Lecturing/teaching/consulting activities of prof. Andrei R. Timerbaev during his visit in The Warsaw University of Technology, Faculty of Chemistry, Chair of Analytical Chemistry, 10 October – 25 November 2009

Special course for Postgraduates/Undergraduates (15 hours): "Advanced Instrumental Analytical Chemistry: Capillary Electrophoresis and Electromigration Methods"

Tentative description of topics:

"Capillary Electrophoresis in Ion Analysis: Principles and Applications"

"Sample Preparation: Advanced Procedures for Various Samples"

"Analysis of Selected Environmental and Biological Samples by Capillary Electrophoresis"

"Speciation Analysis by Capillary Electrophoresis: Pros and Cons"

"Hyphenated Separation Techniques: CE versus HPLC"

"Application of Capillary Electrophoresis for Preclinical Development of Anticancer Metal-Based Drugs – What Benefits of Collaboration between Bioinorganic and Analytical Chemists Are"

Lecture for staff-members (and all interested persons, not only chemists): "Some Considerations on Writing Better Scientific Papers"

Description

The main objective of this presentation (about 40 min.) is to encourage the audience to widely publish the results of its research in highly cited journals. Based on author's experience on writing and reviewing scientific papers, it is demonstrated why one needs to improve her/her scientific English and in which way is better to attain this goal. Using specific examples it is detailed how every part of a scientific paper, from the title to references, could be properly designed. In conclusion, the author invites the colleagues having a similar know-how, to share it with the listeners. This presentation is an update of a similar talk given by the author at Warsaw University of Technology in 2004.

Consulting of PhD/MSc research programs in the field of modern separation science

Scientific activity of prof. Andrei R. Timerbaev during his visit in The Warsaw University of Technology, Faculty of Chemistry, Chair of Analytical Chemistry, 10 October – 25 November 2009

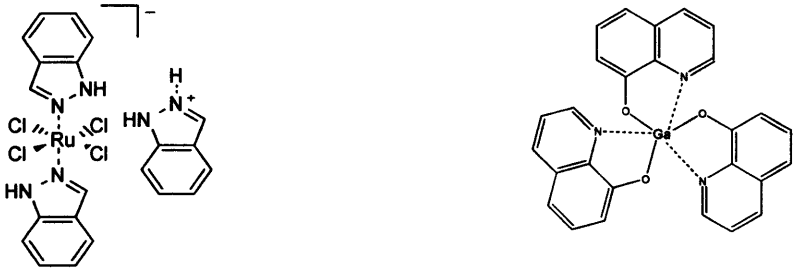
"Application of capillary electrophoresis – mass spectrometry hyphenated technique to in vitro investigation of metabolic transformation of anticancer metallodrugs"

Introduction

Despite the recognized therapeutic success of platinum antitumor agents, harnessing their potency while avoiding unwanted side effects and broadening the array of cancers, for which they can be used, remain important goals. This gives a particular impetus to discovery and development of the complexes of metals other than platinum. In order to provide the cancer researchers an important basis and new insights for developing improved therapeutic strategies and/or the rational design of new metal-based compounds, an understanding of drug's metabolism accompanying transport into the cancer cell and cellular processing appears highly desirable. For that reason, characterization of in vitro interactions between tumor-inhibiting compounds and serum transport proteins and pertinent cytoplasm components (in terms of kinetic rate constants, the dominating reaction pathways and resultant metal-ligand species, etc.) is the major research objective of the proposed project. It will encompass two leading developmental ruthenium(III)- and gallium(III)-based drugs (KP1019 and KP46, respectively; see below; both in advanced clinical trials), the most abundant serum proteins, albumin and transferrin, several cytoplasm compounds with reductive and complexing abilities, at their therapeutic or physiological concentrations and under the complex environment of the real system, as well as real blood serum. To acquire the above information, being relevant to the metabolism of metallodrugs, capillary electrophoresis (CE) coupled to inductively coupled plasma mass spectrometry (ICP-MS) detection technique will be employed as a principal analytical tool.

Background

Since 2003 the CE-ICP-MS technique has been in systematic use at Warsaw University of Technology, in collaboration with the applicant representing two research teams at Vernadsky Institute of Geochemistry and Analytical Chemistry and University of Vienna. The focus of this work is put on in-depth characterization of interaction of established and investigational anticancer metal drugs with serum transport proteins, which are accountable for drug delivery as well as bioavailability, pharmacokinetic profiles, and antiproliferative activity. It was demonstrated that the method provides an insight into the drug reactivity in protein-binding processes and its relative affinity toward different proteins. Particularly important outcome encompasses a knowledge on the equilibrium distribution of platinum species, induced by interaction of cisplatin with human serum albumin [1] and on the evolution of protein-drug reaction until the entire ruthenium(III)-based drug became consumed and unevenly distributed between different protein fractions [2]. Such metal-specific binding profiles present a valid basis for calculating the respective equilibrium and rate constants. In its turn, this information would enable a more faithful interpretation of metabolic transformations of a drug after intravenous administration. Also feasible by means of CE-ICP-MS assaying is comparative estimation of the efficiency of metallodrug transport and the speed of the deactivation via interaction with proteins for structurally similar drugs [3]. It is worthwhile of noting here that in a similar manner interaction of metal-based drugs with intracellular biomolecules can in all likelihood be examined. Perhaps the most essential in this context appears a recent kinetic study [4] in which CE-ICP-MS was applied to determine the speciation changes of the ruthenium-protein adducts under the action of physiological concentrations of ascorbic acid. The results of this investigation would help in developing the CE methodology for in vitro screening of biotransformations of metallodrugs, possibly accompanying the intracellular activation and interaction with drugable cell targets.



