Consorzio Interuniversitario di Ricerca in Chimica dei Metalli nei Sistemi Biologici

XVII WORKSHOP ON PHARMACOBIOMETALLICS

BOOK OF ABSTRACTS

Biomet2018- Book of abstract
Edizione digitale a cura di:
Editor: Diego Tesauro, Dipartimento di Farmacia, Università di Napoli “Federico II”
Art & Design: Luca De Luca, CNR - Istituto di Biostrutture e Bioimmgini, Napoli
Permalink: www.biometworkshop.it/Documenti/2018.pdf

BIOMET 2018

XVII Workshop on Pharmacobiometallics

Napoli 16 – 17 febbraio 2018

Aula Magna Centro di Servizio di Ateneo per le Scienze e Tecnologie della Vita
Università degli studi di Napoli Federico II

Con il patrocinio:

Dipartimento di Farmacia, Università di Napoli “Federico II”
Centro Interuniversitario di Ricerca sui Peptidi Bioattivi
CNR - Istituto di Biostrutture e Bioimmgini
CNR - Istituto di Cristallografia
CESTEV - Centro di Servizio di Ateneo per le Scienze e Tecnologie della Vita
Società Chimica Italiana, Divisione di Chimica Inorganica

Comitato Organizzatore

Diego Tesauro
Giancarlo Morelli
Michele Saviano
Antonella Accardo
Luca De Luca
Alfonso Esposito

Comitato Scientifico

Dott. **Nunzio Denora**	Dipartimento di Chimica, Università degli Studi di Bari "Aldo Moro"
Prof. **Giuseppe Falini**	Dipartimento di Chimica "Ciamician", Università di Bologna
Prof. **Alfredo Burini**	Scuola di Scienze e Tecnologie, Università di Camerino
Prof.ssa **Graziella Vecchio**	Dipartimento di Scienze Chimiche, Università di Catania
Prof. **Lorenza Marvelli**	Dipartimento di Chimica, Università di Ferrara
Prof. **Luigi Messori**	Dipartimento di Chimica Ugo Schiff, Università degli Studi di Firenze
Prof. **Stefano Banfi**	Dipartimento di Scienza e Alta tecnologia, Università dell'Insubria
Prof. **Luigi Monsù Scolaro**	Dipartimento di Scienze Chimiche, Università degli Studi di Messina
Dr. **Diego Tesauro**	Dipartimento di Farmacia, Università degli Studi di Napoli "Federico II"
Prof. **Lisa Dalla Via**	Dipartimento di Biotecnologie, Chimica e Farmacia, Università degli Studi di Padova
Dr **Claudia Pellerito**	Dipartimento di Fisica e Chimica, Università degli Studi di Palermo
Prof. **Giorgio Pelosi**	Dipartimento di Chimica, Università degli Studi di Parma
Prof. **Piersandro Pallavicini**	Dipartimento di Chimica Generale, Università degli Studi di Pavia
Prof. **Mauro Ravera**	Dipartimento di Scienze e Innovazione Tecnologica, Università del Piemonte Orientale
Prof. **Diego La Mendola**	Dipartimento di Farmacia, Università di Pisa
Dr **Elisabetta Giorgini**	Dipartimento di Scienze della vita e dell'Ambiente, Università Politecnica delle Marche
Prof. **Maria Pia Donzello**	Dipartimento di Chimica, Università "la Sapienza"
Prof. **Massimiliano Coletta**	Dipartimento di Medicina Sperimentale e Scienze Biomediche, Università Tor Vergata
Prof. **Francesco Paolo Fanizzi**	Dipartimento di Scienze e Tecnologie Biologiche e Ambientali, Università del Salento
Prof. **Daniela Valensin**	Dipartimento di Biotecnologie, Chimica e Farmacia, Università di Siena
Prof. **Walter Dastrù**	Dipartimento di Biotecnologie Molecolari e Scienze della Salute, Università degli Studi di Torino
Prof. **Ennio Zangrando**	Dipartimento di Scienze Chimiche, Università degli Studi di Trieste

Venerdi, 16 Febbraio 2018

12.00 Registrazione dei Partecipanti

14.00 Saluti inaugurali

14.15 Plenary Lecture. Chairman prof. Francesco Paolo Fanizzi
L. Ambrosio CNR – Istituto per i polimeri compositi e biomateriali, Napoli
Biocomposites as Driving Model for Future Therapy

Sessione I: Nanostrutture di interesse biomedico e ambientale

Chairman: prof. Giuseppe Falini

15.00 OC1 **G. Dacarro** Università di Pavia Unità di Pavia
Self-Assembled Monolayers of Prussian Blue Nanoparticles with Photothermal Effect.

15.20 OC2 **V. Caruso** Università di Catania Unità di Catania
Dipeptide nanocontainers- graphene oxide- copper ions multifunctional assembles for drug-delivery applications.

15.40 OC3 **L. Cucci** Università di Catania Unità di Catania
Gold nanoparticles functionalized with angiogenin peptides modulate different interaction with cell membranes in the presence of copper ions.

16.00 OC4 **M. Pisani** Università Politecnica delle Marche Unità di Ancona
Characterization of lyotropic liquid systems loaded with Gold(I) phosphane compounds for anticancer drug delivery.

16.20 Coffee Break

Sessione II: Metalli e metallo-proteine nella System biology

Chairman Massimiliano Coletta

16.40 OC5 **R. De Zorzi** Università di Trieste Unità di Trieste
New clues on binding mode of EMILIN-1 to alpha4beta1 Integrin from a gC1q domain mutant structure.

17.00 OC6 **D. Sbardella** Università di Roma Torvergata Unità di Roma Tor Vergata
The Insulin-Degrading enzyme is an allosteric modulator of the 20S proteasome and a potential competitor of the 19S.

17.20 OC7 **M.I. Nardella** Università di Bari Unità di Bari
In-cell effects of silver ions and nanoparticles on copper transport proteins.

Sessione III: Metalli nell'ambiente

Chairman Massimiliano Coletta

17.40 OC8 **J. Bartoli** Università di Parma Unità di Parma
Thiosemicarbazones and their copper complexes: evaluation of antifungal and anti-aflatoxigenic activity.

18.00 Consiglio Scientifico C.I.R.C.M.S.B.

18.30 Consiglio Direttivo C.I.R.C.M.S.B.

SABATO, 17 Febbraio 2018

Sessione IV: Farmaci a base metallica

Chairman prof. Giovanni Natile

9.00 OC9 **M. Hyeraci** Università di Padova Unità di Padova
Biological properties of (triphenylphosphine)platinum(II) complexes containing bidentate arylaldoxime ligands.

9.20 OC10 **I. Rimoldi** Università di Milano
Cationic platinum(II) complexes active in vivo as anticancer drugs.

9.40 OC11 **D. Osella** Università Piemonte Orientale Unità Piemonte Orientale
Multifunctional Pt(IV) anticancer prodrugs: the story so far.

10.00 OC12 **G. Canil** Università di Pisa Unità di Pisa
Photoactive Platinum Compounds

10.20 OC13 **D. Marasco** Università di Napoli"Federico II" Unità di Napoli
A comparative analysis of biophysical interactions of cisplatin analogues with Lysozyme.

10.40 OC14 **L. Biancalana** Università di Pisa Unità di Pisa
Ruthenium(II) arene complexes with α-diimine ligands: synthesis, characterization and cytotoxicity.

11.00 Coffee Break

Sessione V: Ruolo dei metalli nelle patologie degenerative croniche

Chaiman prof. Enrico Rizzarelli

11.20 OC15 **F. Bellia** Istituto di Biostrutture e Bioimmagini Unità di Catania
Structural and functional insights into the Aβ-Ubiquitin interaction.

11.40 OC16 **D. La Mendola** Università di Pisa Unità di Pisa
Copper (II) interaction with the N-terminal repeat of opossum prion protein: a glance to prion evolution.

12.00 OC17 **M. Coletta** Università di Roma Torvergata Unità di Roma Tor Vergata
Modulation of proteasome activity by porphyrins.

12.20 OC18 **I. Naletova** Università di Catania Unità di Catania
Metal signaling and BDNF expression

12.40 OC19 **L. Pirone** Istituto di Biostrutture e Bioimmagini Unità di Napoli
Recombinant expression, purification and preliminary characterization of the anserinase from Oreochromis niloticus.

13.00 Pranzo

14.00 Sessione poster

Sessione VI: Farmaci a base metallica

Chaiman prof. Domenico Osella

15.00 OC20 **D. Musumeci** Università di Napoli"Federico II"
Synthesis, characterization and biological activity evaluation of various Pt(II) complexes.

15.20 OC21 **T. Marzo** Università di Pisa Unità di Pisa
Strategies for the development of innovative chemotherapy treatment in colorectal cancer. An overview of our recent results.

15.40 OC22 **F. Guarra** Università di Pisa Unità di Pisa
Novel cytotoxic metal-NHC carbenes induce distortions of calf thymus DNA and TrxR inhibition.

Sessione VII: Biomineralizzazione e biocristallografia

Chaiman prof. Domenico Osella

16.00 OC23 **G. Falini** Università di Bologna Unità di Bologna
Functional matrices from mussel byssus waste.

16.20 Coffee Break

Sessione VIII: Farmaci a base metallica

Chairman dr. Diego Tesauro

16.40 OC24 **L. Massai** Università di Firenze Unità di Firenze
Chemistry, molecular mechanisms and preclinical studies of Gold complexes for ovarian cancer treatment.

17.00 OC25 **F. De Castro** Università di Lecce Unità di Lecce
^{1}H-NMR metabolomic study of SKOV-3 cells, response to the [Pt(O,O'-acac)(γ-acac)(DMS)] treatment.

17.20 OC26 **N. Margiotta** Università di Bari Unità di Bari
Kiteplatin-pyrophosphate derivatives targeted to bone tumors and metastases.

17.40 OC27 **V.Oliveri** Università di Catania Unità di Catania
Porphyrin-Cyclodextrin conjugates inhibit Aβ aggregation and amyloid induced cytotoxicity.

18.00 OC28 **D. Cirri** Università di Firenze Unità di Firenze
Synthesis, characterization and DNA interactions of trinuclear Platinum(II) complex of the TPymT ligand.

21.00 Cena sociale

Indice dei contenuti

Biocomposites as driving model for future therapy

PL

L. Ambrosio, R. De Santis, A. Gloria, M.G. Raucci

Institute of Polymers, Composites and Biomaterials, National Research Council, Viale J.F. Kennedy, 54, Mostra d'Oltremare, Pad.20, 80125 Naples, Italy.

Modern medicine is based on the implementation of a personalised approach together a less invasive surgery for the restoration of human tissues and organs lost to diseases and trauma, this is forced also by the health care system as the related costs are increasing due to the aging population, for the decrease of birth rate and increase of the life expectancy.
Great advances have been made in the composite materials and technologies to design complex structures. Micro or nano-structured materials in the form of nanoparticles, nano-fibers and nano-composites have gained increasing interest in regenerative medicine because they are able to mimic the physical features of natural extracellular matrix (ECM) at the sub-micro and nano-scale level.
More advanced techniques are now available which can clearly produce macromolecular structures of nanometres size with a finely controlled atomic composition and architecture.. Nanocomposites are continuously under intense investigation in regenerative medicine to change the physical or chemical properties of biomaterials and guide the activation of specific cellular signalling. This is an unique approach for designing a multi-scale, multi-functional and cells-instructive materials.
Design of different nanostructures made by rapid prototyping, sol-gel and biomineralization processes, are discussed to develop active platforms to support the regeneration of human tissue. To this aim a 3D rapid prototyped magnetic scaffold made by poly(ε-caprolactone)/iron-doped hydroxyapatite (PCL/FeHA) 80/20 w/w is proposed to provide a morphologically controlled and tailored structure with interconnected pores of specific scale, and the possibility to magnetically "switch-on/switch-off" to stimulate cell adhesion, proliferation and differentiation. The in vitro results demonstrated that the Bone Marrow Stem Cells growth in the magnetized scaffold was 2,2 fold greater than the no-magnetized ones. In vivo results, showed that the PCL/FeHA scaffold was completely filled by new formed bone only after 4 weeks. Functional hybrid materials for tissue engineering are prepared by sol-gel synthesis which appears to be among the most suitable route towards performing injectable calcium phosphate based cements. Following this approach, multifunctional hybrid biomaterials are proposed combining Strontium - modified CaP gels and Hydroxyapatite [$(Ca_{10}(PO_4)_6(OH)_2$, HA] with graphene oxide (GO) gel materials by a dual approach as sol-gel technology and biomimetic method. Biological studies performed by using hMSC demonstrated that both hybrid materials induces an osteogenic differentiation.

References

1. R De Santis, A Russo, A Gloria, U D'Amora, T Russo, S Panseri, M Sandri, Anna Tampieri, Maurilio Marcacci, Valentin A Dediu, Colin J Wilde, Luigi Ambrosio, "Towards the Design of 3D Fiber-Deposited Poly(-caprolactone)/Iron-Doped Hydroxyapatite Nanocomposite Magnetic Scaffolds for Bone Regeneration". Journal of Biomedical Nanotechnology 11 (7), 1236-1246. 2015.
2. M. G. Raucci, D. Giugliano, A. Longo, S. Zeppetelli, G. Carotenuto and L. Ambrosio. "Comparative facile methods to preparing Graphene oxide/Hydroxyapatite for bone tissue engineering". Journal of Tissue Engineering and Regenerative Medicine (2016), DOI:10.1002/term.2119.

Self-assembled monolayers of prussian blue nanoparticles with photothermal effect

OC1

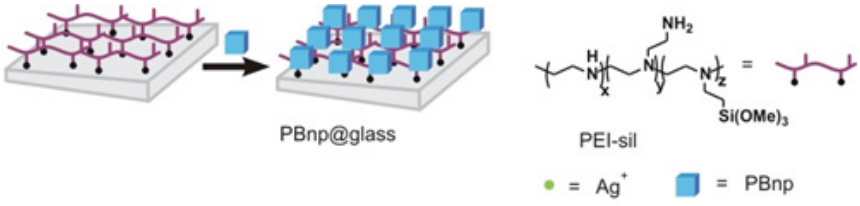
G. Dacarro[1], L. Doveri[1], A. Taglietti[1], C. Milanese[1], P. Grisoli[2], P. Pallavicini[1]

1. Dipartimento di Chimica, Università degli Studi di Pavia, Viale Taramelli 12, 27100 Pavia
2. Dipartimento di Scienze del Farmaco, Università degli Studi di Pavia, Viale Taramelli 12, 27100 Pavia

Prussian blue (PB) is the first synthetic modern pigment and its structure and properties have been extensively studied since the 18th century. PB can be synthesised in colloidal form (prussian blue nanoparticles, PBnp) by mixing Fe^{3+} and $[Fe^{II}(CN_6)]^{4-}$ aqueous solutions. PBnp have already been approved as drugs by the FDA (USA Food and Drug Administration). In addition to this, PB displays an intense absorption band with λ_{max} centred at ~700 nm and extending in the NIR, entering the so-called biotransparent window (750-950 nm) where water, blood and tissues poorly absorb electromagnetic radiation. The irradiation of this band results in thermal relaxation. Accordingly, PBnp have already been studied as NIR photothermal ablation agents for tumour therapy, with a photothermal effect comparable to that of metal nanoparticles.[1,2]

A photo-responsive antibacterial surface was prepared grafting non-toxic Prussian blue nanoparticles on a functionalized glass surface. Colloidal Prussian blue was synthesized as nanoparticles with cubic shape and grafted on a polyamine-functionalized SiO_2 surface, obtaining a good coverage and a homogeneous distribution of the nanocubes. Irradiation of these samples in the so-called "bio-transparent window" of the near-infrared (NIR) allows to exert a switchable antibacterial effect. We tested the photothermal effect due to anchored PBnp on glass slides, by laser-irradiating in the NIR. The local T increase was exploited to exert a switchable antibacterial effect against Gram positive and Gram negative planktonic strains *Escherichia coli* and *Staphylococcus aureus*.[3]

In order to add also an intrinsic antibacterial effect, we synthesized "doped" PBnp containing Cu(II) ions. Cu(II) is a well-known antibacterila agent and can add a microbicidal effect also in absence of the laser-induced hyperthermia. An alternative to a doped material is the preparation of a mixed monolayer, combining the photothermally active PBnp with intrinsic antibacterial agents, *e.g.* Ag+ ions loaded on the polyaminic monolayer. This was the second route exploited to prepare an antibacterial material with a combined intrinsic and switchable effect.



References

1. Dacarro, G., Taglietti, A., Pallavicini P., ***Molecules***, **2018**, manuscript in preparation
2. Fu, G., Liu, W., Feng, S., Yue, X., ***Chem. Commun.***, **2012**, 48, 11567–11569
3. Dacarro, G., Grisoli, P., Borzenkov, M., Milanese, C., Fratini, E., Ferraro, G., Taglietti, A., Pallavicini, P. ***Supramolecular Chemistry***, **2017**, 29(11), 823-833

OC2

Dipeptide nanocontainers - graphene oxide – copper ions multifunctional assembles for drug-delivery applications

V.C.L. Caruso[1], G. Trapani[1,2], L.M. Cucci[1], D. La Mendola[3], C. Satriano[1]

1. Department of Chemical Sciences, University of Catania, Viale A. Doria 6, 95125, Catania, ITALY
2. Scuola Superiore di Catania, via Valdisavoia, 9, 95123 Catania, ITALY
3. Department of Pharmacy, University of Pisa, Via Bonanno Pisano 6, 56126, Pisa, ITALY

Homo-aromatic dipeptides are able to self-assemble into ordered structures such as nanotubes and nanowires, with intriguing potentialities as nanocontainers/carriers for drug delivery applications [1]. Graphene oxide (GO), an ideal 2-Dimensional nanomaterial, due to its high surface-to-volume ratio and the richness of oxygen-containing moieties (including carboxyl, hydroxyls and epoxide groups) represents an ideal nanoplatform for surface functionalisation to obtain, for example, stimuli-responsive systems [2].

In this work, we investigated the interaction of Phe-Phe (FF) and Tyr-Tyr (YY) dipeptides with GO nanosheets, to fabricate a hybrid peptide-GO assemblies. These systems were also prepared in the presence of copper (II) ions, to scrutinise the effect of the metal ion on the peptide aggregation processes as well as to exploit the anti-cancer activity of the multifaceted metal-peptide-GO assemblies.

The systems were scrutinised with several spectroscopic (UV-visible, fluorescence, EPR, circular dichroism) and microscopic (atomic force microscopy and confocal microscopy) techniques.

Quartz crystal microbalance with dissipation monitoring (QCM-D) was used for real-time acoustic sensing of the interaction with supported lipid bilayers, used as model cell membranes (Fig.1). Promising results of cellular uptake in neuroblastoma cells were investigated by confocal microscopy, and the cellular copper homeostasis was mapped dynamically by the use of metal probes and intracellular organelle staining.

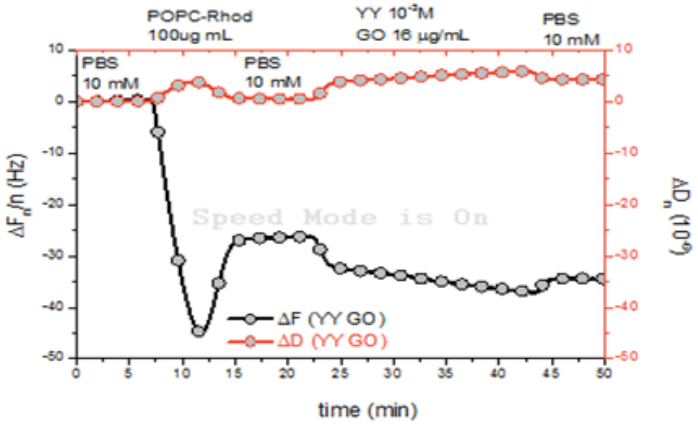


Fig.1- Representative QCM-D shift curves of frequency (black) and dissipation (red) upon the interaction of YY-GO with SLBs.

