemical structure of these agents is illustrated below, where X_1 and X_2 are leaving groups:

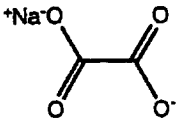
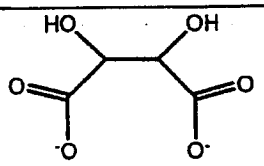
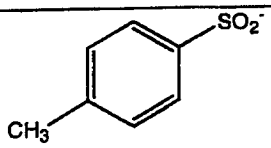
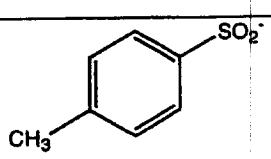
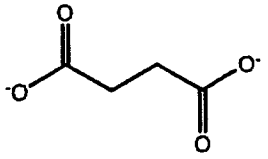
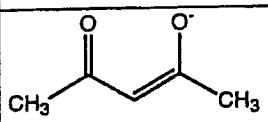
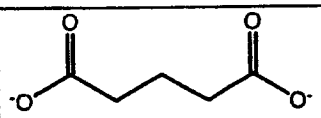
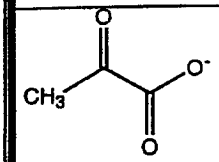
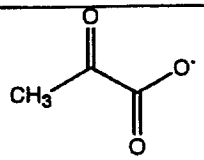
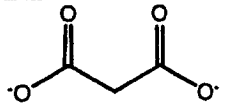
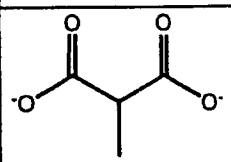


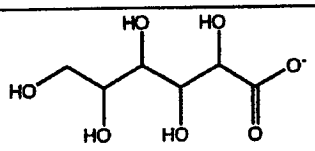
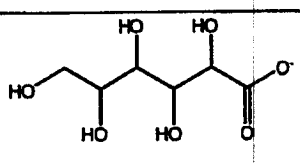
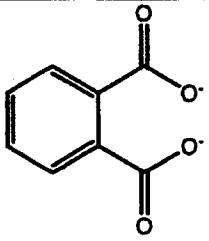
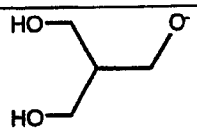
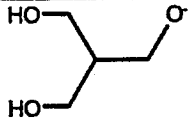
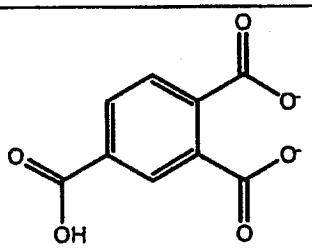
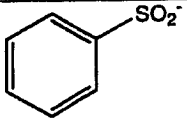
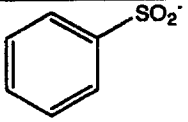
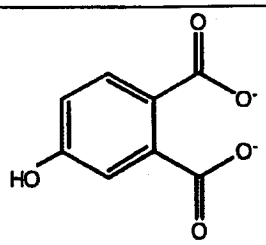
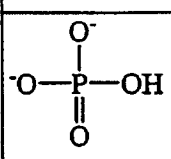
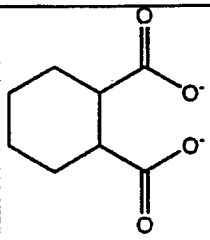
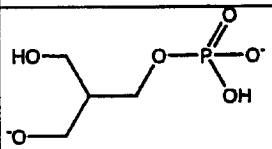
Compound	amine	X_1, X_2
Cisplatin	NH_3	Cl^-
Carboplatin	NH_3	 $(CBDCA)^{2-}$
Oxaliplatin	 (DACH)	

Monodentate and bidentate carboxylate ligands and phosphonate ligands have been extensively used to solubilize platinum-amine complexes, and the literature reports that these compounds are active *in vivo* and *in vitro*.[1] Examples of such compounds are shown in the table below.

[1] Schwartz et al., *Preparation and Antitumor Evaluation of Water-Soluble Derivatives of Dichloride(1,2-diaminocyclohexane) platinum (II)*, 61 Cancer Treat. Rep. 1514, 1519 (1977)



Monodentate Compounds		Bidentate Compounds
X_1	X_2	X_1,X_2
OH^-	NO_3^-	
$CH_3SO_3^-$	$CH_3SO_3^-$	
		
	NO_3^-	
		
^-OH	^-OH	

Likewise, complexes of DACH have also been prepared with inorganic and monocarboxylic acids, including hydrochloric, hydrobromic, nitric and sulfuric acids.[2]

3. Mechanism of Action of Platinum-Based Anticancer Agents.

In the approved platinum-based drugs and other platinum agents reported in the literature, the amine derivative is considered inert (*i.e.* it has a slow rate of substitution) and remains bound to platinum throughout chemical reactions with biomolecules. The platinum-based drugs are activated before eliciting biological effects via substitution of the leaving group to form an aqua reactive species in solution.[3] Consequently, the biological activity (both desirable and toxic) is dependent in part upon the rate of substitution and thus the identity of the leaving group (X). For example, the pharmacokinetic differences between cisplatin and carboplatin are mainly due to their comparative chemical stability due to their different leaving groups.[4] Also, the negligible nephrotoxicity of oxaliplatin and carboplatin in comparison to cisplatin is thought to be related to their slow rates substitution of the leaving groups to form an aqua reactive species in solution.[5]

4. Oxaliplatin Formulations Containing Acids

The kinetics of the alkaline hydrolysis of oxaliplatin has been measured – the first step is ring-opening with a half-life of 16 minutes in which a monodentate oxalato intermediate is formed. This monodentate oxalato group is then lost with a half-life of 92 minutes. At pH 7.4, the monodentate oxalato intermediate constitutes only a very small fraction of the total oxaliplatin concentration.[6]

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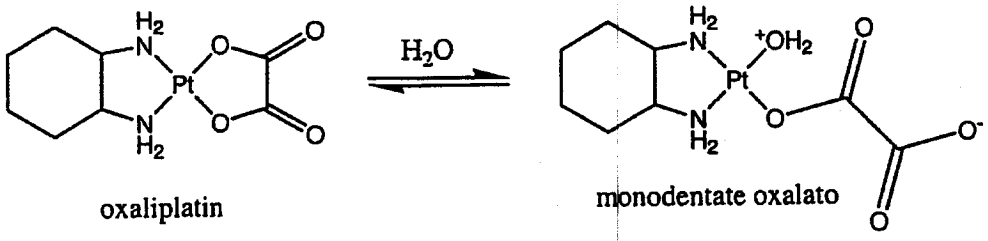
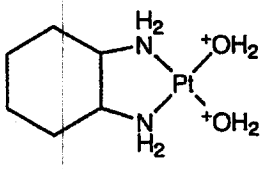
[2] *See* Kidani et al., *Antitumor Activity of Platinum (II) Complexes of 1,2-Diaminocyclohexane Isomers*, 71 GANN 637, 639-41 (1980).
[3] McKeage, M.J., *Comparative Adverse Effect Profiles of Platinum Drugs*,. 13 Drug Safety 228, 230 (1995).
[4] *Id.* at 237-38.
[5] Hartmann, J.T et al., *Toxicity of Platinum Compounds*,. 4 Expert Opin. Pharmacother. 899, 899 (2003).
[6] Jerremalm, et al., *Alkaline Hydrolysis of Oxaliplatin—Isolation and Identification of the Oxalato Monodentate Intermediate*, 91 J. Pharm Sci. 2116, 2120 (2001).



oxaliplatin

monodentate oxalato



diquaDACHPt(II)

It is possible that rapid reaction of the monodentate oxalato intermediate with endogenous compounds and buffer components can occur – these reactions would result in further conversion of the oxaliplatin to the monodentate form. In agreement, the species $[Pt(dach)(H_2PO_4)(H_2O)]^+$ is produced from oxaliplatin in phosphate solution at pH 7.4 at 37°C over 6h.