KP1019 **KP46**

Structural formulas of anticancer metal complexes under investigation

Project Research Goals

While it is well ascertained that binding to serum proteins plays a crucial role in metallodrug's metabolism on the way to delivery to the cancer cell, such interactions are to a different extent investigated for the two anticancer agents of interest. As mentioned above, for KP1019 the reactivity in protein-binding processes and drug's relative affinity toward different proteins have well been characterized in the host laboratory using the CE-ICP-MS technique. On the contrary, for KP46, there are only preliminary data [5], also collected by CE-ICP-MS, showing that the drug does interact with serum albumin and transferrin under simulated physiological conditions.

Taking the stated above into account, the main research trails will be toward:

(1) studying the stability of KP46 (as an orally administered drug) in simulated intestine juice;

(2) examination of the reactivity of KP46 with respect to individual proteins albumin and transferrin, their mixture at the physiological concentration ratio, and blood serum;

(3) identification of KP46-protein adducts based the synergetic use of ICP-MS and ESI-MS detection modes;

(4) studying the reversibility of protein-metallodrug binding in an acidic medium typical for tumor tissue;

(5) assessment of the metabolic alterations for KP1019-protein adducts under action of cellular reducing and complexing agents.

In order to execute these research issues, the existing CE-ICP-MS hyphenated methodology will be adopted to analyze the whole domain of interactions of antitumor metal complexes with extracellular and intracellular bioligands. As an element-specific detection method, ICP-MS will allow functional distinguishing of the metal-bioligand species at their clinical or natural concentrations in chemical environments, modeling in vivo conditions. On the other hand, ESI-MS will be complementary employed for structural identification of metabolite forms.

Note:

items (1-3) are the subject of on-going joint research (in frames of agreements on direct cooperation between Warsaw University of Technology, Vernadsky Institute of Geochemistry and Analytical Chemistry and University of Vienna) to be completed during the applicant stay at the host laboratory;

items (4, 5) present a further progress of this collaboration.

Summary of Expected Results

The advanced CE-ICP-MS methodology, to be developed in this project for in vitro monitoring of interactions that metal-based drugs would experience exterior and inside the cancer cell, is expected to greatly contribute to the area of anticancer drug research. The promising tumor-inhibiting drug candidates with ruthenium and gallium active centers will be characterized from the viewpoint of most plausible biotransformations mediating drug's uptake and activation in the cell. The respective metabolite species will be identified, taking an advantage of high-resolution potential of CE and functional/structural discrimination ability of ICP-MS and ESI-MS. The results of such cutting-edge research will, on one hand, bring the lead anticancer agents closer to finalizing clinical trials and, on the other hand, provide a new insight into the mechanism of intracellular action at the molecular level. These are the means how the project will impact on the fields of medicinal, bioinorganic, and analytical chemistry. It is also anticipated that the hyphenated CE-MS technique applied to accomplish the project aims will take a comprehensive role in further progress of metallodrug discovery and development. This will with no doubt emphasize the status of the host laboratory as a leading research center involved in R&D on biospeciation analysis.

[1] A.R. Timerbaev, S.S. Aleksenko, K. Polec-Pawlak, R. Ruzik, O. Semenova, C.G. Hartinger, S. Oszwaldowski, M. Galanski, M. Jarosz, B.K. Keppler, Electrophoresis 25 (2004) 1988-1995.

[2] K. Połeć -Pawlak, J.K. Abramski, O. Semenova, C.G. Hartinger, A.R. Timerbaev, B.K. Keppler, M. Jarosz, Electrophoresis 27 (2006) 1128-1135.

[3] K. Połeć-Pawlak, J.K. Abramski, J. Ferenc, L.S. Foteeva, A.R. Timerbaev, B.K. Keppler, M. Jarosz, J. Chromatogr. A 1192 (2008) 323-326.

[4] A.R. Timerbaev, L.S. Foteeva, A.V. Rudnev, J.K. Abramski, K. Połeć-Pawlak, C.G. Hartinger, M. Jarosz, B.K. Keppler, Electrophoresis 28 (2007) 2235-2240.

[5] J.K. Abramski, L.S. Foteeva, K. Pawlak, A.R. Timerbaev, B.K. Keppler, M. Jarosz, Proc. 19th Int. Symp. Pharm. Biomed. Anal., 8-12 June 2008, Gdansk, Poland, 317.