References

1. Reches, M., & Gazit, E., 2003. Science, 300, 625.
2. Consiglio, G. et al., 2017, J Coll Interface Sci, 506, 532.

Gold nanoparticles functionalized with angiogenin peptides modulate different interaction with cell membranes in the presence of copper ions

OC3

L. M. Cucci[1], A. Munzone[2], I. Naletova[1], A. Magrì[3], C. Satriano[1], D. La Mendola[4]

1. University of Catania, Department of Chemical Sciences, Viale A. Doria 6, 95125, Catania, ITALY.
2. Aix Marseille Université Faculté des Sciences de Saint Jérôme 52, Avenue Escadrille Normandie-Niemen 13397, Marseille, FRANCE.
3. Institute of Biostructures and Bioimages, CNR-Catania, Via P. Gaifami 18, 95126 Catania, ITALY.
4. University of Pisa, Department of Pharmacy, Via Bonanno Pisano 6, 56126, Pisa, ITALY

Angiogenin (ANG) is a potent inducer of blood-vessel formation [1], it is overexpressed in different type of cancer diseases and downregulated in neurodegenerative disorders [2]. Many cancer types exhibit altered systemic copper distribution and copper ions regulate ANG activity [3]. In this work, plasmonic gold nanoparticles (AuNPs) were functionalized with angiogenin-mimicking peptides and their interaction with artificial membranes of supported lipid bilayers (SLBs) and cellular membranes of cancer (neuroblastoma) and normal (fibroblasts) cell lines was investigated in the presence or absence of copper ions. The used peptides contained the ANG (60-68) sequence, i.e., the putative cellular binding site of the protein [3]. The three following fragments were employed: Ang(60-68), Ang(60-68)Cys (the cysteine derivative for the covalent binding to the metal surface), and Fam-Ang(60-68) (fluorescein-labelled, to exploit also the steric and charge effects). The AuNP-peptide systems were characterized by UV-visible and CD spectroscopies (for the plasmonic shifts and the peptide conformational changes) and AFM (morphology and the nanoparticle coverage). The FRAP technique by confocal microscopy, employed to measure the lateral diffusion coefficients of the model cell membranes, pointed to a stronger membrane interaction of the peptide-functionalized nanoparticles in comparison with the uncoated ones. The cytoskeleton features, observed by confocal microscopy imaging of actin staining, pointed out different levels of interaction between the different AuNP-Ang peptides and the cell membranes (Fig.1). Cell viability and proliferation assays indicated a slight nanotoxicity in neuroblastoma cells and a proliferative activity in fibroblasts.

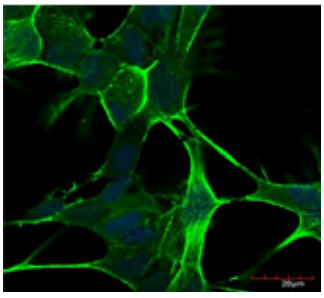


Fig. 1 – Cytoskeleton staining for cells treated with AuNP-Ang(60-68).

References

1. Shapiro, R. et al., (1987). Biochemistry, 26(16), 5141-5146.
2. Chung, S. et al., (2015). PloS one, 10(8), e0134948.
3. Giacomelli, C. et al., (2015). The international journal of biochemistry & cell biology, 60, 185-196.
4. Satriano, C. et al., (2016). Microchemical Journal, 136, 157.

OC4

Characterization of lyotropic liquid systems loaded with Gold(I) phosphane compounds for anticancer drug delivery

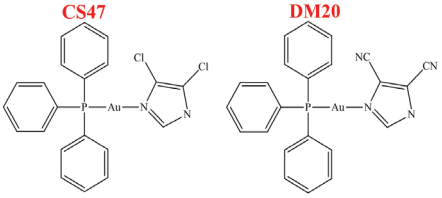
M. Pisani[1], P. Astolfi[1], E. Giorgini[2], B. Rossi[3], F. D'Amico[3], R. Galassi[4]

1. Dipartimento SIMAU, Università Politecnica delle Marche, Via Brecce Bianche, Ancona, I-60131.
2. Dipartimeto DiSVA, Università Politecnica delle Marche, Via Brecce Bianche, Ancona, I-60131.
3. Elettra - Sincrotrone Trieste S.C.p.A., S.S. 14 - km 163.5, Basovizza, Trieste, I-34149.
4. Scuola di Scienze e Tecnologie, Divisione Chimica, Università di Camerino, Via Sant'Agostino, I-62032.

A continuous research effort for the production of efficient nanocarriers for drug delivery in anticancer therapy is in progress in order to develop formulations with higher degree of specificity and reduced adverse effects. In particular, liquid crystalline phases such as cubosomes and hexosomes represent interesting drug delivery matrixes.[1,2] The properties of the hexosomes and cubosomes, such as size, structure, and stability, can be tuned by their internal composition, polymer concentration, and processing conditions. Moreover, the stiffness of these phases could lead to a slower diffusion of the solubilized cargo and hence to a long-term release.

Within this frame, we are currently developing bio-systems based on hexagonal and cubic phases dispersed in a continuous aqueous medium, which could find potential application as anticancer drug delivery vectors. In particular, phytantriol cubic phases have been used to encapsulate both commercial (5-fluororuracil)[3] and non commercial chemotherapy drugs such as Gold(I) phosphane complexes. These latter compounds have shown to possess anti-neoplastic effects on many cancer cell panels[4] and unique *in vitro* ability to induce a dose-dependent inhibition of cell proliferation in both BLBC murine A17 and human MDA-MB-231 cells.

Therefore, ((triphenylphosphine)-gold(I)-(4,5-dichloroimidazolyl-1H-1yl)) (**CS 47**) and ((triphenylphosphine)-gold(I)-(4,5-dicyanoimidazolyl-1H-1yl)) (**DM20**) have been encapsulated in different lipid matrix such as phytantriol, DOPE and monoolein. An integrated experimental approach involving X-ray diffraction, ATR-FTIR and UV Resonant Raman spectroscopies has been employed to establish the effects of drug encapsulation on the structure and phase behavior of the mesophases. In particular, SAXS diffraction experiments have been carried out to investigate the lipid nanostructure and the possible geometrical and topological modifications induced by encapsulation of gold complexes. Additional information at molecular level on the interaction between such complexes and lipid matrix has been obtained by means of ATR-FTIR and UV-Resonant Raman spectroscopy. This study represents an important turning point in Gold(I) bioinorganics. In fact, the encapsulation should prevent the exchange reactions usually occurring with the cysteine groups of serum albumin, leading to a systemic toxicity with homeostatic effects.[5]



References

1. Angelova, A.; Angelov, B.; Mutafchieva, R.; Lesieur, S.; Couvreur, P. Self-Assembled Multiconmpartment Liquid Crystalline Lipid Carriers for Protein, Peptide, and Nucleic Acid Drug Delivery. ***Acc. Chem. Res.*** **2011**, ***44 (2)***, 147-156.
2. Conn, C. E.; Drummond, C. J. Nanostructured bicontinuos cubic lipid self-assembly materials as matrices for protein encapsulation. ***Soft Matter*** **2013**, ***9***, 3449-3464.
3. Astolfi, P.; Giorgini, E., Gambini, V., Rossi, B., Vaccari, L., Vita, F., Francescangeli, O., Marchini, C., Pisani, M. Lyotropic Liquid-Crystalline Nanosystems as Drug Delivery Agents for 5-Fluorouracil: Structure and Cytotoxicity. ***Langmuir*** **2017*, 33,***12369-12378.
4. Galassi R. et al. ***Dalton Transactions***, **2012**, 41, 5307-5318.
5. Bhabak K. B. et al., ***Dalton Trans.***, **2011**, 40, 2099-2111.

New clues on binding mode of EMILIN-1 to α4β1 Integrin from a gC1q domain mutant structure

OC5

R. De Zorzi[1], L. Destefanis[1], R. Doliana[2], A. Colombatti[2], S. Geremia[1]

1. Department of Chemical and Pharmaceutical Sciences, University of Trieste, via L. Giorgieri 1 – 34127 Trieste, Italy
2. Experimental Oncology Department, Centro di Riferimento Oncologico di Aviano National Cancer Institute, Aviano, Pordenone, Italy

Integrins are membrane bound proteins responsible for cell adhesion to the extracellular matrix and for inside-out and outside-in communications between the extracellular matrix and numerous processes inside the cell, e.g. regulation of the cell cycle, location of membrane proteins, architecture of the cytoskeleton. EMILIN proteins, homotrimeric glycoproteins mainly expressed as part of the extracellular matrix, play an important role as partners of integrins in adhesion processes [1].
Integrin-EMILIN binding involves the C-terminal domain of EMILIN proteins, a gC1q domain that presents only 9 of the 10 β-strands of homologous proteins [1]. Besides being the domain responsible for oligomerization of the EMILIN monomers, the gC1q domain presents a large flexible loop whose function is to bind Integrin.
Binding mode of EMILIN proteins to integrins has been analyzed *in silico* [2] and through NMR experiments [3-4], but the binding mechanism is still a matter of debate. Here, we present the structural determination by X-ray crystallography of a mutated form of the gC1q domain of EMILIN-1. While the overall structure shows significantly different features compared to the NMR structure [4], the presence of a larger monomer-monomer interface in the crystallographic model accounts for the high stability of the trimer observed in electrophoresis experiments. Although the mutation involves part of the flexible loop located in the binding site and thought to be responsible for Integrin recognition, analysis of the folding and primary sequence alignment seems to relate EMILIN-1 gC1q domain to a specific family of C1q-like proteins for which binding is mediated by Ca^{2+} ions [5]. In addition, X-ray structure of the trimeric assembly indicates a partial loss of the C3 symmetry. This asymmetry could be important for a productive binding conformation of EMILIN.

References

1. Colombatti A. ***et al.*** The EMILIN/Multimerin family. ***Front. Immunol.*** **2**, 93. (2012)
2. Capuano A. ***et al.*** The α4β1/EMILIN1 interaction discloses a novel and unique integrin-ligand type of engagement. Matrix Biol. doi: 10.1016/j.matbio.2017.10.001. (2007)
3. Verdone G. ***et al.*** The solution structure of EMILIN1 globular C1q domain reveals a disordered insertion necessary for interaction with the α4b1 integrin. ***J. Biol. Chem.*** **283(27),** 18947-56. (2008)
4. Verdone G. ***et al.*** NMR-based homology model for the solution structure of the C-terminal globular domain of EMILIN1. ***J. Biomol. NMR.*** **43(2)**, 79-96. (2009)
5. Ressl S. ***et al.*** Structures of C1q-like proteins reveal unique features among the C1q/TNF superfamily. Structure. **23(4)**, 688-99. (2015)

OC6

The Insulin-Degrading Enzyme is an allosteric modulator of the 20S proteasome and a potential competitor of the 19S

D. Sbardella[1,2,3], G. R. Tundo[1,2], A. Coletta[4], J. Marcoux[5], E.I.Koufogeorgou[5], C. Ciaccio[1,2], A. M. Santoro[6], D. Milardi[6], G. Grasso[7], P. Cozza[1,3], M-P. Bousquet-Dubouch[5], S. Marini[1,2,3], M. Coletta[1,2,3]

1. Department of Clinical Sciences and Translational Medicine, University of Roma Tor Vergata, Roma, ITALY
2. Interuniversitary Center for the Research on the Chemistry of Metals in Biological Systems, Bari, ITALY
3. Interdepartmental Center for TeleInfrastructures, University of Roma Tor Vergata, Roma, ITALY
4. Department of Chemistry, Aarhus University, Aarhus, DENMARK
5. Institut de Pharmacologie et de Biologie Structurale, Université de Toulouse, CNRS, UPS, FRANCE
6. Institute of Biostructures and Bioimaging, National Research Council, Catania, ITALY
7. Department of Chemistry, University of Catania, Catania, ITALY.

Insulin-Degrading Enzyme (IDE) is a metallo-enzyme ubiquitously expressed in human tissues and with a prevalent cytosolic localization. The activity of IDE has been historically associated to the degradation of insulin as well as of other hormones or peptides which share the tendency to form amyloidogenic aggregates, thus envisaging a contribution of IDE to the regulation of proteostasis.
Proteostasis is the maintenance of the equilibrium between the synthesis and the degradation of the intracellular proteins and, under physiological condition, is handled by the intracellular proteolytic pathways and in particular, by the Ubiquitin-Proteasome System (UPS).
The central machinery of the UPS is the proteasome, a hollow barrel-shaped multi-subunit catalytic complex (i.e. the 20S) which degrades proteins tagged with a poly-ubiquitin chain. The recognition, unfolding and translocation of these substrates is mediated by non-proteolytic multi-subunits complexes (i.e. the 19S and PA28), also termed Regulatory Particles (RPs), which bind to either one or two ends of the 20S further stimulating its proteolytic activity.
Proteasome assemblies of different composition exist in the cell cytosol (i.e. the 30S, the 26S and the 20S which correspond, respectively, to a 20S capped by two or one 19S or a 20S in the uncapped form) which deal with the degradation of different subsets of substrates, i.e. the poly-ubiquitinated proteins for the capped species and the oxidized/unfolded proteins regardless of the ubiquitin chain for the 20S. Thus, the relative abundance of these assemblies is tuned on the basis of the metabolic state of the cell. For instance, under oxidative stress conditions, an increase in the pool of uncapped 20S would be favoured to contrast the accumulation of oxidized proteins.
Therefore, several modulators of proteasome activity and composition have been described. Among them, we have identified IDE as a widespread regulator.
In this study, we have first defined the interaction of IDE with the proteasome assemblies by mass spectrometry and native gel electrophoresis on cell extracts, highlighting that IDE is preferentially bound to 20S particles where a free-end (i.e. the same occupied by the RPs) is available. Furthermore, IDE was found to compete with the canonical 19S *in vitro* suggesting that IDE may regulate the proteasome population distribution.
By deepening the effect of IDE binding to the 20S, we found out that IDE stimulates the human and yeast 20S proteasome proteolytic activity in a bimodal fashion, inhibiting at [IDE] ≤ 30 nM and activating at [IDE] ≥ 30 nM. Only an activating effect is observed in a yeast mutant locked in the "open" conformation (*i.e.*, the α3ΔN 20S), envisaging a possible role of IDE as modulator of the 20S "open"-"closed" allosteric equilibrium. With respect to this, protein-protein docking *in silico* envisages that the C-term helix of the 20S α-3 subunit, which critically regulate the "open"-"closed" allosteric equilibrium, is bound by IDE.

In-cell effects of silver ions and nanoparticles on Copper transport proteins

OC7

M. I. Nardella[1], V. Mangini[2], A. Rosato[1], G. Natile[1], F. Arnesano[1]

1. Department of Chemistry, University of Bari, via E. Orabona, 4, 70125 Bari, Italy
2. Center for Biomolecular Nanotechnologies@UniLe, Istituto Italiano di Tecnologia (IIT) via Barsati 73010 Arnesano, Lecce, Italy

Despite the widespread use of silver nanoparticles (AgNPs), little is known about the potential risks arising from AgNPs themselves and from the silver ions released from them. Since Ag(I) or Cu(I) have similar coordination properties, an impact on copper metabolism is expected. Cells utilize several pathways to ensure uptake, storage and export of copper. In humans, the metallochaperone Atox1 delivers Cu(I) to the metal-binding domains (MBDs) of two P1B-type ATPases: the Menkes (Atp7a) and Wilson (Atp7b) disease proteins [1;2].

Atox1 and the first MBD of Menkes (Mnk1) bind one Cu(I) through two Cys residues located in a conserved CXXC motif [3]. Thus, the aim of this work has been to gain direct evidence by NMR of the interaction of Atox1 and Mnk1 with Ag(I) or AgNPs. Although the two proteins have similar structure, their behavior with AgNPs is substantially different.

AgNPs are characterized by a remarkable antibacterial effect, thus monitoring the interactions of AgNPs with bacterial cells can be crucial for elucidating the origin of the bactericidal activity and for expanding their biomedical and environmental applications.

We have investigated Ag metabolism in Gram-negative bacteria by in-cell NMR [4]. E. coli cells over-expressing 15N-labeled Atox1 in the cytosol were treated with Ag salts. In-cell NMR revealed that, within treated cells, Atox1 undergoes only minor changes. In contrast, after the lysis of the cells, the protein appears to be bound to the metal. From these data, it can be inferred that the scarce reactivity of Atox1 with Ag(I) inside the cell can be due to compartmentalization (e.g. in the periplasm) and/or sequestration of the metal ion.

Ag(I) elicits a rapid response in E. coli cells, since it is rapidly eliminated from the cytosol. Proteins involved in this mechanism are CueR, CopA, CusRS and CusCFBA. CueR is a transcriptional regulator controlling the expression of CopA, a transmembrane pump that allows ion translocation from cytosol to periplasm, while CusRS is a two-component signal transduction system regulating the expression of cusCFBA operon that is involved in Cu(I) and Ag(I) translocation outside the cell [5]. In order to obtain a new E.coli strain unable to express CueR, we mutated wild-type (WT) E. coli cells by using a phage infection protocol. Preliminary cell viability measurements in presence of Ag(I) indicate that the mutant strain is more sensitive to Ag(I) than WT cells.

References

1. I. H. Hung, R. L. Casareno, G. Labesse, F. S. Mathews, J. D. Gitlin, J.Biol.Chem. 1998, 273 1749-1754.
2. S. Lutsenko, K. Petrukhin, M. J. Cooper, C. T. Gilliam, J. H. Kaplan, J.Biol.Chem. 1997, 272 18939-18944.
3. F. Arnesano, L. Banci, I. Bertini, S. Ciofi-Baffoni, E. Molteni, D. L. Huffman, T. V. O'Halloran, Genome Res. 2002, 12 255-271.
4. H. Li, H. Sun, Metallomics. 2014, 6 69-76
5. Thieme, D., Neubauer, P., Nies, D. H. & Grass, G. Appl. Environ. Microbiol. 2008, 74, 7463–7470.

OC8

Thiosemicarbazones and their Copper complexes: evaluation of antifungal and anti-aflatoxigenic activity

J. Bartoli[1], M. Carcelli[1], D. Rogolino[1], G. Pelosi[1], F. Bisceglie[1], F. M. Restivo[1], F. Degola[1], A. Buschini[1], S. Montalbano[1], D. Feretti[2], C. Zani[2]

1. Dipartimento SCVSA and Consorzio Interuniv. Ricerca Chimica dei Metalli nei Sistemi Biologici, Università di Parma, Parco Area delle Scienze, 43124 Parma, Italy.
2. Dipartimento di Specialità medico-chirurgiche, Scienze Radiologiche e Sanità Pubblica, Università di Brescia, Viale Europa 11, 25123 Brescia, Italy.

Mould contamination of cereals is considered a social emergency: food deterioration and spoilage is principally related to the presence of fungi, in particular of *Aspergillus*, *Penicillium*, *Fusarium* and *Alternaria* genera. These fungi can produce aflatoxins, secondary metabolites with high carcinogenic potential.(1) Metal ions can influence the growth and the mycotoxin production of the toxigenic fungi and that this effect can be related to the ability of metal ions to intervene on the pattern of gene expressions of *A. flavus*.(2) Metal chelation could improve lipophilicity, facilitating the penetration of the complexes into lipid membranes, and should restrict proliferation of the microorganisms. Thiosemicarbazones represent a very attractive class of metal-chelating ligand for their coordinating versatility and their known antifungal activity. Here we report on the evaluation of the antifungal and anti-aflatoxin activity towards *A. flavus* of some thiosemicarbazones ligands, derived from different ketones, and of some of their metal complexes (Figure 1). The metal complexes were studied both in solution and at the solid state. Tests to assess cyto- and geno-toxic effects on human cells were performed on the most active compounds. Best hits were also evaluated for their toxic and genotoxic activities on bacteria and plants cells. Analysis of structure-activity relationship leaded to the design of a second panel of molecules with higher lipophilicity, with a good activity and safety profile.