Phosphate and carbonate binding to platinum complexes has been observed. Early results on cisplatin indicated that phosphate and acetate complexes will certainly be present in significant quantities in any solution if *cis*-$[Pt(H_2O)_2(NH_3)_2]^{2+}$ is buffered with acetate or phosphate buffers – long before any solid complexes, blue or colorless, precipitate.[7]

Both phosphate and carbonate act as good ligands at physiological concentrations and have been observed to be the main biotransformation products of DACH platinum compounds, including oxaliplatin. The presence of carbonate and/or phosphate species, or

[7] Appleton et al., *Reactions of Platinum (II) Aqua Complexes. 2 ^{195}Pt NMR Study of Reactions between the Tetraquaplatinium (II) Cation and Chloride, Hydroxide, Perchlorate, Nitrate, Sulfate, Phosphate and Acetate*, 23 Inorg. Chem. 3521-3525 (1984).

any other products from buffer, is therefore likely to affect toxic side effects and cellular uptake processes and hence, cytotoxic potency.[8]

As noted above, in attempts to impart solubility on the very water-insoluble [$PtCl_2$(DACH)] a number of dicarboxylic acids have been used as mono and bidentate ligands. It is my belief that should any of these acids be added to a solution of oxaliplatin in water, then they will react with oxaliplatin diaquo DACH platinum to form new platinum compounds.

I have reviewed Patent Application No. WO2005/020980 A1 of Mayne Pharmaceuticals. In that application, they describe formulations of oxaliplatin containing various amounts of tartaric acid:

> In yet another aspect the present invention provides a method for preparing a pharmaceutical formulation, the method comprising the steps of:
>
> (i) dissolving oxaliplatin in water to form a solution;
>
> (ii) dissolving in the solution an additive selected from the group consisting of a tartaric acid, a salt of tartaric acid, a pharmaceutically acceptable derivative of a pharmaceutically acceptable tartaric acid and mixtures thereof;
>
> (iii) optionally, adjusting the pH of the solution with a pharmaceutically acceptable base.
>
> pH adjustment may be carried out with any pharmaceutically acceptable base. Preferably the pharmaceutically acceptable base is a sodium hydroxide (NaOH) solution.

The patent provides specific examples of this procedure, e.g. Example 4.

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[8] *See* Centerwall et al., *Cisplatin Carbonato Complexes. Implications for Uptake, Antitumor Properties and Toxicity*, 127 J. Amer. Chem. Soc. 12768 (2005).

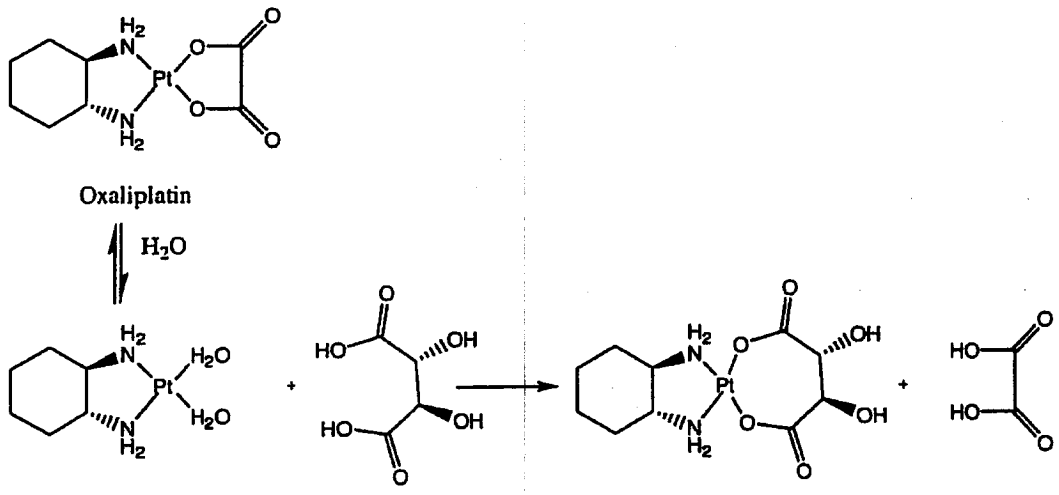
Example 4

The following formulation was prepared for the purpose of regulatory testing:

Oxaliplatin 5mg
Tartaric acid 0.03 mg
NaOH (adjust to pH of approximately 5)
WFI qs 1mL

The pH is adjusted to pH 5 with a range of from 4.7 to 5.5 using NaOH. The concentration of tartaric acid is about 0.2 mM.

Based solely on the patent application and my knowledge of the chemistry of platinum species in aqueous solutions, I would expect that the tartaric acid would react with diaquo-DACH platinum (present as an unreacted material from the process to make oxaliplatin or the disassociation of oxaliplatin in solution) or with oxaliplatin through ligand exchange (*see e.g. Schwartz supra* at p. 1520 showing ligand exchange from oxaliplatin to the diglycerato derivative) to form tartaroplatin, according to the following reaction schemes:



I have calculated a reasonable estimate of the amount of tartaric acid that would be present in a 5 mg / ml solution of oxaliplatin to which 0.03 mg of tartaric acid is added. Theoretically, if all the tartaric acid is ligand exchanged with oxalic acid (and without correcting for the small amount of oxaliplatin consumed), then the amount produced will be in excess of 1.5%.[9] Assuming ligand exchange is not complete, and the range of tartaric acid used by ligand exchange is a quarter to a half the range of tartaroplatin, the weight percentages would be from 0.47% to 0.95%.

I have also reviewed experiments conducted by sanofi-aventis scientists, which formulated solutions of oxaliplatin according to the Mayne patent applications. In those experiments, the sanofi-aventis scientists assessed the possible formation of tartaroplatin through ligand exchange of oxalic acid and tartaric acid in oxaliplatin solutions containing tartaric acid. Those experiments clearly show that tartaroplatin is formed in that solution relative to the amount of added tartaric acid.

In particular, the sanofi-aventis scientists demonstrated that at around pH 4 and pH 5, solutions of oxaliplatin with tartaric acid in concentrations of 0.2 mM, 3.0 mM and 6.7 mM showed formation of tartaroplatin. Moreover, the sanofi-aventis experiments showed that the amount of tartaroplatin increased over the seven-day period that the study was conducted (see Figures 1 and 2 below).

[9] The calculations are as follows: The molecular weight of tartaric acid is 150.09 and the molecular weight of tartaroplatin is 457.3. The number of mols tartaric acid (which is equal to the maximum no mols of tartaroplatin) per ml is calculated to be 0.03 / 150.03 mMols/ml = 0.0002 mMols/ml. The maximum concentration of tartaroplatin would thereby be calculated as 0.0002 mMols/ml * 457.3 g = 0.0915 mg / ml. The weight of tartaroplatin as a percentage of oxaliplatin is calculated as 0.0915 (mg/ml) / 5 (mg/ml) = 1.83%.

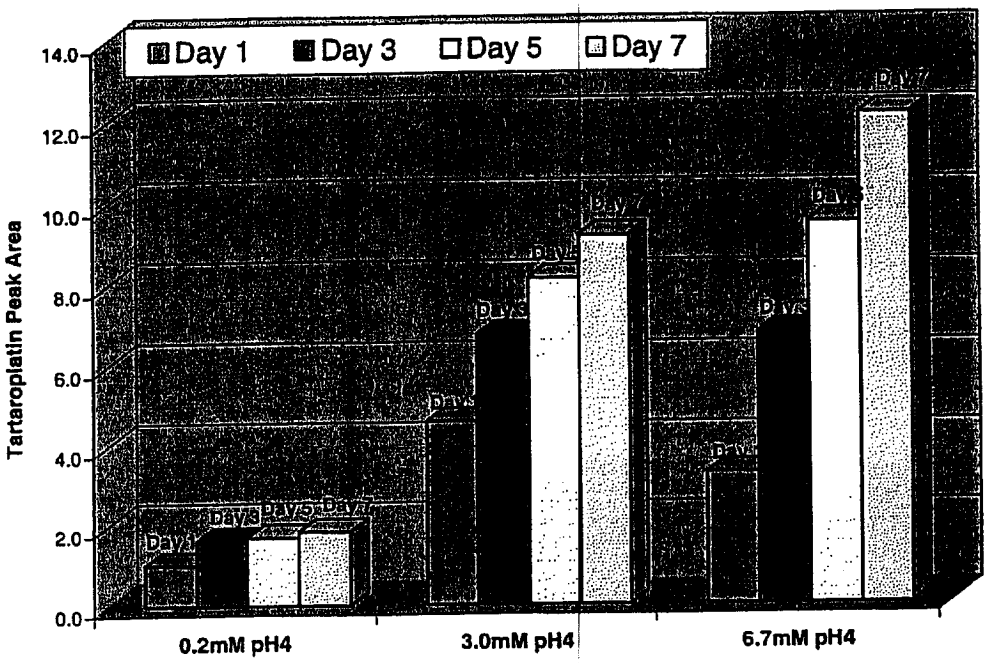


Figure 1. Tartaroplatin Peak Area Comparison of Oxaliplatin Solutions Containing Tartaric Acid at pH 4.

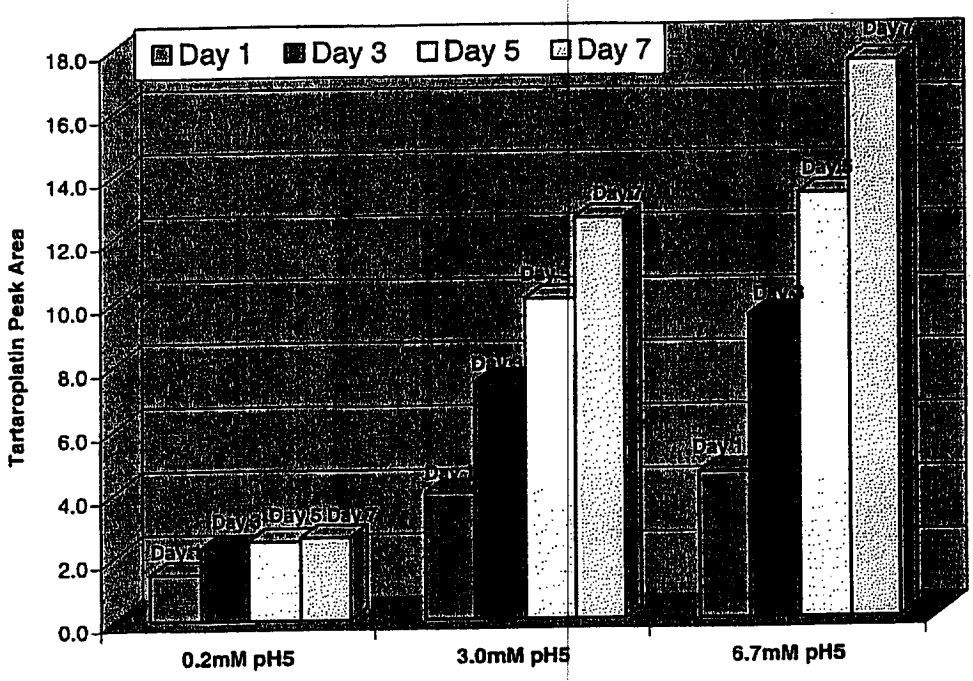


Figure 2. Tartaroplatin Peak Area Comparison of Oxaliplatin Solutions Containing Tartaric Acid at pH 5.

In my opinion, these tests conclusively demonstrate that tartaroplatin can be formed in solutions made according to the Mayne patent application. In addition, based on my knowledge of the chemistry of these compounds, these experiments support the conclusion that ligand exchange is probable in any solution of oxaliplatin to which an acid has been added.

In vivo tests of tartaroplatin compounds in the literature have shown the compound to be active. *See* Schwartz, et al. *supra*, at p. 1523 (compound 265486 (tartaroplatin) has antileukemic activity in mice at doses of 12.5, 25 and 50 mg/kg and an LD50 of 60 mg/kg.); Speer et. al., *Antitumor Activity of Platinum Complexes of 1, 2-Diaminocyclohexane Isomers*, 8 J. of Clin. Hem. & Onc. 44 (1978) (providing antitumor activity of + and – tartrato DACH Pt.). Based on those results, I would expect the tartaroplatin formed in Mayne's formulation to have activity in humans. The extent and type of activity (e.g., toxic or anti-cancerogenic) cannot be predicted without the appropriate studies.

Likewise, in my opinion, formulations of oxaliplatin with other diacid or monoacid compounds would likely form active species. See Schwartz *supra* and Speer *supra* which provide in vitro activity and toxicity data for numerous mono and diacid DACH Pt dervivatives. Such formulations include those discussed in the recent patent literature: *See* European Patent Application EP 1 466 600 A1 by Stada, describing oxaliplatin solutions containing sulfuric, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, or para-toluenesulfonic acid; US Patent Nos. 6,673,805 and 6,476,068 both assigned to Pharmacia Italia S.p.A. describing oxaliplatin solutions containing lactic acid; and U.S. Patent

Application 2003/0109515 A1 also by Pharmacia Italia S.p.A. describing oxaliplatin solutions containing malonic acid.