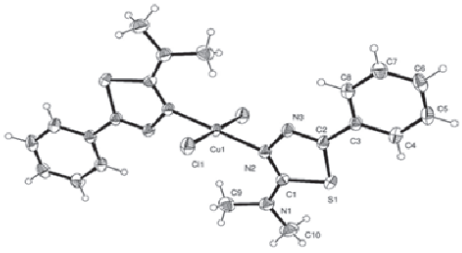


Figure 1

This work is supported by Fondazione Cariplo - Project N. 2014-0555, http: www.aflatox.it

References

1. V. H. Tournas, ***Critical Rev. Microbiol.*** (2005) **31**, 33-44.
2. Cuero, R et al. ***J. Appl. Microbiol.*** (2003) **94**, 953–961.

Biological properties of (triphenylphosphine)platinum(II) complexes containing bidentate arylaldoxime ligands

OC9

M. Hyeraci[1], A.N. Garcia-Argaez[1,2], L. Dalla Via[1], D. Belli Dell' Amico[3], M. Dell' Acqua[3], M. Colalillo[3], L. Labella[3], F. Marchetti[3] , S. Samaritani[3]

1. Dipartimento di Scienze del Farmaco, Università degli Studi di Padova, Via F. Marzolo 5, 35131 Padova, Italy
2. Fondazione per la Biologia e la Medicina della Rigenerazione, via F. Marzolo, 13, 35131 Padova, Italy
3. Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Giuseppe Moruzzi 13, 56124 Pisa, Italy

Cisplatin is a well-known chemotherapeutic drug effectively used against various types of cancers, in particular testicular, ovarian, and bladder, but also lung cancer, neuroblastoma and malignant pleural mesothelioma. Nevertheless, cisplatin therapy has two mayor complications: the occurrence of tumor therapeutic resistance and of significant systemic off target effects, mainly nephrotoxicity and neurotoxicity. To enhance the therapeutic index of cisplatin, since its early preclinical and clinical development, several thousands of analogues have been synthesized and tested for biological properties, and some of them are currently in clinical trials.[1,2]

In this connection, in a previous study we have reported the synthesis and the biological evaluation of some Pt(II) complexes containing triphenylphosphine and N(butyl),N-(arylmethyl)amino ligand. These complexes showed a significant antiproliferative activity on a panel of human tumor cell lines with GI_{50} values in most cases in the low micromolar range. Moreover, interestingly, they were able to induce a comparable cytotoxicity on both cisplatin-sensitive and -resistant tumor cells.[3]

Following our interest concerning triphenylphosphine Pt(II) complexes, more recently, the synthesis and the characterization of some Pt(II) complexes containing PPh_3 and bidentate arylaldoxime ligands were performed[4] (Figure 1).

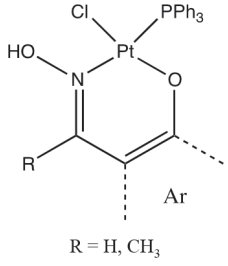


Figure 1. Platinum(II) complexes of triphenylphosphine and bidentate arylaldoxime.

This presentation deals with the biological mechanism of action of these new complexes. In detail, the antiproliferative effect on human tumor cell lines sensitive and resistant to cisplatin was assayed. Moreover, the complexation with DNA was studied by electrophoretic methods and the binding to the macromolecule was quantitatively determined by ICP-AES in comparison with cisplatin, taken as reference drug. The mechanism responsible of cell death was also analysed.

References

1. Johnstone T.C. ***et al.*** Chem. Rev. 116, 3436-3486 (2016)
2. Kelland L. Nat. Rev. Cancer 7, 573-584 (2007)
3. Dalla Via L. ***et al.*** Bioorg. Med. Chem. 24, 2929-2937 (2016)
4. Dell'Acqua M. ***et al.*** Eur. J. Inorg. Chem. (submitted for publication)

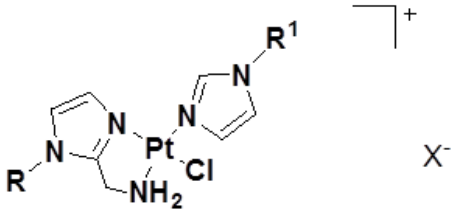
OC10

Cationic Platinum(II) complexes active *in vivo* as anticancer drugs

I. Rimoldi[1], G. Facchetti[1], N. Ferri[2], L. Cavicchini[3] , V. Coccè[3], A. Pessina[3]

1. Dipartimento di Scienze Farmaceutiche, Università di Milano, Via Venezian 21, 20133 Milano, Italia
2. Dipartimento di Scienze del Farmaco, Università di Padova, Via Marzolo 5, 35131, Padova, Italia
3. Dipartimento di Scienze Biomediche, Chirurgiche e Odontoiatriche, Università degli Studi di Milano, Via Pascal 36, 20133 Milano, Italia.

Metal-based antitumor drugs are widely used alone or in combination with organic drugs for the treatment of several tumours including some more aggressive cancer types in which other chemotherapeutics resulted inactive. In this regard, very recently, many cationic monofunctional platinum-based anticancer agents were synthesised and characterized thus violating the apparently neutrality demanded for cytotoxic platinum drugs. In comparison with the bifunctional cisplatin, monofunctional compounds display a distinct mechanism of action and a different antitumor profile taking into consideration their ability to effectively bind to DNA and to inhibit transcription both *in vitro* and *in vivo*. Our research group has synthesised a series of cationic bulky triamine platinum compounds of general formula [Pt(N-N')N'Cl]X^- where *N-N'* is an aminomethylimidazole ligand and the *N'* an imidazole ring, both bearing the same alkyl group at the *N1* position.[1]
Their cytotoxicity closed to a completely different pharmacodynamic and cellular uptake behaviour than cisplatin, make them valid candidates for displaying a successful outcome in tumour cell lines



still lacking an effective treatment. Their use in association with mesenchymal stromal cells (MSCs) from different tissues was also evaluated in early experiments.[2] MSCs proved as innovative tools able to uptake antiproliferative agents (eg.: Paclitaxel, Gemcitabine, Doxorubicin) and release them both as free molecules and exosome associated drugs in a selective way. Moreover, the drug loaded MSCs may be used *in vivo* as a physiological tool for drug delivery by injecting them both *in situ* or through systemic administration.

References

1. Rimoldi, I.; Facchetti, G.; Lucchini, G.; Castiglioni, E.; Marchianò, S.; Ferri, N., ***Bioorg. Med. Chem.*** **2017,** ***25*** (6), 1907-1913.
2. Bonomi, A.; Sordi, V.; Dugnani, E.; Ceserani, V.; Dossena, M.; Coccè, V.; Cavicchini, L.; Ciusani, E.; Bondiolotti, G.; Piovani, G.; Pascucci, L.; Sisto, F.; Alessandri, G.; Piemonti, L.; Parati, E.; Pessina, A., ***Cytotherapy*** **2015,** ***17*** (12), 1687-1695.

Multifunctional Pt(IV) anticancer prodrugs:the story so far

OC11

D. Osella, M. Ravera, E. Gabano, I. Zanellato

Dipartimento di Scienze e Innovazione Tecnologica, Università del Piemonte Orientale,
Viale T. Michel 11, 15121 Alessandria, Italy

Despite the use of cisplatin and its Pt(II) congeners in several chemotherapeutic regimes, the associated heavy side effects and the intrinsic/acquired chemoresistance have prompted inorganic medicinal chemists to design, *inter alia*, alternative Pt(IV) derivatives.
These complexes act as antitumor prodrugs, since they can be selectively reduced in the hypoxic and acidic tumor milieu to the corresponding cytotoxic Pt(II) metabolite with the usual loss of their two axial ligands (*activation by reduction*, Figure 1).
The saturated six-coordinated octahedral geometry of Pt(IV) is characterized by a high kinetic inertness that minimizes off-target effects, thus improving the therapeutic index and, furthermore, allowing oral administration.

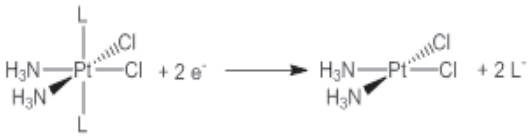


Figure 1

The two axial ligands (L) can be biological carriers addressed towards tumor tissue or adjuvant (synergistic) agents. Indeed, clinicians usually combine the approved Pt(II) drugs with other therapeutics to potentiate their efficacy. The *multifunctional* Pt(IV) derivatives, represent an ideal tool to realize such a combination therapy (Figure 2) [1]. Indeed, being a single chemical entity and containing integrated different drugs, often called “combo”, Pt(IV) multifunctional prodrugs guarantee identical pharmacokinetics and cellular uptake.
The feasibility of this approach will be illustrated through several examples taken from the literature and our own work.

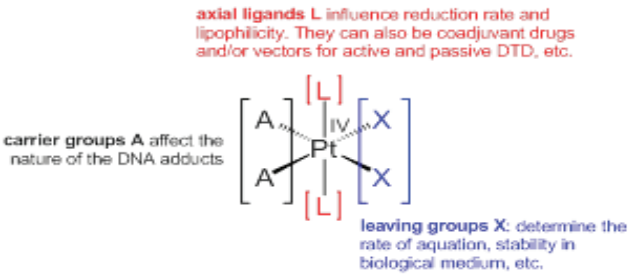


Figure 2

References

1. E. Gabano, M. Ravera, D. Osella, Dalton. Trans. Pespective, 43 (2014) 9813.

Photoactive Platinum compounds

OC12

G. Canil[1], L. Marchetti[2], J. D. Hoeschele[2], C. Gabbiani[1]

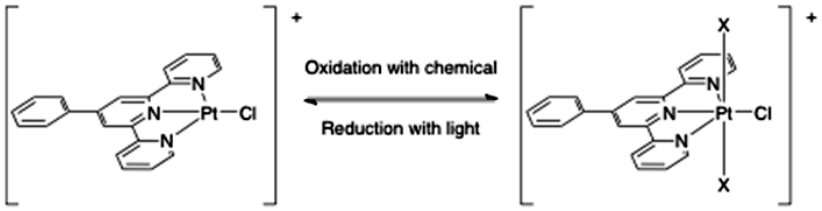
1. Department of Chemistry and Industrial Chemistry, University of Pisa, via Moruzzi 13, 56124 Pisa, Italy
2. Department of Chemistry, 541 Mark Jefferson Science Complex, Ypsilanti, Michigan, US

The first metal-based drug accepted for treating tumors is Cisplatin, 40 years ago in the US. It is still used in therapy, even though second and third generation analogs are now more widely prescribed [1]. Still, they all initiate severe side effects during the treatment and, to overcome this problem, new generations of platinum (IV) inactive and non toxic prodrugs are currently under development for treating cancer. A prodrug should not be toxic for the human body and resistant enough to reach the target site unchanged. A process of activation transforms the prodrug into the active species, which is now able to exert its cytotoxic effect [2].

Among this class of molecules, photoactive Pt(IV) prodrugs can be activated with light to generate the cytotoxic Pt(II) product after a redox reaction. Light is probably the best means to activate a molecule in the body because it can be controlled in terms of location and duration and is easy to manipulate from outside the body [3].

The molecules synthesized in this project are Pt(IV) pseudo-octahedral compounds which bear a substituted terpyridine ligand in the equatorial plane. This ligand should act as an antenna, gathering visible light to promote the photoreaction. On the other hand, the ligands present on the axial sites of the octahedron are mainly responsible for the stability of the prodrug. In fact during the reduction from Pt(IV) to Pt(II) they are released from the molecule. Azide anions seem to be preferable for this purpose [4] and our studies are ongoing to find other good candidates.

We are currently testing the ability of the molecules to interact with biological targets. Preliminary analysis using ESI-MS shows binding between the molecule and the oligonucleotide ODN2 (sequence CTACGGTTTCAC), but only if the platinum is in the reduced oxidation state. Our work is in progress to fully characterize these interactions.



References:

1. J. C. Dabrowiak, Metals in Medicine, Wiley **2009**, Chapter 3.
2. T. C. Johnstone; K. Suntharalingam; S. J. Lippard; Chem. Rev. **(2016)**, 116, 3436.
3. P. J. Bednarski; F. S. Mackay; P. J. Sadler; Anti-Cancer Agents in Medicinal Chemistry **(2007)**, 7, 75.
4. N. J. Farrer; J. A. Woods; L. Salassa; Y. Zhao; K. S. Robinson; G. Clarkson; F. S. Mackay; P. J. Sadler; Ang. Chem. Int. Ed. **(2010)**, 49, 8905.

A comparative analysis of biophysical interactions of cisplatin analogues with Lysozyme

OC13

D. Marasco[1], G. Ferraro[2], I. De Benedictis[1], A. Malfitano[1], G. Morelli[1], E. Novellino[1]

1. Department of Pharmacy, CIRPEB: Centro Interuniversitario di Ricerca sui Peptidi Bioattivi- University of Naples "Federico II", 80134, Naples, Italy
2. Department of Chemical Sciences, University of Naples "Federico II", 80126, Naples, Italy

The biophysical characterization of macromolecule–ligand interactions, including drug binding to proteins, plays a key role in structural biology and in the design and optimization of new compounds of medicinal interest[1]. The search for optimal combinations of biophysical techniques that can correctly and efficiently identify and quantify binding of metal-based drugs to their final target is challenging, due to the physicochemical properties of these agents.
Different cisplatin derivatives demonstrated diverse citotoxicities in common cancer lines, suggesting different mechanisms of action in their anticancer activities. Recently a comparative analysis was carried out in the investigation of three Pt-compounds under the same experimental conditions in different biophysical binding assays to properly deepen the determinants of the different MAOs. The results deriving from surface plasmon resonance, isothermal titration calorimetry, fluorescence spectroscopy and thermal shift assays based on circular dichroism experiments for complexes of cisplatin, carboplatin and iodinated analogue of cisplatin, cis-Pt $(NH_3)_2I_2$, with the model protein hen egg white lysozyme, both at neutral and acid pHs [2] were compared.

References

1. Merlino, A.; Marzo, T.; Messori, L., Protein Metalation by Anticancer Metallodrugs: A Joint ESI MS and XRD Investigative Strategy. ***Chemistry* 2017, *23*** (29), 6942-6947.
2. Ferraro, G.; De Benedictis, I.; Malfitano, A.; Morelli, G.; Novellino, E.; Marasco, D., Interactions of cisplatin analogues with lysozyme: a comparative analysis. ***Biometals : an international journal on the role of metal ions in biology, biochemistry, and medicine* 2017, *30*** (5), 733-746.

OC14

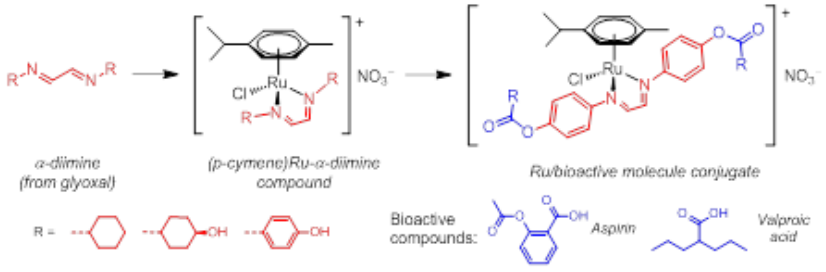
Ruthenium(II) arene complexes with α-diimine ligands: synthesis, characterization and cytotoxicity

L. Biancalana[1], L. K. Batchelor[2], P. J. Dyson[2], T. Funaioli[1], F. Marchetti[1], G. Pampaloni[1], G. Provinciali[1], S. Zacchini[3]

1. Dipartimento di Chimica e Chimica Industriale, Università di Pisa.
2. Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL).
3. Dipartimento di Chimica Industriale "Toso Montanari", Università di Bologna.

Following intensive investigations on Ru(III) compounds as possible alternative to Platinum anticancer drugs, culminated with phase I/II clinical studies, **Ru(II) arene complexes** gained widespread interest for their antitumour properties.[1] Within this context, neutral chelating ***N,N* ligands**, most often α-diamines, are frequently encountered in the structure of anticancer metal compounds: the most notable examples are clinically-approved oxaliplatin, as well as other 3rd generation Pt(II) compounds, and (η^6-arene)Ru-ethylenediamine complexes, displaying potent anticancer activity both *in vitro* and *in vivo*.[2] *In this respect,* **α-diimines** represent another class of *N,N* ligands that have been previously coordinated to Pt(II) and Ru(II)-arene scaffolds, but no biological studies have been reported heretofore.

In the present work, novel water-soluble Ru(II) *p*-cymene compounds with α-diimine ligands, [(η^6-*p*-cymene)RuCl{κ^2*N*-(HCNR)$_2$}]NO_3, were synthesized and characterized by analytical, spectroscopic and electrochemical techniques, and X-ray diffraction in one case. The compound bearing phenol side groups on the α-diimine ligand revealed suitable to modification by esterification: therefore bis-functionalized conjugates with bioactive carboxylic acids Aspirin and Valproic acid were realized. The stability and speciation of all Ru compounds in water or water:DMSO mixtures was investigated. Subsequently, *in vitro* cytotoxicity studies were performed on human ovarian cancer cell lines (A2780 and cisplatin-resistant A2780cisR) and on a non-tumoural cell line (HEK-293) for comparison. Results outlined a broad range of antiproliferative activity, some Ru-α-diimine compounds being ineffective while others being equipotent to cisplatin. Structural factors possibly affecting cytotoxicity will be discussed.



Email addresses: lorenzo.biancalana@for.unipi.it (LB), fabio.marchetti1974@unipi.it (FM)

References

1. L. Biancalana, L. K. Batchelor, A. De Palo, S. Zacchini, G. Pampaloni, P. J. Dyson, F. Marchetti, ***Dalton Trans.***, **2017**, *46*, 12001-12004 and references therein.
2. R. E. Aird, J. Cummings, A. A. Ritchie, M. Muir, R. E. Morris, H. Chen, P. J. Sadler, D. I. Jodrell, **Br. J. Cancer 2002**, **86**, 1652-1657.

Structural and functional insights into the Aβ-Ubiquitin interaction

OC15

F. Bellia[1], G. Grasso[2], G. Malgieri[3], R. Fattorusso[3], A. Pietropaolo[4], C. Iacobucci[5], V. Lanza[1], D. Milardi[1], E. Rizzarelli[1,2]

1. Institute of Biostructure and Bioimaging, CNR – Catania, Italy
2. Department of Chemical Sciences, University of Catania, Italy
3. Department of Environmental, Biological and Pharmaceutical Sciences and Technologies, University of Campania "Luigi Vanvitelli", Caserta, Italy
4. Department of Health Sciences, University of Catanzaro, Italy
5. Department of Pharmaceutical Chemistry and Bioanalytics, Martin Luther University Halle-Wittenberg, Germany

The dyshomeostasis of amyloid-beta peptide (Aβ), the consequent peptide aggregation and accumulation in cerebral senile plaques cause the onset of Alzheimer's disease (AD), the most common neurodegenerative disorder worldwide [1].

The enzymatic degradation of Aβ plays a key role on the peptide homeostasis. A partial or total failure of the Aβ-degrading enzyme could reasonably have a negative impact on the physiological fate of the amyloid peptide. The interaction between insulin-degrading enzyme (IDE) [2] and amyloid substrates are modulated by transition metal ions [3], i.e. copper(II) and zinc(II); they also change the proteolytic cleavage sites of other natural substrates of IDE, such as insulin and amylin [4,5]. However, the molecular mechanism of IDE function, including the structural details of the interaction several metal ions, remains elusive.

Moreover, the failure of all clinical trials of amyloid-targeting drugs suggests that the amyloid hypothesis needs to be somehow amended. In particular, a complete knowledge of the interplay between Aβ amyloid growth and cellular systems managing protein clearance emerges as a promising arena for future studies addressing neurodegeneration. Ubiquitin plays an important role for the protein clearance in eukaryotic systems. By means of a multistep enzymatic process, it binds to proteins and the mono- or poly-ubiquitinated products have a specific fate, also depending on which of the eight lysine residues is involved. Copper and zinc ions also affect this physiological process [6].

In this context, understanding the mutual influence of Aβ, ubiquitin, IDE and transition metal ions on their own specific activity represents the intriguing, albeit difficult, aim of our recent research [7]. The structural interaction between Aβ and ubiquitin, until now is unexplored, has been investigated by means of NMR, LC-MS and *in silico* measurements. The effect that such an interaction has on the metal-affected amyloid aggregation and IDE activity has also been studied.

References

1. Bush A.I. Trends Neurosci., 2003, 26, 207.
2. Farris et al., PNAS, 2003, 100, 4162.
3. Grasso G. et al., Chem. Eur. J., 2011, 17, 2752.
4. Bellia F. et al., J. Mass Spectrom., 2013, 48, 135.
5. Bellia F. et al., J. Mass Spectrom., 2014, 49, 274.
6. Arena G. et al. Inorg. Chem., 52, 16, 9567-9573
7. Grasso G. et al. Chem Commun. 2015, 51:15724-15727

OC16

Copper (II) interaction with the N-terminal repeat of opossum prion protein: a glance to prion evolution

D. La Mendola[1], A. Magrì[2], G. Tabbì[2], L. M. Cucci[3], C. Satriano[3], E. Rizzarelli[3]

1. Dipartimento di Farmacia, Università di Pisa, Via Bonanno Pisano, 6, 56126, Pisa, (Italy).
2. Istituto di Biostrutture e Bioimmagini, Consiglio Nazionale delle Ricerche (IBB-CNR), Via P. Gaifami, 18, 92126, Catania, (Italy).
3. Dipartimento di Scienze Chimiche, Università di Catania, viale A. Doria, 6, 95125 Catania, (Italy).

Prion diseases are progressive neurodegenerative disorders caused by the structural conversion and aggregation of the normal cellular prion protein (PrP^C) to a misfolded, partially protease-resistant and pathogenic isoform (PrP^{Sc}).[1] Prion is mainly expressed in the brain, but its specific biological role is still unknown. Structurally, PrP^C consists of a globular folded C-terminal domain, which is largely α -helical, and a glycine-rich N-terminal domain containing an octapeptide repeat region (OR) composed of four contiguous copies of the highly conserved PHGGGWGQ sequence.

Many studies demonstrate that the N-terminus domain of PrP^C interact with copper ions ions and the protein may act as a receptor for cellular uptake or efflux of metal by cell. On the other hand, it has been proposed that copper binding induces conformational changes driving the toxic switch from PrP^C to PrP^{Sc}. So far, prion diseases have been reported for almost all mammals but precluded to other species, including avian, reptile, amphibian and fish. The comparison between PrPs of different species can unravel functional evolutionary trends related to prion physiological role and its involvement in pathogenesis.[2] Marsupialia is a mammal infraclass and, due to its evolutionary position, represent a model for such a comparison. To date, no prion diseases have been reported in the opossum (Op), animal belonging to marsupialia. The opossum prion protein (Op-PrP) shares approximately 70% sequence identity with mouse PrP (Mo-PrP). Noteworthy, sequence variations are most prominently localized on the N-terminus domain that coordinates Cu(II) ions. The Op-PrP^C contains five tandem deca-repeats with sequence PHPGGSNWGQ. The high number of proline and presence of serine and asparagine residues are typical of avian (PHNPGY) and turtle esarepeat (PHNPSY).

We report here the investigation on the copper(II) binding by the bis-decarepeat sequence of Op-PrP, Ac-$(PHPGGSNWGQ)_2$-NH_2. A multitechnique approach, based on potentiometry, spectroscopies (UV-vis, circular dichroism, EPR), voltammetry, quartz crystal microbalance with dissipation monitoring and atomic force microscopy have been used to elucidate on the metal coordination environment and the conformational/viscoelastic changes induced by the metal binding, respectively. The comparison between the obtained data and those available in literature for avian and humans evidences interesting cues for an increased knowledge about the evolutionary trend of prion proteins related to the interaction with copper ions.

References

1. Prusiner S.B. Proc. Natl. Acad. Sci., 1998, 95, 13363.
2. La Mendola D., Rizzarelli E. Biomolecules, 2014, 4, 546.

Modulation of proteasome activity by porphyrins

OC17

M. Coletta[1,2], A. M. Santoro[3], A. Cunsolo[2,4], A. D'Urso[2,4], G. R. Tundo[1,2], D. Sbardella[1,2], C. Ciaccio[1,2], D. Diana[5], R. Fattorusso[6], M. Persico[7], A. Di Dato[7], M. Stefanelli[8], R. Paolesse[8], C. Fattorusso[7], C. Milardi[3], R. Purrello[2,4]

1. Dip. Scienze Clin. Med. Trasl., Univ. Roma Tor Vergata, Roma;
2. CIRCMSB, Bari;
3. CNR Ist. Biostrutt. Bioimmag., Catania;
4. Dip. Scienze Chimiche, Univ. Catania, Catania;
5. CNR Ist. Biostrutt. Bioimmag., Napoli;
6. Dip. Scienze Tecnol. Amb. Biol. Farmac., Univ. Campania, Caserta;
7. Dip. Farmacia, Univ. Napoli Federico II;
8. Dip. Scienze Chimiche, Univ. Roma Tor Vergata, Roma.

The proteasome is a cytosolic multi-subunit protease. It constitutes the focal point of the Ubiquitin-Proteasome System (UPS), the major venue of regulated protein catabolism. The broad involvement of the UPS in the regulation of key metabolic processes is directly linked to the large number of disorders related to UPS alterations and explains why the proteasome, over the last decade, has become an attractive pharmacological target for the treatment of diverse diseases including, cancer and neurodegenerative disorders. Porphyrins are very special molecules, extremely versatile and attractive synthetic base materials for the design of cutting-edge theranostic probes. In oncology, porphyrins find extended application as photosensitizers in photodynamic therapy (PDT), boron carriers in boron neutron capture therapy (BNCT) and telomerase inhibitors. Recently we investigated the ability of porphyrins to modulate the proteasome activity *in vitro* and in cell-free systems. Cationic porphyrins - depending on the spatial distribution of their electrostatic charges – exhibited an amazing variety of binding modes and inhibition mechanisms. First, they may bind to the 20S proteasome gates bringing about their partial occlusion by competitively hindering the entrance of the substrate into the catalytic chamber. Second, they may bind over different α subunits, thus affecting the dynamic equilibrium between the open and the closed state of the proteasome gates. In addition, it is very interesting to remark that anionic porphyrins, when added to the latent 20S proteasome, may even activate the core particle by facilitating the access of the substrate to the proteasome interior. Thus, the porphyrins charges represent the keys able to interfere with the electrostatic code of proteasome gating phenomena, and the resulting conformational rearrangements also reverberate onto the β subunits indicating that porphyrin influence on the core particle (CP) is essentially allosteric. Taken as a whole, our studies suggest that porphryins represent a unique class of CP binding molecules endowed with either inhibiting or activating potentialities

Based also on the evidence that allosteric proteasome regulation is becoming increasingly important in the treatment of many diseases including cancer and neurodegeneration, we hope that our results may pave the way to studies aimed at designing ever more sophisticated proteasome modulators.

Metal signaling and BDNF expression

OC18

I. Naletova[1], D. La Mendola[2], G. Pandini[3], C. Satriano[1], A. Pietropaolo[4], F. Gianì[3], A. Travaglia[5], V. G. Nicoletti[6], G. Arena[1], S. Zimbone[7], M.L. Giuffrida[7], E. Rizzarelli[1]

1. Department of Chemical Sciences, University of Catania, Viale A. Doria 6, 95125 Catania (Italy)
2. Department of Pharmacy, University of Pisa, Via Bonanno Pisano 6, 56126, Pisa (Italy)
3. Department of Clinical and experimental Medicine, Endocrinology, Garibaldi Hospital, University of Catania, via Palermo n. 636, 95122 Catania (Italy)
4. Department of Health Science, University of Catanzaro, Viale Europa, 88100 Catanzaro (Italy)
5. Centre for Neural Science, New York University, 4 Washington Place, New York, NY, USA
6. Department of biomedical and biotechnological sciences, University of Catania (Italy)
7. Institute of Biostructures and Bioimages, CNR-Catania, Via P. Gaifami 18, 95126 Catania, Italy

Alzheimer's disease (AD) is the most common form of dementia in the elderly. Oligomerization of amyloid beta is fundamental to promote neurotoxicity [1] through different ways [2], including altered levels of neurotrophic factors (NTFs) [3, 4]. NGF dysregulation has been correlated to several neurodegenerative diseases, such as AD [5]. Moreover, this neurodegenerative disorder characterizes by altered metallostasis. The main objective of the present work has been to understand the role of copper ions on the cross-talk between trophic factors and main players of AD.

PC12, primary neuronal culture and differentiated neuroblastoma cells (dSH-SY5Y) have been used as cellular models. By the use of Western Blot analysis we investigated the effect of metal ions on the abilities of Aβ 1-42 / NGF full lengths and their fragments, to promote the increased level of phospho-CREB (ser133). The NGF fragment, NGF1-14, has been shown to mimic the activities of its full lenght, protein [6] including the induction of CREB phosphorylation. Also, the small peptide resulted to induce TrkA internalization even in the presence of these metal ions [7]. Moreover, here we describe the involvement of copper ions in the copper homeostatic machinery adaptation and copper redistribution in intracellular compartments of PC12 and dSH-SY5Y cell lines after treatment with different fragments of both Aβ and NGF. Real time PCR was employed to determine the potential effect of monomeric Aβ and NGD peptides to promote the transcription of the CREB-target gene, BDNF. ELISA assay was used to investigate the release of BDNF protein. Live cell imaging experiments of cells treated with fluorescent labelled peptides show that NGF peptides are able to act as ionophore, increasing the intracellular amount of copper.

Based on our data, metal binding to these peptides modulate their activity similarly to that observed with the respective whole proteins. They are able to exert an effective and specific protein-like action on crucial intracellular targets. In this view, the reported activity of the investigated peptides provide us a promising tool to counteract pCREB and BDNF decrease recently observed in the brain of AD patients.

References:

1. Walsh DM, Selkoe DJ (2007) J. Neurochem 1172–1184.
2. Ferreira ST and Klein WL (2011) Neurobiol. Learn. Mem. 96(4): 529-543.
3. Budni J et al., (2015) Aging Dis., 6(5), 331-341.
4. Calissano P et al., (2010) Cell Death Differ. 17(7):1126-1133
5. Cattaneo A and Calissano P (2012). Mol Neurobiol 46, 588-604.
6. Travaglia A. Pietropaolo A, et al., (2015) ACS Chem Neurosci. 6, 1379-1392.
7. Pandini G, Satriano C, et al., (2016) Front Neurosci. 10, 569.

Recombinant expression, purification and preliminary characterization of the anserinase from *Oreochromis Niloticus*

OC19

L. Pirone[1], F. Bellia[2], S.Di Gaetano[1], E. Rizzarelli[2,3], E. Pedone[1]

1. CNR - Institute of Biostructure and Bioimaging, V. Mezzocannone 16, 80134, Napoli
2. CNR - Institute of Biostructure and Bioimaging, via P. Gaifami 18, 95126, Catania, Italy
3. Department of Chemical Sciences, University of Catania, Viale A. Doria 6, 95125, Catania, Italy.

Anserinase (ANSN) is able to degrade anserine (β-alanyl-1-methylhistidine) and shows a broad specificity not only for multiple dipeptides including carnosine, but also for several N-acetylated amino acids[1]. For the first time Yamada et al.[2] reported the molecular identification of ANSN from the brain of Nile tilapia *Oreochromis niloticus* revealing that it belongs to a subfamily of metallopeptidases. While ANSN and carnosinase (CN1), a Xaa-His dipeptidase located in serum and brain and highly specific metal-ion dependent enzyme, are both secretory enzymes, the substrate specificity of ANSN (broad) is remarkably different from that of CNI (narrow). It has been postulated that CN1 and ANSN are paralogs derived from the most recent common ancestor (MRCA) in vertebrates indeed carnosinase resembles anserinase in hydrolytic ability against carnosine, anserine and homocarnosine, which are unusual dipeptides containing non-α-amino acids[2]. No other enzymes except anserinase and carnosinase can hydrolyze these three dipeptides[2]. As reported in Oku et al.[3] homeothermic vertebrates (mammal and avian) do not contain anserinase while, interestingly, in ectothermic vertebrates, amphibians and a part of ray-finned fish, such as salmonid and eel, contain all both genes[3]. Anserinase results to be a very interesting target of study either from an evolutionistic point of view and for its localization in the brain, retina and vitreous body of all vertebrates containing N-acetyl-histidine in their tissues. Such imidazole-related compound with others have been postulated to have numerous biological roles such as H^+ buffer, divalent ion regulator, neurotransmitter, non-enzymatic free-radical scavenger, antioxidant, and blood glucose regulator[3]. In the present study, we report, for the first time, cloning, expression in *Escherichia coli*, purification and a preliminary characterization of anserinase from *Oreochromis niloticus*. In detail a structural analysis, by circular dichroism spectroscopy, and a functional study, by enzymatic assays in the presence of different metals, were carried out. Finally, a comparative study with the anserinase expressed in an eukaryotic system was performed. Moreover, by means of a mass spectrometry-based proteomic approach, we got insight into the structural features of the protein sequence and post-translational modifications.

References

1. Bellia F, Vecchio G, Rizzarelli E. Carnosinases, their substrates and diseases. Molecules. 2014 Feb 21;19(2):2299-329. doi: 10.3390/molecules19022299.
2. Yamada, S.; Tanaka, Y.; Ando, S. Purification and sequence identification of anserinase. FEBS J. 2005, 272, 6001–6013.
3. Oku T, Ando S, Hayakawa T, Baba K, Nishi R, Shiozaki K, Yamada S. Purification and identification of a novel primitive secretory enzyme catalyzing the hydrolysis of imidazole-related dipeptides in the jawless vertebrate ***Lethenteron reissneri***. Peptides. 2011 Apr;32(4):648-55.

OC20

Synthesis, characterization and biological activity evaluation of new Pt(II) complexes

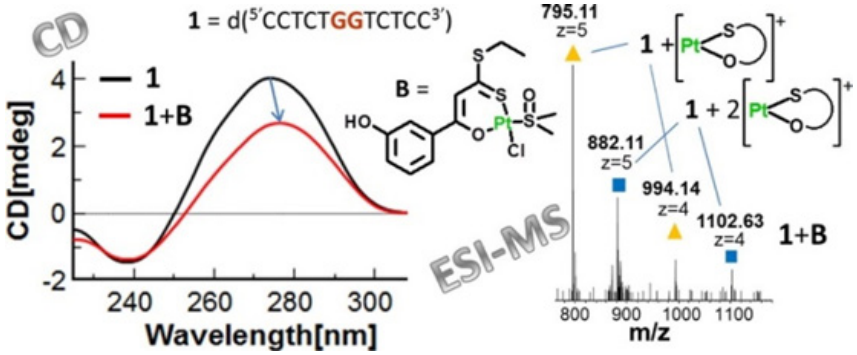
D. Musumeci[1], G. M. Rozza[1], C. Platella[1], C. Riccardi[1], F. Moccia[1], A. Coppola[1], L. Messori,[2] T. Marzo,[2] D. Capasso,[3] S. Di Gaetano,[4] G. N. Roviello,[4] D. Montesarchio[1]

1. Department of Chemical Sciences, University of Naples Federico II, Napoli, Italy;
2. Department of Chemistry "Ugo Schiff", University of Florence, Sesto Fiorentino, Italy;
3. CESTEV, University of Naples Federico II, Napoli, Italy;
4. Institute of Biostructures and Bioimaging - CNR, Napoli, Italy.

Cisplatin is one of the most active chemotherapeutic agents in use for the treatment of a variety of malignancies, especially testicular and ovarian carcinoma,[1] even if its clinical utility is restricted by both toxicological and especially tumour resistance considerations.[1] Therefore, much attention has been focused on the development of new Pt complexes with improved pharmacological properties and broader anticancer activity.[1] Aiming at further enhancing the cytotoxicity of metal-based drugs, the identification of the mode of action of selected lead compounds and of their biological targets of is of the utmost importance.

Here we report our studies on the synthesis, characterization and biological activity of new Pt complexes, and on their interaction with DNA, using various model systems, and combining several bioanalytical techniques including circular dichroism, UV-visible spectroscopy and mass spectrometry (see an example in figure).[2,3]

On the whole, it was demonstrated that the tested compounds interact with DNA and produce



conformational changes of different extent depending on kind of complex, the sequence and structure of the examined oligonucleotide. Guanine was established as the preferential target within the DNA sequence, but in the absence or unavailability of guanines, alternative binding sites can be addressed. The implications of these results are thoroughly discussed.

References

1. Dasari S. and Tchounwou P. B., Eur J Pharmacol. **2014**; 364–378.
2. Mügge C., Musumeci D., Michelucci E., Porru F., Marzo T., Massai L., Messori L., Weigand W., Montesarchio D., J Inorg Biochem. **2016**; 160: 198-209.
3. Musumeci D., Platella C., Riccardi C., Merlino A., Marzo T., Massai L., Messori L., Montesarchio D., Dalton Trans. **2016**; 45(20):8587-600.

Strategies for the development of innovative chemotherapy treatment in colorectal cancer. An overview of our recent results

OC21

T. Marzo[1,2], D. Cirri[2], C. Gabbiani[1], T. Biver[1], A. Pratesi[2], S. Pillozzi[3,4], M. Stefanini[4], L. Massai[2], L. Ciofi[2], A. Arcangeli[3], L. Messori[2]

1. Department of Chemistry and Industrial Chemistry (DCCI), University of Pisa, Via Moruzzi, 13, 56124 Pisa, Italy
2. Laboratory of Metals in Medicine (MetMed), Department of Chemistry "U. Schiff", University of Florence, Via della Lastruccia 3, 50019 Sesto Fiorentino, Italy
3. Department of Experimental and Clinical Medicine, University of Florence, Viale GB Morgagni 50, 50134 Firenze, Italy
4. DI.V.A.L Toscana S.R.L., Via Madonna del Piano, 6, 50019 Sesto Fiorentino, Italy

Colorectal cancer (CRC) is the fourth most common cause of death for cancer worldwide. Prognosis is highly correlated with the staging, having a 5-year survival of 90% for patients in earlier stages but less than 25% for those with metastatic disease. The cornerstone of therapy is represented by "en bloc" surgical resection of tumor and regional nodes, although perioperative chemotherapy is mandatory in subjects with advanced disease and metastases. Adjuvant chemotherapy for CRC mainly relies on fluoropyrimidine compounds combined with platinum Pt-based drugs, mainly cis-platin and its analogue oxaliplatin. Indeed, either the FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOx (capecitabine and oxaliplatin) regimens are used most often. In general, those based on Pt-containing drugs are among the most used chemotherapeutic approaches in solid cancers, including CRC. Yet, the two mentioned Pt compounds, cisplatin and oxaliplatin, despite a consistent rate of initial responses, manifest a few relevant limitations such as an important systemic toxicity and the frequent insurgence of resistance that may lead to eventual treatment failure; the important limitations of Pt compounds for CRC management have inspired our work in the last few years. More precisely, we have focused our efforts in treatment improvement using an integrated *in vitro* and *in vivo* approach, through three different strategies:

1) Drug repurposing;
2) Slight modifications of clinical established metal-based drugs;
3) Novel drug combinations.

Distinct examples based on the results obtained in our laboratories are here reported and discussed.[1-3] Overall, interesting results emerge indicating as these strategies are in principle suitable to improve/optimize adjuvant chemotherapy in CRC treatment.