Consequently, addition of any buffer should necessitate clinical studies to determine whether the active compounds formed as byproducts due to the reaction of the diaquo-DACH species, or oxaliplatin and the buffered products, have any toxic effects.

Dated: 09/07/06

N Farrell

Nicholas P. Farrell

Exhibit A

[redacted]

CURRICULUM VITAE

NICHOLAS FARRELL, Ph. D.

POSITION: Professor
Department of Chemistry
Virginia Commonwealth University
Richmond, VA 23284-2006
U.S.A.

TELEPHONE: 804-828-6320 (Work)
[redacted]
FAX: 804-828-8599
E-MAIL: npfarrel@vcu.edu

LANGUAGES: Irish, English, Spanish, Portuguese, French (reading)

EDUCATION:

B.Sc. Chemistry/Mathematics (Hons.), University College, Dublin, Ireland [ ].
Ph.D. Chemistry, Sussex University, Brighton, England [ ].
Thesis: Uses of Reactive Alkylating Agents in Transition-Metal Chemistry (Supervisors A. Pidcock and C. Eaborn)

Postdoctoral Fellowships

[ ] Simon Fraser University, Vancouver, B.C., Canada
Studies on Aryldiazonium Metal Complexes (D. Sutton)
[ ] University of British Columbia, Vancouver, B.C., Canada
Studies on Ruthenium Porphyrins (D. Dolphin/B.R. James)

PROFESSIONAL EXPERIENCE AND VISITING PROFESSORSHIPS

Chair, Chemistry Department, Virginia Commonwealth University, Richmond, VA 23284-2006, USA September 2005-
Professor, Virginia Commonwealth University, Richmond, VA 23284-2006, USA 1996-
Associate Professor, Virginia Commonwealth University, Richmond, VA 23284-2006, USA 1993-1996.
Research Associate Professor, University of Vermont, Burlington, VT 05405, USA 1984-1993.
Associate Professor, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brasil 1977 - 1984.
Visiting Professor, Instituto Venezolano para Investigaciones Cientitificas. Caracas, Venezuela. March 2002
Visiting Professor, Foundation for Inorganic Chemistry, University of Sydney, New South Wales, Australia, July 1996 - September 1996.
Visiting Professor, University College Dublin, Ireland, November 1994 - January 1995
(Under auspices of International Union against Cancer, UICC).
Visiting Associate Professor, Simon Fraser University, May 1981 - June 1982.
Visiting Professor, Cambridge University, England, May/June 1980.
(With Prof. B.F.G. Johnson, under auspices of Conselho Nacional de Pesquisa, CNPq Brasil and British Council).
Visiting Professor, University of British Columbia, May/July 1979.
(With Prof. B.R. James under auspices of Conselho Nacional de Pesquisa, CNPq Brasil and National Research Council, NRC Canada).

GRANTS AND AWARDS
(TITLE, AGENCY, INVESTIGATORS, PERIOD)

Current Grants

Mechanistic Studies on New Platinum Clinical Agents
National Institutes of Health (RO1 CA 78754-05)
N. Farrell
8/1/02 – 7/31/07 ($1,540,000 total costs; $317,250 Year 1)
This is Year 3 of a 5-year renewed grant to study the DNA interactions and mechanism of action of clinically relevant polynuclear platinum compounds.

DNA interactions of polynuclear platinum. Mechanistic NMR studies probing the origin of the unique antitumour activity of BBR3464.
Australian Research Council DP0208117
PI: S. Berners-Price; co-PI: N.Farrell
01/01/01-12/31/03 ($290,000 total costs to SBP)
This proposal allowed SBP to obtain funding in Australia to execute her part of this research.

NMR studies on DNA interactions of polynuclear platinum
Australian Research Council LX0346972
PI: S. Berners-Price; co-PI: N.Farrell
01/01/02-12/31/04 ($32,000 total costs to SBP/NF for travel related to ARC DP0208117
A travel grant for student and investigator exchange.

Platinum Metal Complexes as DNA-Protein Cross-Linking Agents
(National Science Foundation CHE-0616768)
N. Farrell
07/01/06 - 06/30/09 ($ 462,000 total costs)
This grant studies DNA-protein interactions of transplatinum and related complexes.

Pending

Metabolism Studies on Platinum Anti-cancer Drug Agents
National Institutes of Health (To be Submitted Mar. 1st 2006)
N. Farrell
8/1/05 – 7/31/09 ($725,000 total costs)
This is to support the synthesis and testing of new "2nd-generation" polynuclear platinum derivatives through the auspices of the NIH Rapid Access to NCI Discovery Resources (R*A*N*D) program compounds.

Mechanistic Studies on the Mode of Action of Non-Classical Platinum Antitumor Agents
United States-Israel Binational Science Foundation
PI: D. Gibson and N. Farrell
8/1/05 – 06/30/09 ($228,000 total costs)
This proposal looks at novel NMR methods to examine metabolism of platinum-based anticancer agents in cells.

Awards and Service Activities to the Profession.

I recently served as Chair of the IXth International Symposium on Platinum Compounds in Cancer Chemotherapy held in New York in October 2003. I also recently served as Chair of the first Gordon Research Conference on "Metals in Medicine" in July 2002. Together with Professors Mike Clarke and Frank Shaw, we took the initiative to submit a proposal to GRC, set the program and obtain external funding for this meeting, which was very successful and will give the field its own dedicated conference in the future.

Awards and Lectureships

Lonsdale Lecturer, NUI Maynooth, Ireland, November 2004
Distinguished Research Scholarship Award, Virginia Commonwealth University, 2003
Center for Synthesis and Chemical Biology, University College Dublin/Royal College of Surgeons Ireland, Dublin, Ireland December 2003.
Distinguished Scholar, College of Humanities and Sciences, Virginia Commonwealth University, 1997
Yamagiwa-Yoshida International Cancer Fellowship from International Union
against Cancer (UICC), November 1993 - January 1994.
Jambor Lectureship, British Columbia Cancer Research Center, May 1994.
Juckett Fellowship from Vermont Cancer Center, 1992/1993 ($50.000.00).

PATENTS AND RELATED EXPERIENCE

I have gained considerable experience in consulting with the pharmaceutical industry on issues of drug development and as an expert witness in legal matters. The patent portfolio and intimate experience in the drug development process from patent protection and licensing negotiations to participation and consultancy on FDA submissions also gives me considerable experience in all aspects of technology transfer which is at the service of organizations, colleagues and other researchers.

Primary patents only. From 20 primary patents, a total of over 70 patents includes selections, continuations-in-part and international filings.

"Transplatinum Complexes with N_2O_2 Donor Sets as Cytotoxic and Antitumor Agents. N. Farrell. US Provisional patent 60/707,176. Conversion filed 08/11/06.

"Transplatinum Complexes as Cytotoxic and Anticancer Agents". N. Farrell. US Patent 6, 350, 740 B1.

"Targeted Bis(platinum)polyamines as Pro-Drugs". A. Hegmans, J.D. Roberts and N. Farrell. US Patent Application 2003-0114433-A1

"Multinuclear Cationic Platinum Complexes with Antitumor Activity". G. da Re, R. DiDomenico, S. Spinelli and N. Farrell. US Patent 6,313,333 B1.

"High Affinity DNA Binding Compounds as Adjutants in Antisense Technology". N. Farrell and M.G.B. Kloster. US Patent 6,310,047.

"Platinum Complexes With Anti-viral Activity and Method of Using Same" N. Farrell and U. Bierbach. US Patent 6,113,934.

"Water-Soluble Transplatinum Complexes". N. Farrell and U. Bierbach. US Patent 6,001,872.

"New Bisplatinum Complexes as Chemotherapeutic Agents". N. Farrell. US Patent 5,107,007.

"Bisplatinum Complexes as Chemotherapeutic Agents". N. Farrell, S.G. de Almeida, M.P. Hacker, J.J. McCormack. US Patent 4,871,729.

"Triplatinum Complexes". J.D. Hoeschele, Y. Qu and N. Farrell. US Patent 5,380,897.

"New Bis-Platinum Complexes With Polymethylene Derivatives As Ligands Having Antitumor Activity" N. Farrell, E. Menta, R. DiDomenico and S. Spinelli. WO 98/03518.

"New Bis-Platinum Complexes With Polyamine Ligands As Antitumor Agents" N. Farrell, E. Menta, R. DiDomenico and S. Spinelli. WO 98/03519.

"Trinuclear Cationic Platinum Complexes having Antitumor Activity and Pharmaceutical Compositions containing them". M. Valsecchi, M. Conti, L. del Greco, C. Bugatti, E. Menta, F.C. Giuliani, C. Manzotti, S. Spinelli and N. Farrell. US Patent 5,744,497.

"Trinuclear Cationic Platinum Complexes having Antitumor Activity and Pharmaceutical Compositions containing them". M. Valsecchi, P. Pavesi, C. Bugatti, E. Menta, F.C. Giuliani, C. Manzotti, S. Spinelli and N. Farrell. Italy Patent MI94A 002383 (Selection of US Patent 5,380,897). November 1994.

"Bisplatinum (IV) Complexes". N. Farrell, S. Spinelli, M. Valsecchi and E. Menta. US Patent 5,409,915.

"Trans-Platinum (IV) Compounds". N. Farrell.US Patent 5, 624,919.

"Platinum Complexes with One Radiosensitizing Ligand". K.A. Skov, N. Farrell, D.J. Chaplin. US Patent 4,921,963.

"Platinum Complexes with Sulfoxide Leaving Groups". N. Farrell.US Patent Application SN 180956.

"Platinum Amine Sulfoxide Complexes". N. Farrell. US Patent Application SN 07/476235. Awarded February 1991.

"Ruthenium Complexes Containing Tetramethylenesulphoxide and Nitroaromatic Ligands as Radiosensitizers". K.A. Skov, P.K. Chang, B.R. James, N. Farrell. Canadian Patent SN 561931.

PUBLICATIONS

As of July 1, 2006, 3 books, 19 primary patents and patent applications, 23 review chapters and invited papers, 162 refereed papers as well as over 150 conference posters and published abstracts . The posters and published abstracts are not included in this curriculum vitae.

Books

Transition Metal Complexes as Drugs and Chemotherapeutic Agents, Farrell, N. in "Catalysis By Metal Complexes", James, B.R. and Ugo, R., Eds., Kluwer Academic Press (1989). ISBN 9027728283.

Uses of Inorganic Chemistry in Medicine, Farrell, N., Ed., Royal Society of Chemistry (1999). ISBN 0 85404 444 2.

Platinum-Based Drugs in Cancer Therapy, Kelland, L.R. and Farrell, N. Eds., in "Cancer Drug Discovery and Development", Teicher, B.A., Ed. Humana Press (2000). ISBN 0896035999.

Volumes Edited

Muggia, F.M. and Farrell, N.: The International Symposium on Platinum Coordination Compounds in Cancer Chemotherapy. Seminars in Oncology *vol.31* (2004)

Farrell N. and Berners-Price, S.J.: The International Symposium on Platinum Coordination Compounds in Cancer Chemotherapy. Journal of Inorganic Biochemistry *vol. 98(10)* (2004).

Farrell, N.: Biomedical Uses and Applications of Coordination Chemistry. An Overview. Coord. Chem. Rev., *vol. 232* (2002).

Reviews, Chapters and Invited Papers

23. Guiseppe-Elie, A., Taylor, S., Ligerfelt, L., Nixon, C., Georgiana, R., Kim, J., Smith, S., Mangrum, B. and Farrell, N.: Studies of the Interaction of Platinum Drugs with DNA Using Oligonucleotide Microarrays. Macromolecular Symposia, 235 (Issue 1), 115-120 (2006).

Billecke, C., Malik, I., Movsisyan, A., Sulghani, S., Hermanspan, B., Sharif, A., Mikklesen, T., Farrell, N. and Bolgler, O.: Analysis of Glioma Cell Platinum Response by Metacomparison of 2-D Chromatographic Proteome Profiles. Molecular and Cellular Proteomics Jun 10 (2005).

Farrell, N.: Platinum Anti-cancer Drugs. From Laboratory to Clinic. ACS Symposium Series 903 " Medicinal Inorganic Chemistry", Sessler, J.A., Doctorow, S.E., McMurry, T.J. and Lippard, S.J. Eds., 62-79 (2005).

20. Farrell, N. Pre-clinical perspectives on the use of platinum compounds in cancer chemotherapy. Seminars in Oncology. 31:1-9 (2004).

Farrell, N.: Polynuclear Platinum Drugs. Metal Ions in Biol. Sys. 41:252-296 (2004)

Farrell, N.: Inorganic Complexes as Drugs and Chemotherapeutic Agents in "Comprehensive Coordination Chemistry, II, eds. J.A. McCleverty and T.J. Meyer, (2004) Elsevier Pergamon (Oxford, UK) vol. 9, pp. 809-840.

Farrell, N.: Biomedical Uses and Applications of Coordination Chemistry. An Overview. Coord. Chem. Rev. (2002), *232(1-2)* pp.1 - 4.

Farrell, N.: Polynuclear Charged Platinum Compounds as a New Class of Anticancer Agents. Toward a New Paradigm. In "Platinum-Based Drugs in Cancer Therapy", Kelland, L.R. and Farrell, N. Eds., Humana Press (2000) pp. 321-338.

Farrell, N., Qu, Y., Bierbach, U., Valsecchi, M., Menta, E.: Structure-Activity Relationships Within Di- and Trinuclear Platinum Phase I Clinical Agents. In "30 Years of Cisplatin - Chemistry and Biochemistry of a Leading Anticancer Drug". Lippert, B. Ed., Verlag, (1999) pp. 479-496.

Farrell N., Spinelli, S. Dinuclear and Trinuclear Platinum Anticancer Agents. In "Uses of Inorganic Chemistry in Medicine", Farrell, N., Ed., Royal Society of Chemistry, (1999) pp.124-134.

Farrell, N., Qu, Y. And Roberts, J.D.: Multifunctional DNA-Binding Metal Complexes. In "Topics in Biological Inorganic Chemistry" Clarke, M.J., Sadler, P.J. Springer, 1999 pp.99-115.