References

1. T. Marzo et al.; ACS Med Chem Lett., 2017,8, 997-1001
2. T. Marzo et al.; Dalton Trans., 2015, 44,14896-905
3. S. Pillozzi et al.; British Journal of Cancer 2018, 118, 200-212

OC22

Novel cytotoxic metal-NHC carbenes induce distortions of calf thymus DNA and TrxR inhibition

F. Guarra[1], T. Biver[1], C. Gabbiani[1], N. Busto[2], B. Garcìa[2], T. Marzo[3]

1. Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via G. Moruzzi 13, 56124, Pisa, Italia
2. Departamento de Quìmica, Universidad de Burgos, Plaza M. Bañuelos, s/n, 09001 Burgos, España
3. Dipartimento di Chimica Ugo Schiff, Università degli studi di Firenze, Via della Lastruccia 3, 50019, Firenze, Italia

Cisplatin and other platinum drugs currently used in the treatment of cancer have many drawbacks such as systemic toxicity, related resistance and tolerance mechanisms. Therefore, many efforts are being spent in the development of metal based antitumor drugs and in selective targeting strategies. Among these, metal N-heterocyclic carbenes (NHCs) turned out to be particularly promising: NHC ligands bear stable complexes with tunable properties. Moreover, many reports show the interesting biological properties of gold and silver NHCs found to be selectively cytotoxic toward cancer cell lines and to have antimitochondrial activity.[1] In particular NHCs have been found to be potent inhibitor of Thioredoxin reductase (TrxR),[2] a selenoenzyme involved in the maintenance of the redox balance. This target may represent a valuable strategy to achieve selectivity towards cancer cells because it has been proven to be overexpressed in some tumor types.[3] These complexes are, indeed, commonly known to target proteins, yet more recent studies also consider the interaction of gold compounds with dsDNA or g-quadruplexes.[4,5]

Herein, we present the synthesis of a gold-NHC and of its silver precursor. In particular, our designed complexes aim at combining metal inhibition of TrxR with the possible intercalating activity of the NHC ligand.[6,7] In this frame, novel compounds were chemically characterized and different biochemical, biophysical and spectroscopical methods were used to study their interaction with target proteins and natural DNA. The compounds have been found to inhibit TrxR in the low micromolar range and to bind DNA probably through intercalation. Furthermore, preliminar *in vitro* studies on solid tumour cell lines were performed.

References

1. Alessio E., Bioinorganic Medicinal Chemistry, Alessio E., Bioinorganic Medicinal Chemistry, Wiley-VCH Verlag & Co. KGaA.
2. Rubbiani R., Schuh E., Meyer A., Lemke J., Wimberg J., Metzler-Nolte N. Meyer F., Mohr F., Ott I., Med. Chem. Commun., 2013,**4**, 942-948.
3. Rigobello M.P., Scutari G., Folda A., Bindoli A., Biochem. Pharmacol., 2004, 67, 689-696.
4. Zou T., Lum C.T., Lok C-N., Zhanga J-J., Che C-M., Chem. Soc. Rev., 2015, 44, 8786-8801.
5. Gratteri P., Massai L., Michelucci E., Rigo R., Messori L., Cinellu M.A.,Musetti,C., Sissi C., Bazzicalupi C., Dalton Trans., 2015, 44, 3633-3639.
6. Meyer A., Oehninger L., Geldmacher I., Alborzinia H., Wölfl S., Sheldrick W. S, Ott I., ChemMedChem, 2014, 9, 1794-1800.
7. Citta A., Schuh E., Mohr F., Folda A., Massimino M.L., Bindoli A., Casini A., Rigobello M.P., Metallomics, 2013, 5, 1006.

Functional matrices from mussel byssus waste

OC23

G. Falini[1] , D. Montroni[1], S. Fermani[1], M. Calvaresi[1], M. J. Harrington[2]

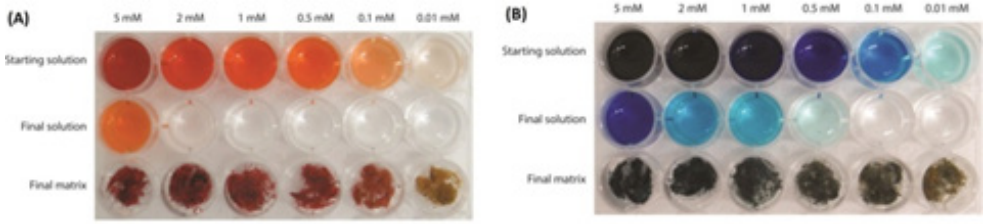
1. Dipartimento di Chimica "Giacomo Ciamician", Alma Mater Studiorum Università di Bologna, via Selmi 2, 40126 Bologna, Italy.
2. Department. of Biomaterials, Max-Planck Institute for Colloids and Interfaces, Research Campus Golm, Am Mühlenberg 1, Potsdam 14424, Germany.

The mussel byssus is a biorenewable, protein-based material produced by marine mussels, which has attracted the interest of material scientists due to its remarkable mechanical and self-healing properties. Large quantities of byssus waste material from mussel mariculture are produced every year, which have great potential as a raw starting material for producing sustainable advanced materials.

In this research, these two environmental issues are addressed by proposing the reuse of mussel's proteic anchoring threads, the byssus, as disposable material for dye water removal. The byssus was selected as substrate also because it contains a distinctive variety of functional groups that can be exploited for diverse chemical interactions. This material was utilized in its native metaled state and in the de-metaled one, in order to study how the chemical state of the functional groups influences the adsorption properties of both anionic and cationic aromatic dyes. The results of comparative experiments of adsorption showed a higher uptake in the native metaled byssus for a model cationic dye, methylene blue (MB), while the de-metaled byssus showed a higher uptake for a model anionic dye, Eosin Y (EosY).[1]

A facile and scalable method to synthesize whole byssus-based porous matrices that retain part of the hierarchical organization of the pristine material at the nano-scale is also presented. The resulting material is biocompatible and maintains important native byssus features - metal ion chelation, collagen domains and hierarchical organization, with tunable properties controlled via metal ion content. Furthermore, these biocompatible matrices showed a dye absorbing efficiency that was similar to or higher than that of the pristine byssus, a proof of preservation of structural motifs. These findings indicate that biorenewable matrices originating from byssus waste could have potential use in biomedical engineering and applied material science.[2]

Figure. Camera photographs illustrating the dye removal experiments using (A) de-metaled byssus on EosY solutions, and (B) native byssus on MB solutions.



References

1. D. Montroni, C. Piccinetti, S. Fermani, M. Calvaresi, M. J. Harrington, G. Falini ***RSC Adv.*** (2017) 7, 36605–36611.
2. D. Montroni, F. Valle, S. Rapino, S. Fermani, M. Calvaresi, M. Harrington, G. Falini ***ACS Biomaterials Science & Engineering*** (2018) 4, 57–65.

OC24

Chemistry, molecular mechanisms and preclinical studies of Gold complexes for ovarian cancer treatment

L. Massai[1], T. Gamberi[2], I. Landini[3], S. Pillozzi[4], S. Gabbiani[5], L. Messori[1]

1. Laboratory of Metals in Medicine, Dept. Chemistry, University of Florence, via della Lastruccia 3, 50019 Sesto Fiorentino, Florence, Italy
2. Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Viale GB Morgagni 50, 50134 Firenze, Italy.
3. Department of Health Sciences, University of Florence, viale Pieraccini, 6 – 50139 Firenze, Italy,
4. Department of Experimental and Clinical Medicine, University of Florence, Viale GB Morgagni 50, 50134 Firenze, Italy.
5. Department of Chemistry and Industrial Chemistry, University of Pisa, via Risorgimento 35, 56126 Pisa, Italy

The basic form of therapy of ovarian cancer, besides surgery, is chemotherapy, usually consisting in a combination of different drugs, usually carboplatin and a member of taxanes. Although ovarian cancer is considered a chemosensitive cancer, drug resistance occurs in most of cases. Thus, there is still a strong need for novel and highly effective drugs for the treatment of advanced epithelial ovarian cancer. Gold complexes form a promising class of anticancer drug candidates, endowed with prominent cytotoxic properties. A panel of gold compounds of potential medical interest was thus built up. Panel compounds were extensively analyzed from the chemical point of view, the solution chemistry and reactivity have been investigated under physiologically relevant conditions and reactions with model proteins were comparatively investigated taking advantage of advanced mass spectrometry methodologies [1].

Then, they were explored for cytotoxic properties against an ovarian cancer (OC) model, (*i.e.* A2780/S and R, where S indicates sensitive and R resistant to cisplatin cells line) and several mechanistic studies, some of which conducted in our laboratory, demonstrated that these compounds possess innovative modes of action, deeply distinct from those of well-known anticancer platinum drugs. [2].

It was possible to establish that some of the investigated gold compounds perturb the mitochondrial functions, trigger ROS production and induce remarkable changes in redox metabolism and glycolysis. These effects are believed to lead (or contribute) to apoptotic cancer cell death. However, rather different mechanistic profiles were delineated for the tested gold compounds in dependence of their specific structural features and reactivity.

As a further and indispensable step in assessing gold complexes as candidate drugs for OC treatment, *in vivo* studies have been carried out on suitable models to establish safety and efficacy. The anticancer activity of better performers, have been investigated in ovarian cancer mouse xenograft models.

References

1. L. Messori, L. Marchetti; L. Massai, F. Scaletti, A. Guerri, I. Landini, S. Nobili; G. Perrone, E. Mini, P. Leoni, M. Pasquali, C. Gabbiani, Inorg.Chem. (2014) 53(5), 2396-2403
2. T. Gamberi, F. Magherini, T. Fiaschi, I. Landini, L. Massai, E. Valocchia, L. Bianchi, L. Bini, C. Gabbiani, S. Nobili, E. Mini, L Messori, A. Modesti. Molecular BioSystem (2015), 11(6),1653-1667.

^{1}H-NMR metabolomic study of SKOV-3 cells, response to the [Pt(*O,O'*-acac)(γ-acac)(DMS)] treatment

OC25

F. De Castro[1], M. Benedetti[1], G. Antonaci[1], L. Del Coco[1], S.A. De Pascali[1], A. Muscella[1], S. Marsigliante[1], F.P. Fanizzi[1]

1. Department of Biological and Environmental Sciences and Technologies - University of Salento, Via Monteroni, I-73100 Lecce, Italy.

NMR-based metabolomic analysis of cells, tissues and biological fluids represents a helpful technique to assess drugs' tumour response and to explore the mechanism of action and resistance of drugs. [1] The novel Pt(II) complex, [Pt(*O,O'*-acac)(γ-acac)(DMS)], $Ptac_2S$, has recently gained increasing attention as potential anticancer agent for its pharmacological activity shown in different *in vitro* cultured tumoral cell lines, and *in vivo*. [2-3] In this work, an ^{1}H NMR metabolomic approach was used to evaluate the pharmacological activity of on Epithelial Ovarian Carcinoma (EOC) *cisplatin* resistant cultured cell line (i.e. SKOV-3 cell line). The multivariate spectroscopic NMR data of both intracellular cell extracts (aqueous and lipidic fractions) and extracellular medium, recover of $Ptac_2S$ treated cells, as made by using chemo-metric and pattern recognition techniques. These metabolic profiles were compared to those of untreated and *cisplatin* treated (at the IC_{50} dose) SKOV-3 cells, following the same cells for a range of culture times (6-24 h) to evidence variations. The multivariate data analysis revealed the ability of the considered complex to act already 6h after treatment. In particular, it was observed a fast decreasing of succinate (a Krebs' cycle intermediate) and phosphocholine (an intermediate in the synthesis of phosphatidylcholine, a major component of biological membranes), with respect to untreated and cisplatin treated cells. Similar effects were observed in *cisplatin* treated cell samples only 24h after treatment. Furthermore, $Ptac_2S$ samples showed a decrease of the relative content of cholesterol, triglycerides and polyunsaturated fatty acids. On the contrary, controls and *cisplatin* treated cells showed an increase of these latter metabolites, which is often associated to proliferation and/or apoptosis phenomena. [4] Finally, the analysis of recovered culture media revealed a preferential release of pyruvate from $Ptac_2S$ treated cells, with respect to the *cisplatin* treated and control cells, characterized by a higher release of lactate. This suggests a possible inhibition of both pyruvate entrance, in the Krebs cycle, and/or pyruvate conversion into lactate. Last condition seems typical of cancer cells (Warburg Effect). [5] In conclusion, these results confirm that $Ptac_2S$ limits the proliferation of cancerous cells with a mechanism very different from that of *cisplatin*.

References

1. Griffin, J.L.; Shockcor, J.P. Metabolic profiles of cancer cells. Nat. Rev. Cancer 2004, 4, 551.
2. De Pascali, S. A.; Papadia, P.; Ciccarese, A.; Pacifico, C.; Fanizzi. F. P. Eur J Inorg Chem, 2005, 788.
3. Muscella, A.; Vetrugno, C.; Biagioni, F.; Calabriso, N.; Calierno, M. T.; Fornai, F.; De Pascali, S. A.; Marsigliante, S.; Fanizzi, F. P. British J. of Pharmacology .2016, 173(17), 2633.
4. Duarte, I. F.; Lamego, I.; Marques, J.; Marques, M. P. M.; Blaise, B. J.; Gil, A. M. Cells. J. Proteome Res. 2010, 9, 5877.
5. Warburg, O.; Wind, F.; Negelein, E. J. Gen. Physiol. 1927, 8, 519.

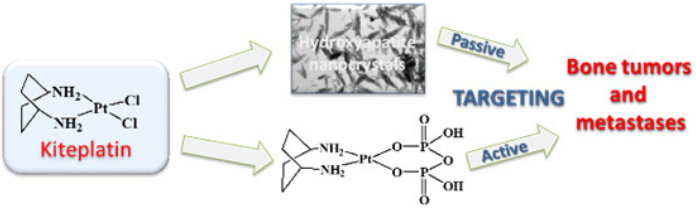
OC26

Kiteplatin-pyrophosphate derivatives targeted to bone tumors and metastases.

N. Margiotta,[1] A. Barbanente,[1] A. Ruello,[1] V. Gandin,[2] C. Marzano,[2] J. D. Hoeschele,[3] G. Natile[1]

1. Dipartimento di Chimica, Università degli Studi di Bari Aldo Moro, Bari (Italy)
2. Dipartimento di Scienze del Farmaco, Università di Padova, Padova (Italy)
3. Department of Chemistry, Eastern Michigan University, Ypsilanti, Michigan, (United States)

Clinically used platinum-based anticancer agents have poor pharmacokinetic profile and un-specific distribution in the body that lead to systemic toxicity. Therefore, the development of antitumor platinum complexes with ligands specific to target the tumor site is highly desirable. In addition, drugs can be preferentially delivered to the tumor by a nanoparticle formulation that can take advantage of the leaky vasculature surrounding the malignant tissue (enhanced permeability and retention effect). In the last decade, we have prepared bone-targeted platinum-bisphosphonate anticancer drugs to be loaded onto inorganic silica xerogels or hydroxyapatite (HA) nanocrystals with the aim of using these matrices for the local treatment of bone tumors.[1] In the present study, we have investigated the adsorption on and the release from biomimetic HA nanocrystals of kiteplatin [$PtCl_2$(*cis*-1,4-DACH)] (DACH = diaminocyclohexane) and of its 1,1-cyclobutanedicarboxylate derivative [Pt(CBDCA)(*cis*-1,4-DACH)]. The release has been studied as a function of pH to mimic the different physiological environments of healthy (including blood) and tumor tissues and the *in vitro* cytotoxicity of the releasates from the HA matrices has been assessed against various human cancer cell lines.[2] As an alternative strategy, active targeting of kiteplatin towards bone tumors has been pursued by preparing its pyrophosphate derivatives that can be activated at the hypoxic and low-pH environment surrounding a tumor mass. The pyrophosphate derivatives of kiteplatin have been tested *in vitro* to assess their cytotoxicity against a panel of human tumor cell lines and to get information on their mechanism of action.



Acknowledgments

We acknowledge the University of Bari (Italy) and the Inter-University Consortium for Research on the Chemistry of Metal Ions in Biological Systems (C.I.R.C.M.S.B.) for support.

References

1. a) Iafisco, M.; Margiotta, N. *J. Inorg. Biochem.* **2012**, *117*, 237–247. b) K. Farbod, K. Sariibrahimoglu, A. Curci, A. Hayrapetyan, J.N.W. Hakvoort, J.J.J.P. van den Beucken; M. Iafisco, N. Margiotta, S.C.G. Leeuwenburgh. *Tissue Eng. - Part A* **2016**, *22*, 788-800.
2. Lelli, M.; Roveri, N.; Marzano, C.; Hoeschele, J. D.; Curci, A.; Margiotta, N.; Gandin, V.; Natile, G. *Dalton Trans.* **2016**, *45*, 13187–13195.
3. a) A. Curci, V. Gandin, C. Marzano, J.D. Hoeschele, G. Natile, N. Margiotta. *Inorg. Chem.* **2017**, *56*, 7482–7493. b) J. Kasparkova, H. Kostrhunova, V. Novohradsky, J. Pracharova, A. Curci, N. Margiotta, G. Natile, V. Brabec. *Dalton Trans.* **2017**, *46*, 14139–14148.

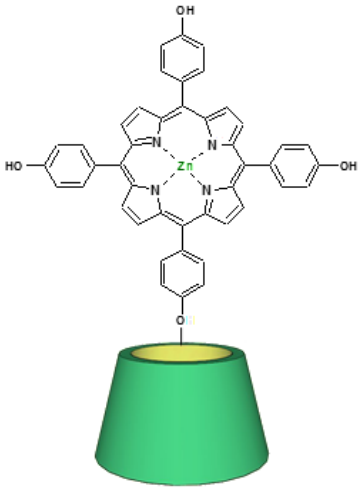
Porphyrin-Cyclodextrin Conjugates Inhibit Aβ aggregation and amyloid induced cytotoxicity

OC27

V. Oliveri[1], S. Zimbone[2], M.L. Giuffrida[2], F.M. Tomasello[2], F. Bellia[2], G. Vecchio[1]

1. Dipartimento di Scienze Chimiche, Università degli Studi di Catania, 95125 – Catania;
2. Istituto di Biostrutture e Bioimmagini, CNR, 95126–Catania;

Aggregation of Amyloid-beta (Aβ) is one of the crucial events occurring during Alzheimer's disease (AD). Preventing or reducing aggregation and cytotoxicity of Aβ is one of the therapeutic strategies under development or in clinical trials. Numerous studies have shown that sugars such as cyclodextrins (CyDs) provide neuroprotection in AD (1). Moreover, we have recently reported that the conjugation of cyclodextrins with chelating aromatic moieties could provide a new avenue to the identification of novel and important modulators of self- and metal-induced Aβ aggregation (2,3,4,5). Herein, we show that a cyclodextrin compound bearing a porphyrin moiety and its zinc complex are effective in inhibiting Aβ cytotoxicity. We tested the ability of the cyclodextrin-porphyrin conjugate (CDTHPP) and its zinc complex (ZnCDTHPP) to affect the toxicity of Aβ oligomers in differentiated neuroblastoma cells (SH-SY5Y). We also studied in parallel the parent compounds of the conjugates, β-cyclodextrin (CD) and 5,10,15,20-tetra(4-hydroxyphenyl)porphyrin (THPP), to demonstrate that the conjugate activity against Aβ toxicity could arise from the synergy of the THPP and CD properties.



Dot Blot analysis, dynamic light scattering and high-performance liquid chromatography-mass spectrometry studies were performed to investigate the nature of the interaction between Aβ and the porphyrin-cyclodextrin conjugates. Finally, we took advantage of the intrinsic fluorescent properties of the derivatives to verify the cell internalization of these systems. Overall, the conjugation with cyclodextrins may be a new avenue for modulating Aβ cytotoxicity.

E-mail valentina.oliveri@unict.it

References

1. Oliveri et al. (2016). Chem.-Asian J., 11, 1648.
2. Oliveri et al. (2013). Chem.-Eur. J., 19, 13946.
3. Oliveri et al. (2014). Chem.-Eur. J., 20, 8954.
4. Oliveri et al. (2015). Chem.-Eur. J., 21, 14047.
5. Oliveri et al. (2017), Chem.-Eur. J., 23, 4442.