Farrell, N.: DNA Binding of Non-Classical Platinum Antitumor Complexes. In "Advances in DNA Sequence Specific Agents". Vol. 3. Palumbo, M. Ed., JAI Press Inc. 179-199 (1998).

Qu, Y., Bloemink, M.J., Mellish, K.J., Rauter, H., Smeds, K.A. and Farrell, N.:
Factors Affecting Formation and Structure of DNA Intrastrand Cross-links by Dinuclear Platinum Complexes in "Cytotoxic, Mutagenic and Carcinogenic Potential of Heavy Metals Related to Human Environment" Hadjiliadis, N. Ed. NATO ASI Series 2, vol.26, 435 (1997).

Farrell, N.: Current Status of Structure-Activity Relationships of Platinum Anticancer Drugs. Activation of the trans Geometry. Metal Ions in Biol. Sys., 32:603 (1996).

Farrell, N.: DNA Binding of Dinuclear Platinum Complexes. In "Advances in DNA Sequence Specific Agents". Vol. 2. Hurley, L.H., Chaires, J.B., Eds., JAI Press Inc. 187-216 (1996).

Farrell, N.: DNA Binding and Chemistry of Dinuclear Platinum Complexes. Comments in Inorganic Chemistry, 16 (6), 373-389 (1995).

Farrell, N.: Metal-Potentiated Drugs: In "Metal-Ligand Interactions in Human Biology and Medicine"; Handbook on Metal-Ligand Interactions in Biological Fluids, vol. 2, 1312-1317, Berthon, G. Ed. (1995).

Farrell, N.: Non-classical Platinum Antitumor Complexes. Perspectives for Design and Development of New Drugs Complementary to Cisplatin. Cancer Investigation, 11, 578-589, (1993).

Farrell, N: Structurally Novel Platinum Antitumor Compounds: Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy, Howell, S,B. Ed., Plenum Press, New York, pp. 81-91 (1991).

Hoeschele, J.D., Kraker, A.J., Qu, Y., Van Houten, B., and Farrell, N.: Bis(platinum) Complexes. Chemistry, Antitumor Activity and DNA-Binding. In " Molecular Basis of Specificity in Nucleic Acid-Drug Interactions", Pullman, B. and Jortner, J., Eds., Kluwer Academic Publishers, Dordrecht, pp. 301-321 (1990).

Farrell, N.: Metal Complexes as Radiosensitizers: Prog. Clin. Biol. Med., Clarke, M.J. Ed. 10:90 (1989).

Farrell, N.: Chemical and Biological Activity of Metal Complexes Containing Dimethylsulfoxide. ACS Symposium on the "Chemistry and Biochemistry of Platinum, Gold, and Other Chemotherapeutic Agents", S.J. Lippard, Ed. 209:279 (1983).

James, B.R., Addison, A.W., Cairns, M., Dolphin, D., Farrell, N., Paulson, D.R., and Walker, S.: Progress in Dioxygen Complexes of Metalloporphyrins, in "Fundamental Research in Homogeneous Catalysis", Vol. 3, M. Tsutsui, Ed. Plenum Press, pp. 751-772 (1979).

Refereed Papers

162. Kabolizadeh, P., Ryan, J.J. and Farrell, N.: Differences in the Cellular Response and Signaling Pathways of Cisplatin and BBr3464 ([{*trans*-$PtCl(NH_3)_2$}$_2\mu$-(trans-$Pt(NH_3)_2(H_2N(CH_2)_6NH_2)_2$)]$^{4+}$) Influenced by Copper Homeostasis. Biochem. Pharmacol. Submitted.

Komeda, S., Moulaei, T., Woods, K.K., Chikuma, M., Farrell, N. and Williams, L.D.: Phosphate Clamps: A Novel Mode of DNA Interaction by a Polynuclear Platinum(II) Complex. J. Amer. Chem. Soc. Accepted for Publication.

160. Bulluss, G.H., Knott, K.M., Ma, E.S.F., Aris, S.M., Alvarado, E. and Farrell, N.: *Trans*-Platinum Planar Amine Compounds With [N_2O_2] Ligand Donor Sets: Effects of Carboxylate Leaving Groups and Steric Hinderance on Chemical and Biological Properties. Inorg. Chem. 45:5733-5735 (2006).

Chválová, K., Kašpárková, J., Farrell, N. and Brabec, V.: Deoxyribonuclease I footprinting reveals different DNA binding modes of bifunctional platinum complexes. FEBS Journal 273:3467-3478 (2006).

Billecke, C., Finniss, S., Tahash, L., Miller, C., Mikkelsen, T., Farrell, N. and Bögler, O.: Sensitivity of glioma cells *in vitro* and *in vivo* to platinum anticancer drugs. Polynuclear agents are more potent than cisplatin and induce cell cycle arrest. Neuro-oncology 8:215-226 (2006).

Anzelotti, A., Liu, Q., Bloemink, M.J., Scarsdale, J.N. and Farrell, N.: Targeting the Retroviral Zinc Finger-DNA Interaction. A small molecule approach utilizing the electrophilic nature of *trans*-Platinum-Nucleobase Compounds. Chemistry and Biology. 13:539-548 (2006).

Anzelotti, A., Stefan, S., Gibson' D. and Farrell, N.: Donor Atom Preferences in Substitution Reactions of Trans-Platinum Mononucleobase Compounds. Implications for DNA-Protein Selectivity. Inorg. Chim. Acta 359:3014-3019 (2006).

155. Liu, Q., Qu, Y., van Antwerpen, R. and Farrell, N.: Mechanism of the Membrane Interaction of Polynuclear Platinum Anticancer Agents. Implications for Cellular Uptake. Biochemistry 45:4248-4256 (2006).

Anzelotti, A., Sabat, M. and Farrell, N.: Study of covalent and non-covalent interactions for [Metal(dien)nucleobase]$^{2+}$ complexes with l-tryptophan derivatives: Formation of metal-tryptophan species by nucleobase substitution under biologically relevant conditions. Inorg. Chem. 45:1638-1645 (2006).

Harris, A.L., Ryan, J.J. and Farrell, N.: Biological Consequences of Trinuclear Platinum Complexes: Comparison of BBR 3464 to its Non-covalent Congeners. Mol. Pharmacol. 69:666-672 (2006).

Quiroga, G. A., Pérez, J.M., Navarro-Ranninger, C. and Farrell, N: Novel Transplatinum(II) complexes with [N_2O_2] donor sets. Cellular Pharmacology and Apoptosis Induction in Pam 212-ras Cells. J. Med. Chem. 49:224-231 (2006).

Harris, A.L., Yang, X., Hegmans, A., Povirk, L. Ryan, J., Kelland, L.R. and Farrell, N.: Synthesis and Characterization of the DNA Binding and Cytotoxicity of a Novel Trinuclear Highly Charged Compound. Inorg. Chem. 44:9598-9600 (2005).