OC28

Synthesis, characterization and DNA interactions of trinuclear Platinum(II) complex of the TPymT ligand

D. Cirri[1], T. Marzo[2,1], L. Ciofi[1], C. Gabbiani[2], A. Feis[3], N. Di Pasquale[2], T. Biver[2], L. Messori[1]

1. Laboratory of Metals in Medicine, Department of Chemistry "U. Schiff", University of Florence, Via della Lastruccia 3, 50019 Sesto Fiorentino, Italy
2. Department of Chemistry and Industrial Chemistry, University of Pisa, Via Moruzzi, 13, 56124 Pisa, Italy
3. Department of Chemistry "U. Schiff", University of Florence, Via della Lastruccia 3, 50019 Sesto Fiorentino, Italy

The TPymT ligand has been known for more than 60 years [1] and still appears to be very attractive for its peculiar coordination chemistry properties. Indeed, this ligand has the potential to bind tight three metal ions at three identical sites through a N_3 donor set (Fig.1).

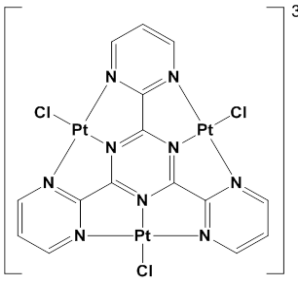


Fig.1

However, only a limited number of studies on this ligand have appeared so far owing to its general unavailability, poor solubility in common solvents, and to the facile hydrolysis of the central triazine fragment; among these, complexes of TPymT with Pb^{2+}, Tl^{+}, UO_2^{2+} and Ag^{+} have been obtained and characterized by Lippard and Murugesu [2,3]. In this frame, of particular interest are the recent results concerning the trisilver complex of TPymT [4].

We noticed that the platinum(II) complex of the TPymT ligand ($Pt_3L_3^{+}$)has not been reported and described so far, either in solution or in the solid state. We argued that this complex might be prepared and characterized quite straightforwardly in analogy to the case of the trisilver complex. Owing to its putative planar structure and to the presence of positive charges, we supposed that $Pt_3L_3^{+}$ might interact strongly with double helix DNA through intercalation. This prompted us to investigate its interactions with DNA through a variety of biophysical methods. However, in contrast with expectations, results point out the occurrence of a non-intercalative binding mode. Indeed, a clear -though moderate- destabilization of the DNA double helix was observed in contrast to the usually large stabilization expected for intercalation.

References

1. F. H. Case and E. Koft, J. Am. Chem. Soc., 1959, 81, 905.
2. E. I. Lerner, S. J. Lippard, Inorg. Chem., 1977, 16, 1537.
3. D. A. Safin, J. M. Frost, M. Murugesu Dalton Trans., 2015, 44, 20287.
4. D. A. Safin, A. Pialat, I. Korobkov, M. Murugesu, Chem. Eur. J., 2015, 21, 6144.

Advanced mass spectrometry tools for cancer research: novel applications in proteomics, metabolomics and nanomedicine

P1

L. Ciofi[1], A. Pratesi[1], T. Marzo[1,2], L. Massai[1], D. Cirri[1], L. Messori[1]

1. Laboratory of Metals in Medicine (MetMed), Department of Chemistry "U. Schiff", University of Florence, Via della Lastruccia 3, 50019 Sesto Fiorentino, Italy
2. Department of Chemistry and Industrial Chemistry (DCCI), University of Pisa, Via Moruzzi, 13, 56124 Pisa, Italy

Cancer research is becoming increasingly multidisciplinary. Its complex structural, functional and therapeutic problems require several complementary methods including biochemical manipulations, chromatographic or electrophoretic separations, sequencing strategies, and the use of biophysical and bioanalytical methods.

High resolution mass spectrometry (HRMS) represents an essential tool in current biological and molecular research. The high resolving power of modern instrumentation represents a very powerful and versatile analytical tool. The application field of HRMS ranges from the simultaneous determination of the elemental compositions of thousands of small molecules to the identification of proteins from proteolytic peptides, up to the characterization of large molecules, such as intact protein (including posttranslational modifications).

Moreover, thanks to its high sensitivity and selectivity, HRMS plays a particularly important role in the emerging "omics" sciences, being capable to detect subtle changes in the cellular proteomes and metabolomes.

So far, the instrumentation already available to our research group allowed characterizing the interactions between candidate metallodrugs and small model proteins (such as lysozyme, ribonuclease and cytochrome) or small oligopeptide fragments. The recent acquisition of a hybrid Q-TOF high resolution mass spectrometer coupled to a microLC system will allow for the molecular characterization of adducts formed between metallodrugs and a variety of proteins of greater complexity (such as serum albumins, transferrin, ferritins), as well as to perform metabolomics measurements complementary to NMR measurements.

P2

Gd(III)-complex derivatives of aromatic oligopeptides as novel supramolecular MRI contrast agents

C. Diaferia[1], G. Morelli[1], E. Gianolio[2], A. Accardo[1]

1. Department of Pharmacy, Research Centre on Bioactive Peptides (CIRPeB), University of Naples "Federico II" Via Mezzocannone 16, 80134 Naples (Italy)
2. Department of Molecular Biotechnologies and Health Science, University of Turin, Via Nizza 52, 10125, Turin (Italy)

Supramolecular contrast agents (CAs) can be prepared for self-assembling of a monomeric units containing two different portions: i) a chelating agent able to allow kinetically and thermodynamically stable coordination of paramagnetic metal ions (like Gd^{3+} for T1 positive CAs) for diagnostic applications in MRI, ii) a hydrophobic portion (one or more alkyl chains or a peptide sequence) able to prompt the self-assembling in water.[1] Due to the well-known capability of the diphenylalnine and of its strictly related derivatives (FFF, FFFF, Fmoc-FF, Boc-FF) to self-assemble in a large variety of supramolecular nanostructured materials,[2] FF sequence can be used as hydrophobic portion to prepare supramolecular CAs. Gd-complex can be alternatively positioned at the end or at the center of the aromatic framework. The water solubility can be improved by insertion of PEG moiety of different length. FF derivatization with Gd-complexes causes a drastic decrease of the self-assembling capability. The elongation of the aromatic framework[3] and/or the replacement of Phe with others non-coded amino acids,[4] having a more extended aromatic side chain (eg: naphthylalanine), are two possible strategies to restore monomer interactions.

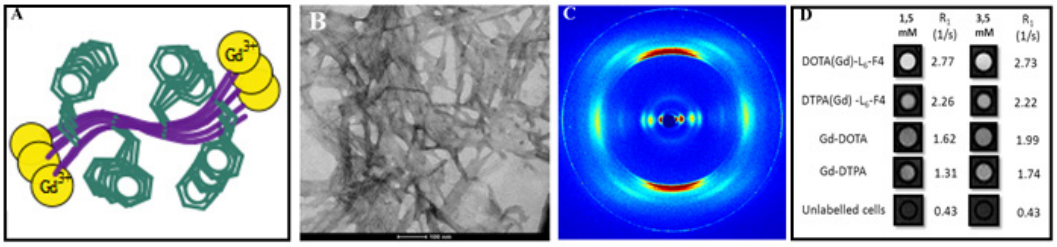


Figure 1: A) Schematic representation of a supramolecular CA based on tetra-phenylalanine Gd-conjugate, B) TEM image of self-assembled Gd(III)-derivative; C) WAXS diffraction pattern acquired on the solid fiber and D) T1-weighted images and observed relaxation rates of pellets of cells.

References

1. A. Accardo, D. Tesauro, L. Aloj, C. Pedone, G. Morelli, ***Coord. Chem. Rev*** **2009**, 253, 2193-2213.
2. X. Yan, P. Zhu, J. Li, ***Chem. Soc. Rev*** **2009**, 39 ,1877-1890.
3. C. Diaferia, E. Gianolio, P. Palladino, F. Arena, C. Boffa, G. Morelli, A. Accardo, ***Adv. Funct. Mater.*** **2015**, 25, 7003-7016.
4. C. Diaferia, E. Gianolio, T. Sibillano, F.A. Mercurio, M. Leone, C. Giannini, N. Balasco, L. Vitagliano,
5. G. Morelli, A. Accardo, ***Sci. Rep.*****2017**, 7, 307.

Toward personalized medicine: RGD-peptide as scaffold for the comprehension of structural determinants for integrin specific recognition

P3

L. Zaccaro[1,2], A. Del Gatto[1,2], L. Russo[3], B. Farina[4], G. Malgieri[3], S. Di Gaetano[1,2], D. Capasso[5], D. Comegna[1], R. Fattorusso[3], M. Saviano[2,6]

1. Institute of Biostructures and Bioimaging-CNR, Via Mezzocannone 16, 80134, Naples, Italy
2. CIRPeB, University of Naples Federico II, Via Mezzocannone 16, 80134 Naples, Italy
3. Department of Environmental, Biological and Pharmaceutical Science and Technology, University of Campania - Luigi Vanvitelli, via Vivaldi 43, 81100 Caserta, Italy
4. Advanced Accelerator Applications, via Vivaldi 43, 81100 Caserta, Italy
5. Department of Pharmacy, University of Naples Federico II, Via Mezzocannone 16, 80134 Naples, Italy
6. Institute of Crystallography-CNR, Via Amendola 122/O, 70126 Bari, Italy

In the past decades the scientific community has focused the attention mainly on a_vb_3, $a_v\beta_5$, and α_5b_1 integrins due to their relevance in tumor vascularization and metastasis (1), in wound healing acceleration, drug resistance and tumor recurrence in different types of solid cancers, as well as in hematological malignancies. Unfortunately, the precise roles in pathological angiogenesis and in tumor progression of these proteins, alone or combined with other integrins, are not yet fully understood and thus the availability of integrin sub-type-exclusive antagonists is highly desirable. The majority of the ligands described so far as selective agents have residual, yet significant, affinity for the other integrins, thus stimulating extensive research to develop novel integrin specific molecules.
Over the last decade we developed the selective peptide RGDechi, a chimeric molecule encompassing a cyclic portion containing the RGD triade for integrin binding and a linear sequence for the b_3 subunit specificity (2). We demonstrated anti-adhesive and pro-apoptotic effects on tumor cells and antiangiogenic activity in vivo (3,4). SPECT, PET and optical imaging studies in xenograft models confirmed the ability of RGDechi peptide to selectively visualize this integrin (5,6). NMR and computational analyses on cell membranes allowed us to understand the a_vb_3/RGDechi recognition mechanism (7), and consequently prompted us to use RGDechi for its bifunctional nature as scaffold to elucidate the molecular determinants to drive the selectivity toward $a_v\beta_5$ or α_5b_1 integrins.

References

1. Ganguly, K. K., Pal, S., Moulik, S., Chatterjee, A., Cell adhesion & migration, 7, 251-261 (2013)
2. Del Gatto A., Zaccaro L., Grieco P., Novellino E., Zannetti A., Del Vecchio S., Iommelli F., Salvatore M., Pedone C., Saviano M. J Med Chem 49, 3416-3420, doi:10.1021/jm060233m (2006).
3. Capasso, D., de Paola, I., Liguoro, A., Del Gatto, A., Di Gaetano, S., Guarnieri, D., Saviano, M., Zaccaro, L. PLoS One, 9, e106441 (2014). doi: 10.1371/journal.pone.0106441
4. Santulli G., Basilicata M.F., De Simone M., Del Giudice C., Anastasio A., Sorriento D., Saviano M., Del Gatto A., Trimarco B., Pedone C., Zaccaro L., Iaccarino G. J Transl Med 9, 7, doi:10.1186/1479-5876-9-7 (2011).
5. Zannetti A., Del Vecchio S., Iommelli F.,. Del Gatto A, De Luca S., Zaccaro L., A. Papaccioli, Sommella J., M. Panico, Speranza A., Grieco P., Novellino E., Saviano M., Pedone C. and Salvatore M., Clin Cancer Res 15, 5224-5233, doi:10.1158/1078-0432. CCR-08-3270 (2009).
6. Comegna D, Zannetti A, Del Gatto A, de Paola I, Russo L, Di Gaetano S, Liguoro A, Capasso D, Saviano M, Zaccaro L. "Chemical modification for proteolytic stabilization of the selective αvβ3 integrin RGDechi peptide: in vitro and in vivo activities on malignant melanoma cells". J Med Chem. 2017 Nov 16. doi: 10.1021/acs.jmedchem.7b01590.
7. Farina B., de Paola I., Russo L., Capasso D., Liguoro A., Del Gatto A., Saviano M., Pedone P.V., Di Gaetano S., Malgieri G., Zaccaro L, Fattorusso R. A Combined NMR and Computational Approach to Determine the RGDechi-hCit-αv β3 Integrin Recognition Mode in Isolated Cell Membranes. Chemistry. 22, 681-93 doi: 10.1002/chem.201503126 (2016).

P4

New designed bifunctional peptides modulate Cu(II)-induced amyloidogenicity and redox activity of Amyloid beta peptide

F. Attanasio[1], D. Campisi[1], I. Monaco[1], M.F.M. Sciacca[1], C. Satriano[2], M.F. Tomasello[2]

1. Istituto di Biostrutture e Bioimmagini (IBB-CNR), via P.Gaifami 18, 95126, Catania
2. Dipartimento di Scienze Chimiche, Università di Catania, V.le A. Doria 6, 95125 Catania

Objectives: There is a general consensus that the copper ions participate in two processes related to AD pathology: accelerating amyloid-β (Aβ) aggregation and catalyzing the production of neurotoxic reactive oxygen species (ROS). Here we report the inhibition of copper catalyzed oxidation of Aβ peptide and the modulation of the copper- induced Aβ aggregation by Semax, a synthetic analog of $ACTH_{4-10}$, and two new designed bifunctional peptides, that combine the known beta-breaker properties of the oligomerization inhibitors KLVFF and LPFFD with the chelating and redox silencing ability of Semax.

Methods: The inhibitory effect of Semax and its derivatives on Aβ aggregation, ROS production and cytotoxicity with and without copper was assessed by thioflavin T (ThT) fluorescence assay, Atomic Force Microscopy, coumarin-3-carboxilic acid (CCA) fluorescence assay for *cell free* experiments. For *in cell* experiments, human neuroblastoma SH-SY5Y were exposed to stress generated by a mixture of copper and ascorbic acid, Aβ-Cu(II) and ascorbic acid, Aβ, Aβ and copper and the inhibitory effect of the peptides were assessed by MTT and flow cytometry assay.

Results: Semax and its bifunctional derivative peptides were able to quench ROS generation mediated by Cu(II)/ascorbate and Aβ-Cu(II)/ascorbate either in the *cell-free* system or in cultured neuroblastoma cell line. Furthermore, the bifunctional peptides had nearly identical efficacy to inhibit copper-induced Aβ aggregation and cytotoxicity

Conclusions: Semax and its bifunctional derivative peptides modulate copper-induced Aβ cytotoxicity by limiting ROS production and inhibiting aggregation. Overall, these molecules may be a promising therapeutic drug for AD.

Tau-peptide fragments and their copper(II) complexes: effects on amyloid-β aggregation.§

P5

G. Pappalardo, G. Di Natale, F. Bellia, M.F.M. Sciacca, T. Campagna

CNR-Institute of Biostructures and Bioimaging, Catania Via Paolo Gaifami 18, 95126 Catania, Italy

Recent studies suggest that the interaction of Aβ and Tau may be significant in the pathogenesis of Alzheimer's diseases (AD). In addition, the potential influence of copper on Tau-related pathology in AD has not been previously addressed and the interaction between Tau protein, Aβ and copper has even more recently been associated with AD.[1] While the copper(II) interaction with the Aβ peptide has exhaustively been studied, the few studies carried out on copper(II) complexes with peptide fragments from Tau protein have been focused on the pseudo-repeats of Tau protein in the microtubule-binding region. No data have been reported about the metal complexes with peptides derived from the N-terminal portion of Tau protein, outside the microtubule-binding domain, despite increased levels of peptide fragments from this region have been detected in the Cerebrospinal fluid (CSF) of AD patients.[2] Here we examine the interaction of two peptides fragments, encompassing the 1–25 or 26–44 residues of the human Tau protein sequence, with Aβ as well as the Cu^{2+}-binding features of these two naturally occurring peptides. The CD experiments showed that copper(II) differently affects the peptide conformation of the two ligands and provided also insight into the donor atoms involved in metal coordination. Stoichiometry of copper(II) complexes was obtained by means of High resolution ESI-MS. Finally, the influence of the studied peptide on Aβ's fibrillogenesis, either in the presence or absence of Cu^{2+}, was investigated by means of Th-T fluorescence coupled with turbidimetric measurements. The observed different effect on the in vitro Aβ's aggregation, was correlated with the affinity of copper(II) with the two peptide ligands. The overall results indicate that copper(II) can bind these peptides using the histidine residue or amino group as anchoring sites and that copper(II) binding may have a possible involvement in AD.

§ Inorg. Chim. Acta. In press, doi: 10.1016/j.ica.2017.09.061.

References

1. L.M. Sayre, G. Perry, P.L. Harris, Y. Liu, K.A. Schubert, M.A. Smith, J. Neurochem. 74 (2000) 270–279.
2. N.R. Barthélemy, A. Gabelle, C. Hirtz, F. Fenaille, N. Sergeant, S. Schraen-Maschke, J. Vialaret, L. Buée, C. Junot, F. Becher, S. Lehmann, J. Alzheimers Dis. 51 (2016) 1033–1043.

P6

Peptide-based-fluorescent chemosensors for Hg^{2+} detection in Water

A. Caporale[1,2] , A. Aliberti[3], P. Vaiano[3], M. Consales[3], A. Cusano[3] , M. Ruvo[1, 2]

1. Institute of Biostructure and Bioimaging, National Research Council, I-80143 Naples, Italy
2. Interuniversity Research Centre on Bioactive Peptides (CIRPeB), University "Federico II", Naples, Italy
3. Optoelectronics Group, Department of Engineering, University of Sannio, I-82100 Benevento, Italy

Water contamination by heavy metals, such as mercury, is an ever increasing emergency for the environment and human health. The presence of metal ions in water can be revealed by several analytical methods, however the availability of inexpensive and sensitive chemosensors that alert on their presence would represent an important step for on-site quick detections. Recently, we described the design, synthesis and spectral characterization of a set of dansyl-amino acids able to recognize Hg^{2+} ions via different fluorescence emission modes. [1]. Here, we present the design, synthesis and spectral characterization of a set of small peptide-based chemosensors for Hg^{2+} that exploit the intrinsic fluorescence of tryptophan (Trp) and take advantage of the previous study. Peptides have been therefore designed in order to contain acetamidomethylated cysteine, Cys(Acm), and methionine as complexing units for Hg^{2+} and a tryptophan as a fluorescence sensor responsive to the chemical events on its surrounds. Measurements of intrinsic fluorescence emissions in the presence of different amounts of Hg^{2+} ion indicate that a very small peptide containing two Cys(Acm) and a Trp in the middle is the most sensitive and specific probe for the detection of the metal.