150. Zhang, J., Thomas, D.S., Davies, M.S., Berners-Price, S.J. and Farrell, N.: Effects of geometric isomerism in dinuclear platinum antitumor complexes on aquation reactions in the presence of perchlorate, acetate and phosphate. Journal of Biological Inorganic Chemistry. 10:652-666 (2005).

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[$PtCl_2(NH_3)$(thiazole)]. Nuc. Acids Res.33:5819-5828 (2005).

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Ma, E.S., Bates, W.D., Edmunds, A., Kelland, L.R. and Farrell, N.: Enhancement of Aqueous Solubility and Stability Employing a *Trans* Acetate Axis in *Trans*planar Amine Platinum Compounds while Maintaining the Biological Profile. J. Med. Chem.48: 5651-5654 (2005).

Liu, Q., Golden, M., Darensbourg, M.Y. and Farrell, N.: Thiolate-Bridged heterodinuclear Platinum-Zinc chelates as models for ternary Platinum-DNA-Protein Complexes and zinc ejection from zinc fingers. Evidence from studies using ESI-Mass Spectrometry. Chem. Commun, 4360 – 4362 (2005).

145. Ourliac-Garnier. I., Elizondo-Riojas, M., Redon, S., Farrell, N.P. and Bombard, S.: Cross-linking of the quadruplex structures of the $AG_3(T_2AG_3)_3$ human telomere sequences in Na+ and K+ solutions by dinuclear platinum complexes. Biochemistry. 44;10620-10634 (2005).

Quintal, S.M.O., Qu, Y., Gomez-Quiroga, A., Moniodis, J., Nogueira, H.I.S. and Farrell, N : Pyridine-carboxylate complexes of platinum. Effect of N,O-chelate formation on model bifunctional DNA-DNA and DNA-protein interactions. Inorg. Chem. 44:5247-5253 (2005).

Oehlsen, M.E., Hegmans, A., Qu, Y. and Farrell, N.: A Surprisingly Stable Macrochelate Formed from the Reaction of cis-dinuclear Platinum Antitumor Compounds with Reduced Glutathione. Identification by the Use of (1H-15N and 195Pt) NMR Spectroscopy and Electrospray Ionization Mass Spectrometry. Inorg. Chem. 44:3004-3006 (2005).

Harris, A., Qu, Y. and Farrell, N.: Unique cooperative binding interaction observed between a minor groove binding Pt anti-tumor agent and Hoeschst Dye 33258. Inorg. Chem. 44:1196-1198 (2005).

Anzellotti, A.I., Ma, E.S. and Farrell, N.: Platination of nucleobases to enhance non-covalent recognition in protein-DNA/RNA complexes. Inorg. Chem. 44:483-485 (2005).

140. Fojo, T., Farrell, N., Ortuzar, W., Tanimura, H., Weinstein, J. and Myers, T.G.: Identification of non-cross-resistant platinum compounds with novel cytotoxicity profiles using the NCI anticancer drug screen and clustered image map visualizations. Crit. Revs. Oncol./Hematol. 53:25-34 (2005).

Kasparkova, J., Fojta, M., Farrell, N. and Brabec, V.: Differential recognition by the tumor suppressor protein p53 of DNA modified by the novel antitumor trinuclear platinum drug BBR3464 and cisplatin. Nuc. Acids Res. 32:5546-5552 (2004).

Qu, Y., Harris, A., Hegmans, A., Petz, A., Penazova, H. and Farrell, N.: Synthesis and DNA Conformational Changes of Non-covalent Polynuclear Platinum Complexes. Journal of Inorganic Biochemistry. 98:1591-1598 (2004).

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Davies, M.S., Berners-Price, S.J., Cox, J.W. , Farrell, N.: The nature of the DNA template (single-stranded versus double-stranded) affects the rate of aquation of a dinuclear Pt anticancer drug. J. Chem. Soc. Chem. Commun. 122-123 (2003).

130. Kasparkova, J., Novakova, O., Farrell, N., Brabec, V.: DNA binding by antitumor *trans*-[$PtCl_2(NH_3)$(thiazole)]. Protein recognition and nucleotide excision repair of monofunctional adducts. Biochemistry. 42:792-800 (2003).

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125. McGregor, T.D., Bousfield, W., Qu, Y. and Farrell, N.: Circular Dichroism Study of the Irreversibility of Conformational Changes Induced by Polyamine-linked Dinuclear Platinum Compounds. J. Inorg. Biochem. 91:212-219 (2002).

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Eaborn, C., Farrell, N., and Pidcock, A.: Activation of Platinum Complexes by Methyl Fluorosulphonate: Olefin-isomerization and Alkyne Insertion. J. Chem. Soc. Chem. Commun. 766 (1973).

Eaborn, C., Farrell, N., Murphy, J.L., and Pidcock, A.: Reactions of Methyl Fluorosulphonate and Triethyloxonium Tetrafluoroborate with Metal Complexes. J. Organomet. Chem. 44:C68-70 (1973).

INVITED CONFERENCE TALKS (2000 to present)

I have been a regular invited lecturer at the major meetings of the field such as the International Symposium on Platinum Compounds in Cancer Chemotherapy (ISPCC, 1991, 1995, 1999) and International Conference on Bioinorganic Chemistry (ICBIC, 1995, 1997, 1999. In February 2003 I was Plenary lecturer at the Royal Australian Chemical Institute Inorganic '03 meeting. My invited talk at the Pacifichem conference in Hawaii in December 2000 was abstracted for press release and publicity resulting in world-wide coverage including WebMD, Reuters and The Times of London. I was invited to give a sunrise session lecture at the American Association for Cancer Research meeting in San Francisco, April 2000. This prestigious invitation to present a "state-of-the-art" lecture to cancer researchers resulted in an informational brochure for clinicians released by Astra Zeneca on "New Platinum Compounds".

"Platinum Anticancer Agents. Structures and Targeted Biomolecules". International Chemical Congress of Pacific Basin Societies (Pacifichem), Honolulu, Hawaii, December 2005.

"Platinum Anticancer Agents. Structures and Targeted Biomolecules". American Chemical Society, Washington DC, August 2005.

"Polynuclear Platinum Complexes. Chemistry and Biology" Gordon Research Conference on Metals in Medicine, Colby College, Maine, June 2004.

"Platinum Anticancer Agents. Structures and Targeted Biomolecules", Plenary Lecturer, COST D20 Workshop Metal Complexes in the treatment of Cancer and Viral diseases, Trieste, September 2003.

"Platinum Anticancer Agents. Structures and Targeted Biomolecules", American Chemical Society Symposium on Medicinal Inorganic Chemistry, ACS Fall meeting, New York, September 2003.

Platinum Anticancer Agents. Structures and Targeted Biomolecules", Plenary Lecturer, Royal Australian Chemistry Institute, Inorganic Chemistry Symposium, Melbourne, February 2003.

"Polynuclear Platinum Drugs. Platinum-DNA Interactions". 10th International Conference on Bioinorganic Chemistry (ICBIC 10), Florence, Italy, August , 2001.

"Platinum-DNA Interactions. Implications for New Drugs". In "New Trends in Biofunctional Metal Complexes", International Chemical Congress of Pacific Basin Societies, Hawaii, December, 2000

"Platinum-DNA Interactions. Implications for New Drugs". In "Recent Advances on the Interaction of Metal Complexes with Nucleic Acids and Their Components". American Chemical Society Meeting, Washington, DC, August, 2000.

"Platinum-DNA Interactions. Implications for New Drugs". International Conference on DNA Conformation, Modification and Recognition in Biomedicine, Brno, Czech Republic, July, 2000.

"Principles of Medicinal Chemistry for Inorganics". Metals in Medicine workshop, National Institutes of Health, Bethesda, MD June, 2000.

"New Platinum Compounds". Meet the Expert Sunrise Session, 91st AACR, San Francisco, April, 2000.

GRADUATE THESES DIRECTED

The Interactions Between Multinuclear Platinum Compounds and DNA: Investigation of Non-covalent Compounds by Chemical and Biological Methods. A.L. Harris (Ph.D. VCU, August 2005).

Model Studies on the Metabolism of Anticancer Active Polynuclear Platinum Complexes. M.C. Oehlsen (Ph.D. VCU, May 2003).

Dinuclear platinum complexes with Polyamine Derivative Linker Groups. Focus on Binding and conformational changes of DNA. T.D. McGregor (Ph.D. VCU, May 2001).

Interactions Between Multinuclear Platinum Complexes and DNA with a Focus on Ligands, Linker groups, and Kinetics: A Molecular Modelling and [^{1}H, ^{15}N] NMR Study. J. W. Cox (Ph.D., VCU, April 2000).

New Platinum Antitumor drug (1,0,1/t,t,t) Interaction with DNA: DNA Conformational changes and Long-Range Pt-DNA Adduct. M.-C. Tran (M.S., VCU, November 1998)

In Vivo and In Vitro Characterization of Novel Dinuclear and Thiazole-Containing Platinum Compounds. L.A. Eckel (M.S., VCU, April 1997).

DNA Interactions of Bis(platinum) Complexes. P.Wu (Ph.D. University of Vermont (UVM), 1995).

Activation of the Trans Geometry in Platinum Anticancer Agents. M.-J. van Buesichem-Doedee, (Ph.D. UVM, 1994).

Synthesis and Invesitigation of the Mechanism of Antitumor Activity of New Platinum Complexes. A.P. Soares-Fontes, (Ph.D. Universidade Federal de Minas Gerais (UFMG) 1993).

Synthesis and Characterization of Bis(platinum) Complexes. S.G. de Almeida, (Ph.D. UFMG, 1990).

(All M.Sc. Universidade Federal de Minas Gerais):
Synthesis and Characterisation of Complexes of Palladium and Platinum with Nitroimidazoles and Nitrothiazoles. T.M. de Gomes Carneiro (1984)

Aspects of the Chemistry of Group VIII Metal Complexes with Dimethylsulfoxide Relevant to the Biological Activity of Metal Complexes. H.G. Luna (1984)

Synthesis, Characterization and Properties of Some Complexes of Ruthenium(II) with Amines and Nitroimidazoles. M.H. Moreira (1984)

Interaction of the Complex Oxobis(acetylacetonato)vanadium(IV) with Purine and Pyrimidine Bases. S.B. Barczewski (1983).

The Use of 3-imino-2-ketoisoindoline as Intermediate in the Synthesis and Characterisation of Ruthenium-phthalocyanine. L.M. Souza (1981)

Synthesis and Characterisation of Model Complexes of Nitrogenase. A.A. Neves (1981)

Synthesis and Characterisation of Some Complexes of Ruthenium with Acetylacetone.
S.G. de Almeida (1981)

Synthesis and Characterisation of Complexes of Ruthenium with Purines, Pyrimidines and Nucleosides. N.G. de Oliveira (1980)

A Study of the Reactions of Aryldiazonium Salts with Some Macrocyles of Cobalt. M.N. Bastos (1980)

Undergraduate Researchers. My laboratory plays host to a number of undergraduate researchers every semester, from both my current institution and from abroad. We also host undergraduates as part of the Department's REU program (NSF funded). All undergraduate researchers in my laboratory have ended with at least one publication from their stay.

Visiting Professors and Students to my Laboratory. I have hosted graduate and undergraduate students in my laboratory as part of our extensive international collaborations - in most cases these visits have been initiated from the visitors side. Recent students include J. Moniodis (University of Western Australia), A. Gomez-Quiroga (Universidade Autonoma, Madrid, Spain, 2001); S. Quintal (Aveiro, Portugal, 2000/2001). J. Malina and H. Penazova (Institute of Biophysics, Brno, Czech Rrepublic), A. Jones (University of Sydney, Australia, Spring, 1998); B. Miller (University of Munich, Germany, Spring 1998); T. Varga (University of Debrechen, Hungary, 1996/1997); K. Lövquist (University of Lund, Sweden, Summer 1994) and Emese Kozma (University of Debrechen, Hungary 1993/1994) have also visited in my laboratory. Faculty members (S. Berners-Price, University of Western Australia, 2003/4, T.G. Appleton, University of Queensland, Australia, Spring 1994) and R. Roat, Washington College in Maryland, Chestertown, MD, Academic Year 1995/1996) have visited in recent years in my laboratory at VCU. All of these visits received funding from their national research councils to work with us. In Professor Roat's case, she received a prestigious 1-year NSF award for Visiting Professorship for Women (VPW) to a total of approximately $ U.S. 100,000.00.

Research Collaborations. I have a number of active national and international collaborations including that of Dr. Viktor Brabec (DNA Binding of Platinum Drugs, Brno, Czech Republic, funded as subcontract to NIH proposal); S. Berners-Price (NMR of Pt-DNA Interactions; Brisbane, Australia, funded through an ARC research proposal to SBP); D. Gibson (DNA-protein interactions, Hebrew University, Jerusalem, Israel funded through US-Israeli BNSF); T.W. Hambley (crystallography; Sydney, Australia); J.D. Burgess (QCM of Pt-DNA, Case Western Reserve, Cleveland); R. Georgiadis (SPR of Pt-DNA, Boston University); L.I. Elding (kinetics of Pt substitution reactions, Lund, Sweden); M. J. Danks (pro-drug and VDEPT approaches, St. Judes Childrens Hospital); P.J. O'Dwyer (gene expression, University of Pennsylvania); D. Gewirtz and L. Povirk (transplatinum compounds in breast cancer, Medical College of Virginia), O. Bogler, Henry Ford Hospital, brain cancer and p53 expression) and T. Fojo (National Cancer Institute, gene expression)

REFEREES

Prof. L.H. Hurley
College of Pharmacy
University of Arizona
hurley@pharmacy.arizona.edu

Professor B. Lippert
Facherbeich Chemie
Univeristät Dortmund
D-44221, Dortmund
Germany
49-231-755-3840
lippert@pop.uni-dortmund.de

Sue Berners-Price
Professor and Head of Chemistry
School of Biomedical & Chemical Sciences
The University of Western Australia
35 Stirling Highway
Crawley Perth WA 6009
61-8 9380 3258
sbp@chem.uwa.edu.au