References

1. Aliberti A., Vaiano P., Caporale A., Consales M., Ruvo M., Cusano A., ***Sensors and Actuators B: Chemical***, 247, **2017**, 727-735

Hydrophilic gold nanoparticles and nanorods as drug delivery systems for anticancer copper complexes

P7

I. Venditti[1], M. Porchia[2], F. Tisato[2], C. Santini[3], M. Pellei[3], I Fratoddi[4], G. Testa[4], G. Iucci[1], V. Secchi[1], C. Battocchio[1]

1. Department of Sciences, University of Rome TRE, Italy
2. ICMATE, National Research Council (CNR), Padua, Italy
3. School of Science and Technology, University of Camerino, Italy
4. Department of Chemistry, Sapienza University of Rome, Italy

Gold nanoparticles and nanorods (AuNPs, AuNRs) are widely applied for biomedical uses such as imaging/diagnostic tools, drug and gene delivery, photothermal therapy, sensors, and biotechnologies.[1-3] Their success is due to their unique chemical and physical properties, biocompatibility, and well-established strategies for surface modification. In this framework we report a study about drug delivery systems based on functionalized AuNPs or AuNRs. These nanomaterials are optimized to increase the hydrophilia of the drug delivery systems and improve the bioavailability of the water insoluble drugs. AuNPs (Figure 1) and AuNRs were synthesized using hydrophilic thiols as capping agents in several molar ratios Au/S (1/1;1/2;1/4). The nanosystems were characterized by means of several spectroscopic techniques (Uv-visible, FTIR, XPS) and by DLS, confirming their nanodimension and the surface functionalizations. The AuNPs were tested as carrier for Cu(I) and Cu(II) complexes. [4] Depth studies were performed to improve the drug loading on AuNPs (loading efficiency 80%) and the stability of the conjugate systems. Moreover preliminary release studies show a slow release in PBS. These results open new exciting perspectives in the field of "*in vitro*" and "*in vivo*" studies.

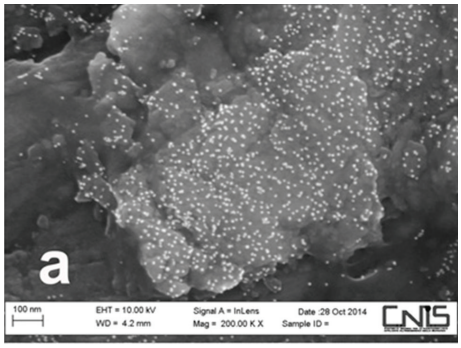


Figure 1. FESEM image of functionalized gold nanoparticle (Ø~ 7 nm)

References

1. I. Fratoddi, et al., Nano Research 2015, 8, 1771-1799
2. K. Park, et al., ACS Appl. Mater. Interfaces 2017, 9, 26363−26371
3. I. Venditti, et al., Colloids and Surfaces B: Biointerfaces 2015, 131, 93
4. V. Gandin, et al., J. Med. Chem. 2014, 57, 4745

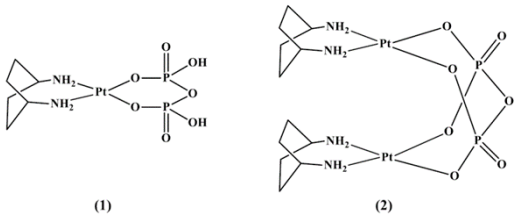
P8

Delivery of Kiteplatin-pyrophosphate antitumor complexes by hydroxyapatite nanocrystals

A. Barbanente[1], N. Margiotta[1], A. Curci[1], G. Natile[1], R. A. Nadar[2], J. J.J.P. van den Beucken[2], S. C.G. Leeuwenburgh[3]

1. Dipartimento di Chimica. Università degli Studi di Bari Aldo Moro. Bari (Italy);
2. Department of Biomaterials. Radboud University Medical Center. Nijmegen (The Netherlands).

Bone cancer has a high morbidity and is responsible for disorders in bone homeostasis, which causes uncontrolled bone formation or resorption. In addition, bone is the most common tissue affected by metastatic cancer such as prostate or breast cancer. Treatment of bone tumors may include surgery, chemotherapy and/or radiotherapy.[1] However, surgical treatment, such as tumor resection, does not prevent tumor recurrence and is associated with a high risk of spreading tumor cells. In addition, the surgical resection is often intolerable for patients with comorbid conditions and limited life expectancy. Systemic antitumor chemotherapy is not specific for cancer cells and leads to severe side-effects such as nephrotoxicity or neurotoxicity. In the case of bone tumors and metastases, the above-mentioned drawbacks can be overcome by drug delivery of cytostatic drugs from locally implanted bone substitute biomaterials. Local target delivery of chemotherapeutics would allow efficient delivery of anticancer drugs at the tumor site (after bone resection) and minimize toxic side effects. For this purpose, novel biomaterials that are able to generate a local release of chemotherapeutic drugs in a controlled and sustained manner, are strongly required. In this study, we focus on the adsorption and release behavior of novel platinum-based anticancer drugs (Kiteplatin-pyrophosphate complexes[2] reported in Figure) from hydroxyapatite (HA) nanoparticles. Two type of HA nanoparticles were used: platelet-shaped HA (HAps) and needle-shaped HA (HAns). The release of the platinum complexes **1** and **2** was investigated at different pH values that mimic the pH of healthy tissues (pH 7.4) and tumors (pH 5-6). Moreover, in order to evaluate the cytostatic efficacy of the drug releasates from the matrices at different pH and free kiteplatin-pyrophosphate complexes, human prostate cancer cells (PC3) were used in *in vitro* assays.



(1) (2)

Acknowledgments

We acknowledge the University of Bari (Italy) and the Inter-University Consortium for Research on the Chemistry of Metal Ions in Biological Systems (C.I.R.C.M.S.B.) for support.

References

1. Malawer M.M., Helman L.J., ***et al***. Sarcomas of Bone, in Cancer: Principles and Practice of Oncology, DeVita, V.T., Hellman, S., Rosenberg, S.A. (Eds.), (9th Ed.). Philadelphia **2011**, 1578–1609.
2. a) A. Curci, V. Gandin, C. Marzano, J.D. Hoeschele, G. Natile, N. Margiotta. ***Inorg. Chem.*** **2017**, *56*, 7482–7493. b) J. Kasparkova, H. Kostrhunova, V. Novohradsky, J. Pracharova, A. Curci, N. Margiotta, G. Natile, V. Brabec. ***Dalton Trans.*** **2017**, *46*, 14139–14148.

Mass spectrometry as powerful approach to characterize the binding of metal-based drugs to biological targets. From a general protocol to specific applications.

P9

A. Pratesi[1], T. Marzo[1,2], D. Cirri[1], L. Massai[1], E. Michelucci[3], L. Ciofi[1], L. Messori[1]

1. Laboratory of Metals in Medicine (MetMed), Department of Chemistry "U. Schiff", University of Florence, Via della Lastruccia 3, 50019 Sesto Fiorentino, Italy.
2. Department of Chemistry and Industrial Chemistry, University of Pisa, Via Moruzzi 13, 56124 Pisa, Italy.
3. Mass Spectrometry Center (CISM), University of Florence, via Ugo Schiff 6, 50019 Sesto Fiorentino, Italy.

Owing to their growing importance in anticancer chemotherapeutic strategies, there is today a general consensus on the need to elucidate the mechanism of action of metal based drugs at the molecular level in such a way to rationally design novel and better anticancer metallodrugs through the so called "mechanism oriented" approach. In general, DNA is considered as the primary target for cisplatin and its close analogues[1] while proteins appear to play crucial roles in the transport, uptake, excretion, biodistribution, toxicity profile and resistance phenomena related to Pt drugs themselves. Even more interesting, proteins are involved in crucial aspects of the mode of action of various non-platinum anticancer agents, like ruthenium or gold complexes[2].

MS represents today a fast, sensitive, specific and high-throughput tool for the analysis of bio-molecules; in particular, electrospray ionization mass spectrometry (ESI-MS) potentially provides a wealth of structural and functional information mainly due to its non-destructive nature that even preserves non-covalent interactions. Yet, the stability of metal-protein coordination bonds may be a critical issue. This led us to build up a general protocol to test metallodrug-protein adduct stability under the typical conditions of the filter-aided sample preparation (FASP)/bottom-up procedure, ranging from the analysis of solutions containing metal-protein adducts to tandem mass spectrometry experiments[3].

Through this protocol we achieved strong evidences in the mode-of-action of oxaliplatin and its halido-derivatives highlighting the structurally-related reactivity for these metal complexes[4].

Now, the availability in our lab of a new high-resolution Sciex Triple TOF 5600$^+$ with M3 microLC and equipped with SWATH® analysis software, will open the way to a more precise, powerful and reliable proteomic and metabolomic research even in complex matrices or in real biological samples.

References

1. V. Brabec; Prog. Nucleic Acid Res. Mol. Biol., 2002, 71, 1–68.
2. P.J. Dyson et al.; Dalton Trans., 2006, 1929–1933.
3. E. Michelucci et al.; Talanta, 2017, 167, 30–38.
4. D. Cirri et al.; Dalton Trans., 2017, 46, 3311–3317.

P10

Polydopamine-functionalized superparamagnetic clusters as potential magnetic carriers for delivery of Platinum anticancer drugs

M. Benedetti[1], G. Mandriota[2], F. De Castro[1], R. Di Corato[2], F. P. Fanizzi[1], R. Rinaldi[2,3]

1. Dip. di Scienze e Tecnologie Biologiche ed Ambientali, Università del Salento, Via Monteroni, I-73100 Lecce, Italy. e-mail: michele.benedetti@unisalento.it
2. Dip. di Matematica e Fisica "Ennio De Giorgi", Università del Salento, Via Arnesano, Lecce, Italy.
3. S.S. ISUFI, Università del Salento, Via Arnesano, Lecce, Italy

One of the major challenges of antitumor drugs delivery is the development of suitable carriers for therapeutic molecules [1,2]. Superparamagnetic iron oxide nanoparticles (SPIONs) are promising magnetic drug carriers as they are biocompatible, biodegradable, readily tunable in size and shape, and controllable by external magnetic fields [3,4].

We propose and demonstrate the possible synthesis of bioinspired polydopamine-functionalized superparamagnetic clusters (MNC@PDO) to be applied to the anticancer drug *cisplatin* [*cis*-dichloro-diammino-platinum(II), CDDP] loading and delivery processes. For these specific nanosystems the drug release capacity has been tested. In this context, the first synthetic step is based on an oil-phase evaporation-induced self-assembly strategy, to fabricate the magnetic nanocrystal clusters (MNC). We demonstrated that for the choice of the best size and volume of SPIONs, the adopted solvent and the surfactant concentration are very important parameters. With this strategy, we can produce nanoclusters with a high density of magnetic cores, a size comprised between 90 and 100 nm, and a multilayer structure. Secondly, the surface of the MNCs was functionalized with polydopamine (PDO) for improving their stability, moreover different concentrations of dopamine were assayed to determine the best compromise between stability of the clusters and loading capacity. Finally, the CDDP was grafted to the surface of stable MNC@PDO systems (MNC@PDO-CDDP), studying its release efficiency from these nanoparticles. The MNC@PDO systems reveal to be promising models for the uptake and specific tissue delivery of chemotherapeutic drugs, in antitumor therapy. Moreover, the MNC@PDO nanosytems show a pH-responsive behaviour of great significance in controlled drug delivery and targeting of specific sites.

References

1. Thakor, A. S., & Gambhir, S. S. (2013). Nanooncology: The Future of Cancer Diagnosis and Therapy. *Ca Cancer J Clin*, 395–418.
2. Huang, J., Li, Y., Orza, A., Lu, Q., Guo, P., Wang, L., Mao, H. (2016). Magnetic Nanoparticle Facilitated Drug Delivery for Cancer Therapy with Targeted and Image-Guided Approaches. *Adv. Funct. Mater.*, 3818–3836.
3. Lim, E.-K., Kim, T., Paik, S., Haam, S., Huh, Y.-M., & Lee, K. (2014). Nanomaterials for Theranostics: Recent Advances and Future Challenges. *Chemical Reviews*, 327–394.
4. Thakor, A. S., & Gambhir, S. S. (2013). Nanooncology: The Future of Cancer Diagnosis and Therapy. *Ca Cancer J Clin*, 395–418.

In vitro evaluation of clofibric acid-Pt(IV) dual-action anticancer "combos"

P11

M. Ravera[1], E. Gabano[1], I. Zanellato[1], M. B. Gariboldi[2], E. Monti[2], D. Osella[1]

1. Dipartimento di Scienze e Innovazione Tecnologica, Università del Piemonte Orientale, Viale Michel 11, 15121 Alessandria, Italy. E-mail: mauro.ravera@uniupo.it
2. Dipartimento di Biotecnologie e Scienze della Vita, Università dell'Insubria, Via Manara 7, 21052 Busto Arsizio (VA), Italy.

Multi-action cisplatin-based mono- (**1**, Figure 1) and di-clofibric acid (**2**) Pt(IV) derivatives were synthesized *via* both traditional and microwave assisted procedures. The two complexes offered good performance (IC_{50} values in nanomolar range, see Table 1 for some examples) on a panel of human tumor cell lines, including the highly chemoresistant malignant pleural mesothelioma ones. Moreover, both **1** and **2** bypass the cisplatin resistance. Indeed, cisplatin and clofibric acid, the metabolites of the Pt(IV)-Pt(II) intracellular reduction, proved to act synergistically. The adjuvant action of clofibric acid relies on activation of peroxisome proliferator-activated receptor α (PPARα) as testified by the upregulation of its target genes. Both compounds induced extensive apoptosis in tumor cells, and, finally, **2** exhibited good performances also under the hypoxic conditions typical of solid tumors, where cisplatin is less effective.

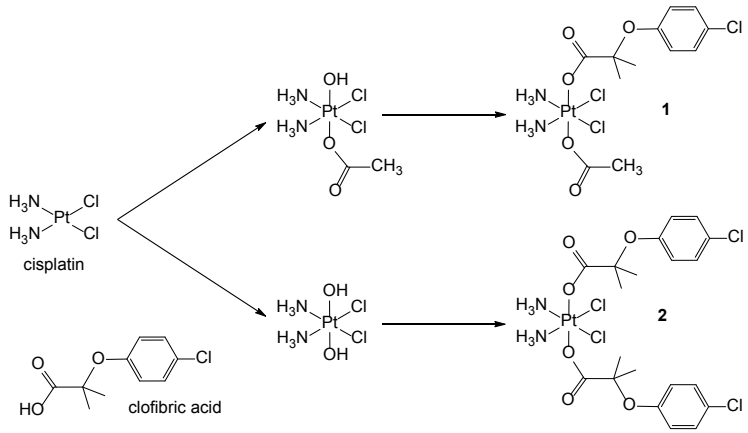


Figure 1. Synthetic pathways for the clofibrato-containing Pt(IV) compounds **1** and **2**.

Cell lines	IC_{50} [μM]		
	cisplatin	**1**	**2**
ovarian carcinoma A2780	0.46 ± 0.11	0.081 ± 0.006	0.028 ± 0.006
testicular carcinoma NT2/D1	0.11 ± 0.05	0.031 ± 0.002	0.022 ± 0.008

Table 1. Antiproliferative data (IC_{50}) of cisplatin and Pt(IV) complexes **1**-**2**.

P12

Anticancer activity of a new Pt(IV)-based prodrug releasing cisplatin and a novel HDAC inhibitor in B50 neuroblastoma rat cell line.

B. Rangone[1], B. Ferrari[2], V. Astesana[2], I. Masiello[2], P. Veneroni[2], I. Zanellato[1], M. G. Bottone[2], D. Osella[1]

1. Dipartimento di Scienze e Innovazione Tecnologica, Università del Piemonte Orientale, viale Teresa Michel 11, 15121 Alessandria, Italy.
2. Dipartimento di Biologia e Biotecnologie "L. Spallanzani", Università di Pavia, via Ferrata 9, 27100, Pavia, Italy.

Neuroblastoma is a rare cancer that affects children, mostly under the age of 5. To date the Pt(II)-based drug cisplatin, an important DNA-damaging chemotherapeutic agent, represents one of its therapeutic options. However, the onset of systemic side effects, the induction of drug resistance, and the poor pharmacokinetic profile limit its use. In recent years, in order to overcome these limits, research has moved towards new Pt(IV)-based complexes, that act as prodrugs, because they are activated by reduction within hypoxic cancer milieu [1]. Reduced Pt(IV) species release the corresponding Pt(II) complex and two axial ligands. These ligands can be bioactive molecule *per se*, providing a synergistic antineoplastic activity with Pt(II) drug [2]. On the other side, Histone deacetylases (HDAC) represent a promising target to increase the efficacy of neuroblastoma chemotherapy. Thus, a new cisplatin-based Pt(IV) prodrug, containing an inert acetato and the bioactive 2-(2-propynyl)octanoato (POA) as axial ligands was tested on B50 neuroblastoma rat cells. POA is a potent HDAC inhibitor superior to valproic acid (VPA). The Pt(IV)Ac-POA treatment induced apoptosis and other different cell death pathways at a concentration several times lower than cisplatin (*Fig. 1*). Cell death was assessed by means of immunohistochemistry, transmission electron microscopy and flow cytometry. The results showed that Pt(IV)Ac-POA could represent a promising alternative to cisplatin for neuroblastoma chemotherapy.

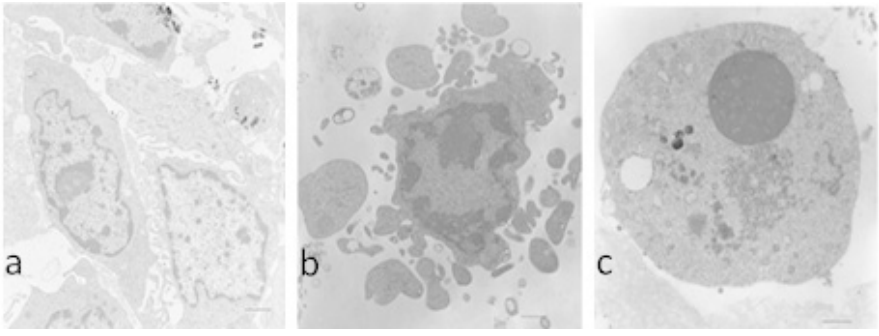


Figure 1 Ultrastructural morphology of: **a**) control cells, **b**) cells after cisplatin 40 µM 48h CT and **c**) cells after Pt(IV)Ac-POA 4 µM 48h CT. Bar 1.1 µM.

References

1. T.C Johnstone, K. Suntharalingam, S.J. Lippard, Chem Rev, 2016, 116 ,3436-3486.
2. E. Gabano, M. Ravera, D. Osella, Dalton Trans, 2014, 43, 9813-9820.

Antibacterial and antitumoral activities of new organotin(IV)-Shiff bases derivatives

P13

M. Scopelliti[3], F. Amato[1], R. Alduina[2], P. Cancemi[2], S. Rubino[2]

1. Dipartimento di Scienze Chimiche e Farmaceutiche (DSCF), Università degli Studi di Trieste
2. Dipartimento di Scienze e Tecnologie Biologiche Chimiche e Farmaceutiche (SteBiCeF), Università degli Studi di Palermo
3. Dipartimento di Fisica e Chimica (DiFC), Università degli Studi di Palermo

This preliminary report shows eight complexes of triorganotin(IV): Ph_3SnOH and $(CH_3)_3SnOH$ with four chelating imines on new synthesis. Of these ligands, two are salen-like (four coordination sites, two imidic, two phenoxidic) [1], one is a tetradentate pyrrole derivative [2] while the fourth, a vitamin B_6 derivative, is pentadentate [3].

Ligands have been characterized by means of FT-IR, UV-Vis, Fluorescence, ^{1}H- and ^{13}C-NMR, LC-MS ESI triple quadrupole; complexes by means FT-IR, ^{1}H- and ^{119}Sn-NMR, LC-MS ESI, using the isotopic distribution pattern as a discriminant [4].

Geometry and nature of coordination complexes have been also evaluated using the ^{119}Sn chemical shifts.

Solid-state synthesis of the complexes (with a ball mill [5]) was also explored; such method reduces both solvent consumption and time – from 8-10 h under controlled atmosphere to about 1 h, with results identical to the wet synthesis.

Antitumoral and antibacterial activities of the triorganotin (IV) complexes (BS01M, BS01P, BS02M, BS02P, BS03M, BS03P, BS04M, BS04P) were tested *in vitro*. In both analyses, the Shiff bases alone showed no biological activity.

Antimicrobial activity was evaluated by Kirby-Bauer method against the Gram-negative *Escherichia coli*, and the two Gram-positive *Kocuria rizophila* and *Staphylococcus aureus* strains.

All the ML_2 complexes were active in inhibiting bacterial growth, with BS02P and BS03P showing the best antibacterial performance. Among the ML complexes, BS01M was not active, BS02M showed a weak antibacterial activity only against the Gram-positive bacteria, BS04M was mainly active against the Gram-negative *E. coli* and BS03M was active against all the tested strains.

Antitumor activity was evaluated by MTT assay against cervical (HeLa), colon adenocarcinoma (HT-29) and breast (MDA-MB231) cancer cell lines. Results showed that ML_2 complexes are more active than ML ones, with HeLa cells more sensitive to treatments.

These complexes (especially the ML_2) showed promising results; their mechanism of action is under investigation.

References

1. K. Tayade, S.K. Sahoo, S. Chopra, N. Singh, ***Inorganica Chimica Acta***, 421, 538-543 (2014); https://doi.org/10.1016/j.ica.2014.05.014
2. S. Meghdadi, M. Amirnasr, K. Mereiter, ***Polyhedron***, 30, 1651-1656 (2011); https://doi.org/10.1016/j.poly.2011.03.041
3. D. Sharma, S.K. Sahoo, S. Chaudhary, R. Kanta Bera, J.F. Callan, ***Analyst***, 138, 3646-3650 (2013); https://doi.org/10.1039/C3AN00199G
4. G. Lawson, R.H. Dahm, N. Ostah, E.D. Woodland, ***Applied Organometallic Chemistry***, 10, 125-133 (1996); https://doi.org/10.1002/(SICI)1099-0739(199603)10:2<125::AID-AOC491>3.0.CO;2-1
5. G.A. Bowmaker, ***Chemical Communications***, 49, 334-348 (2013); http://doi.org/10.1039/C2CC35694E
6. R. Di Stefano, M. Scopelliti, C. Pellerito, G. Casella, T. Fiore, G.C. Stocco, R. Vitturi, L. Ronconi, I.D. Sciacca, L. Pellerito, ***Journal of Inorganic Biochemistry***, 98, 534-546 (2004); https://doi.org/10.1016/j.jinorgbio.2003.12.013
7. C. Pellerito, L. Nagy, L. Pellerito, A. Szorcsik, ***Journal of Organometallic Chemistry***, 691, 1733-1747 (2006); https://doi.org/10.1016/j.jorganchem.2005.12.025

P14

The “Aflatox” database: a tool for QSAR studies and for the development of new antifungal and anti-aflatoxigenic compounds

G. Pelosi[1], M. Pioli[1], F. Bisceglie[1], N. Orsoni[1], J. Bartoli[1], A. Buschini[1], M. Carcelli[1], F. Degola[1], F. M. Restivo[1], D. Rogolino[1], C. Zani[2], D. Feretti[2]

1. Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma.
2. Department of Medical and Surgical Specialities, Radiological Sciences and Public Health, University of Brescia.

The aim of the Aflatox project (www.aflatox.it) is the development of an innovative biotechnological multi-step approach to design and test new compounds with a biological activity on fungi. The full-experimental database that we have been creating constitutes a powerful source of data to identify important requirements to be taken into account for the development of new generation pesticides, responding to “greener” and environmentally sustainable agricultural strategies. In particular, the compounds must be active against phytopathogenic genera contaminating cereals and food/feed derivatives, with a particular focus on aflatoxigenic species. The requirements to become a good candidate, are not only the high effectiveness in preventing fungal proliferation and mycotoxin biosynthesis, but also the non-toxicity for the environment and the human health.

The project has been divided into three different sections: the first is the design and synthesis of some parent compounds from natural molecules, the second is the study of their biological effect and cytotoxicity, and the third is the chemical modification of the most active compounds in order to study the mechanism of action and to improve the biological activity. In particular, in this last stage of the project, the compounds which had shown good results were modified not only in their chemical scaffold, but also used as chelating agents for bio-metal ions like zinc, copper or iron. In fact, molecules bound to transition metal ions present the capacity of promoting the cellular uptake and, in most cases, to introduce a source of oxidative stress in the target.

At present, we have managed to create a database containing a panel of 162 compounds which have been synthesized, characterised and tested for antifungal and antimicotoxigenic properties. Toxicological and genotoxicological evaluation were conducted on human cell lines and *A. cepa* root apex. All these data have been collected in a database that will allow us to produce Q-SAR (Quantitative structure-activity relationship) evaluation profiles.

Acknowledgements:

This work was funded by Cariplo Foundation, Lombardia, Italy, Grant N. 2014-0555.

Tuning the cytotoxicity of diiron dicarbonyl dicyclopentadienide complexes by varying the substituents on a bridging vinyliminium ligand

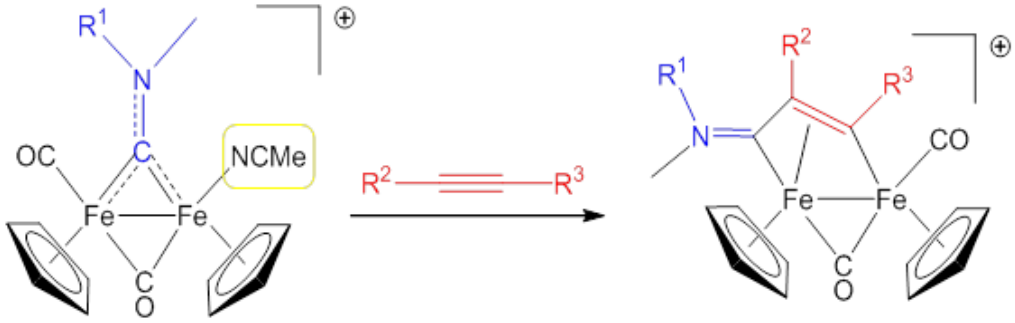
P15

G. Agonigi[1], L. K. Batchelor[2], T. Biver[1], P. J. Dyson[2], T. Funaioli[1], F. Marchetti[1], G. Pampaloni[1], D. Rocco[1], M. Ruggeri[1], S. Zacchini[3]

1. Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Moruzzi 13, 56124 Pisa (Italy).
2. Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne (Switzerland).
3. Dipartimento di Chimica Industriale "Toso Montanari", Università di Bologna, Viale Risorgimento 4, I-40136 Bologna (Italy).

Diiron complexes containing a bridging vinyliminium ligand are easily prepared through a three-step synthetic procedure starting from $Fe_2Cp_2(CO)_4$ and through the intermediacy of aminocarbyne compounds [1]. Electronic and steric properties of the vinyliminium moiety can be differentiated by an appropriate choice of substituents (see Scheme below).

Despite the final compounds result from classical organometallic synthesis, they are all indefinitely



air and water stable, and display variable water solubilities depending mainly on the nature of R^3. The antiproliferative activity has been assessed towards A2780 and A2780cisR cancer cell lines, and non tumoral HEK-293 cells. The obtained IC_{50} values indicate that the cytotoxic activity and also cancer cell selectivity significantly vary on modifying the nature of R^1, R^2 and R^3. Preliminary investigations on the possible mode of action of the compounds will be discussed.

Email addresses: g.ago2@hotmail.it (GA), fabio.marchetti1974@unipi.it (FM)

References

1. G. Agonigi, M. Bortoluzzi, F. Marchetti, G. Pampaloni, S. Zacchini, V. Zanotti, ***Eur. J. Inorg. Chem.***, **2018**, DOI 10.1002/ejic.201701115. b) V. G. Albano, L. Busetto, F. Marchetti, M. Monari, S. Zacchini, V. Zanotti, ***Organometallics***, **2003**, *22*, 1326.

P16

Tridentate thiosemicarbazone ligands and their Copper(II) complexes as anticancer agents: *in vitro* and *in vivo* preliminary studies

M. Carcelli[1], D. Rogolino[1], G. Pelosi[1], C. Marzano[2], M. Tegoni[1], V. Gandin[2]

1. Dipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale and Consorzio Interuniversitario di Ricerca in Chimica dei Metalli nei Sistemi Biologici, Università di Parma, Parco Area delle Scienze, 43124 Parma, Italy.
2. Dipartimento di Scienze del Farmaco, Università di Padova, Via Marzolo 5, Padova, Italy.

Adverse effects and the occurrence of resistance hampered the use of cisplatin, the drug employed against various types of cancer (1, 2). Therefore, extensive research is actually focused on the development of other metal-based anti-tumor compounds with improved pharmacological properties. In this *scenario*, the use of essential metals such as copper can lead to the development of less toxic and more effective drugs (3). Thiosemicarbazones (TSCs) are a class of compounds that have been studied for a long time due to their biological properties (4). Triapine™ (3-aminopyridine-2-carboxyaldehyde-TSC), for example, entered phase II of clinical trials against many types of cancer (5). Here we report on the synthesis and characterization, both in solution and at the solid state, of novel copper(II) complexes of O,N,S-tridentate TSC ligands. Experimental data indicate a 1:1 metal to ligand *ratio*, as confirmed also by X-ray diffraction analysis (Figure 1). The antiproliferative activity of the complexes has been studied both in two-dimensional and three-dimensional cell cultures. Cytotoxicity tests were conducted against a large panel of human tumor cell lines of different histology, and collected data allowed to formulate some preliminary structure-activity relationships. Mechanistic studies by appropriate biochemical and microscopy tests evidenced that all the complexes have significant inhibitory activity towards protein disulfide isomerase and are effective in hampering cancer cell endoplasmic reticulum homeostasis. In addition, as a step following the *in vitro* assays, preliminary *in vivo* studies performed in a syngeneic murine tumor model revealed a very promising pharmacological profile for this class of novel copper(II) complexes with O,N,S-tridentate TSC ligands .

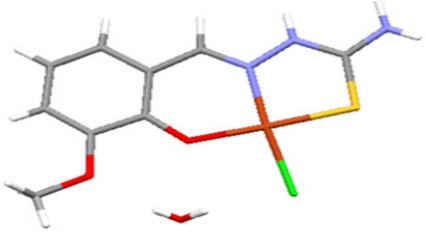


Fig. 1 X-Ray structure of one of the TSC-Copper(II) complexes studied

References

1. Kelland L. Nat. Rev. Cancer, 2007, 7, 573-84.
2. Zhang C.X., Lippard S.J. Curr. Opin. Chem. Biol., 2003, 7, 481-9.
3. Tisato F., Marzano C., Porchia M., Pellei M., Santini C. Med. Res. Rev., 2010, 30, 708-49.
4. Pelosi G., Bisceglie F., Bignami F., Ronzi P., Schiavone P, Re M.C., Casoli C., Pilotti E. J. Med. Chem., 2010, 53, 8765-9.
5. Yu Y., Kalinowski D.S., Kovacevic Z., Siafakas R.A., Jansson, P.J., Stefani, C., Lovejoy, D.B., Sharpe, P.S., Bernhardt, P.V., Richardson, D.R. J. Med. Chem., 2009, 52, 5271–5294.

A thiosemicarbazone nickel complex for the targeting of hexapeptide NH_2ThrGluSerHisHisLysAc, the C-terminal tail of histone H2A.

P17

F. Bisceglie, N. Orsoni, M. Pioli, G.Pelosi.

Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parma, Italy

Thiosemicarbazones are a family of compounds with wide biological properties that are able to chelate metal ions. They are obtained from the condensation of an aldehyde or a ketone with a thiosemicarbazide. Usually, metal complexes are more active than their parent ligands.
In this context, citronellal thiosemicarbazone (Htcitr) has been synthesized, with its nickel ([Ni(t-citr)$_2$]) [1] (Fig.1) complex. This complex shows a square planar geometry.
This complex is able to interact with DNA [1] causing the cell-cycle block with consequent induction of apoptosis in proliferative cells. DNA could be a direct target, with the interaction of the metal complex with nucleobases, or an indirect target, when the metal complex interacts with histones, chromatin protein components. For this reason, I studied the interaction of the hexapeptide TESHHK (this peptide is a model of the ESHH motif, a terminal part of the protein exposed to the solvent), with [Ni(tcitr)$_2$] through various techniques (NMR, UV-vis and CD)[2].
An interaction is observed by UV-vis and circular dichroism (CD) spectroscopy: in fact the spectra of the peptide incubated in the presence of the complex are considerably different compared with both single-species spectra.
A ^{1}H-NMR titration has shown that in solution this complex releases one molecule of ligand and becomes able to bind to the amidic groups of the peptide backbone; this type of interaction is confirmed by two-dimensional homonuclear NMR (COSY and TOCSY) experiments.

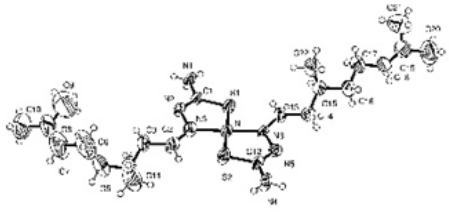


Figure 1. ORTEP view of [Ni(tcitr)$_2$].

References

1. Buschini, A.; Pinelli, S.; Alinovi, R.; Mussi, F.; Bisceglie, F.; Rivetti, C.; Doniselli, N.; Pelosi, G.; Unravelling mechanisms behind the biological activity of bis(S-citronellalthiosemicarbazonato)nickel(II). *Metallomics,* **2014**, *6, 783—792.*
2. Bal, W.; Lukszo, J.; Bialkowski, K.; Kasprzak, K. S.; Interactions of Nickel(II) with Histones: Interactions of Nickel(II) with CH3CO-Thr-Glu-Ser-His-His-Lys-NH2,a Peptide Modeling the Potential Metal Binding Site in the "C-Tail" Region of Histone H2A. *Chem. Res. Toxicol.* **1998***, 11, 1014-1023.*

P18

Identification of the biological target of new platinum, copper and nickel complexes

S. Montalbano[1], M. Pioli[1], F. Mussi[1], M. Marozzi[1], F. Bisceglie[1,2,3], G. Pelosi[1,2,3], A. Buschini[1,2,3]

1. Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parma, Italy
2. Centre for Molecular and Translational Oncology, University of Parma, Parma, Italy
3. CIRCMSB, Parma Unit, University of Parma, Parma, Italy

In cells, metals play a dual role: some, such as zinc, copper and manganese, are essential cellular components and are involved in several biological processes; others, such as nickel, cadmium, chromium and arsenic, are associated with cancer induction and progression. Thiosemicarbazones and their metal complexes are molecules with interesting biological activities and, thanks to these characteristics, are promising, as drugs, in the treatment of many diseases. In previous studies, we showed the antiproliferative properties of the nickel [Ni(tcitr)$_2$] (1) and copper [Cu(tcitr)$_2$] complexes (2). In particular, [Ni(tcitr)$_2$] enters the U937 cells and induces G_2M cell cycle arrest, p53 independent-intrinsic-apoptosis by down-regulation of Bcl-2, mitochondrial membrane potential loss and caspase activation (1). [Ni(tcitr)$_2$] also causes DNA damage and alters DNA conformation creating knot-like structures and hairpins but it does not induce gene mutation or chromosomal damage (3). In this study, we compare the biological activity of citronellal thiosemicarbazone complexes of other metal ions. Starting from the platinum, copper and nickel derivatives, we also detected the antiproliferative activity of dimethylated derivatives toward a selection of cancer cell lines. More recently, we used cell line U937 to understand if these metal complexes induce alterations on the DNA molecule and to determine the correlation between proliferation inhibition and cell cycle blockage. An analysis of a *S. cerevisiae* deletants collection has shown that [Ni(tcitr)$_2$] causes an enrichment in the classes of genes coding for components involved in nucleic acids metabolism, such as ribonucleotide reductase (RNR). This enzyme is necessary for DNA synthesis and repair, and consists of two different subunits needed for enzymatic activity. The treatment with the complexes induces a modulation of the expression of both subunits. These results suggest that probably RNR is not the main target of metal complexes but could be involved in cellular response. To identify the mechanism underlying the cell sensitivity to thiosemicarbazone complexes, we plan to investigate further the relationship between the modulation of RNR subunits and the mechanisms of response to DNA damage.

References

1. A. Buschini, S. Pinelli, C. Pellacani, F. Giordani, M. Belicchi Ferrari, Franco Bisceglie, M. Giannetto, G. Pelosi, P. Tarasconi. “Synthesis, characterization and deepening in the comprehension of the biological action mechanisms of a new nickel complex with antiproliferative activity”. Journal of Inorganic Biochemistry 103 (2009) 666–677.
2. Bisceglie F, Pinelli S, Alinovi R, Tarasconi P, Buschini A, Mussi F, Mutti A, Pelosi G. “Copper(II) thiosemicarbazonate molecular modifications modulate apoptotic and oxidative effects on U937 cell line”. J Inorg Biochem. (2012);116:195-203.
3. A. Buschini, S. Pinelli, R. Alinovi, F. Mussi, F. Bisceglie, C. Rivetti, N. Doniselli, G. Pelosi. “Unravelling mechanisms behind the biological activity of bis(S-citronellalthiosemicarbazonato)nickel(II)”. Metallomics. (2014) 6:783-92.

Ruthenium(III) complexes loaded in liposomes with enhanced cytotoxic properties

P19

D.Tesauro[1], M. E. Cucciolito,[2] R. Iannitti,[3] R. Palumbo,[3] G. Morelli,[1] F. Ruffo,[2,] A. D'Amora[2]

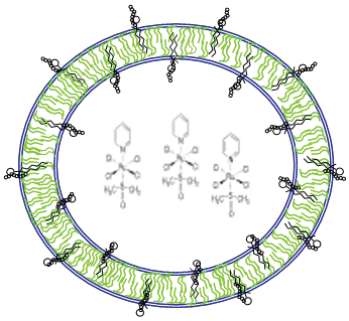
1. Dipartimento di Farmacia & CIRPeB Università degli studi di Napoli "Federico II" Via Mezzocannone 16, 80134 Napoli
2. Dipartimento di Scienze Chimiche Università degli studi di Napoli "Federico II" Via Cinthia 80126 Napoli
3. Istituto di Biostrutture e Bioimmagini (IBB) CNR Via Mezzocannone 16, 80134 Napoli

The use of cisplatin as antitumoral drug is strongly limited by many and severe side effects and acquired tumor resistance (1). These restrictions could be overcome by other metal complexes. In the last thirty years ruthenium compounds have been tested showing a remarkable antitumoral and antimetastatic activity associated with a lower toxicity. A hexacoordinate Ru(III) complex (NAMI-A) is currently undergoing advanced clinical evaluation (2).

All data indicate that NAMI-A acts as a pro-drug, but the integrity of ruthenium complexes is essential to store the cytotoxic activity. In this scenario the condition of administration of ruthenium drugs are crucial to exploit their anticancer activity (3). In the last years innovative strategies have been produced to vehicle ruthenium ions in tumor cells like aggregates. This study aims to incorporate the ruthenium complexes in the inner aqueous compartment of liposomes and to test biological properties of two NAMI-A like pyridine derivatives. Specifically, we have investigated the pyridine derivatives of the sodium-compensated analogue of NAMI-A, Na[trans-$RuCl_4$(pyridine)(DMSO)] (NAMI-Pyr) and Na[trans-$RuCl_4$(Pytri)(DMSO)] (NAMI-Pytri).

In the latter complex the pyridine ligand is functionalized with a sugar moiety so as to increase biocompatibility and the ability to cross the cell membrane. The stability of the complexes was studied and compared in solution at different pH following UV-VIS spectra. Lipid formulations based on Egg PC were prepared adding Cholesterol, DSPE-PEG_{2000} joining molar ratio 57/38 /5% w/w respectively in MeOH/$CHCl_3$ (50/50 v/v) mixture and hydrated with 0.9% w/w of NaCl.

This composition was selected to reproduce analog supramolecular aggregates in clinical use to vehicle doxorubicin (Doxil). Ruthenium complexes were loaded into liposomes using the passive equilibration loading method. Full drug containing liposomes were structurally characterized by dynamic light scattering (DLS) measurements. Data indicate the formation of stable aggregates with size and shape in the right range for in vivo applications. The amount of encapsulated ruthenium complexes was evaluated by means of ICP-AES. Stability and drug release properties of ruthenium containing liposomes were confirmed in buffer.



The growth inhibitory effects of both liposomal and free complex drugs were tested on prostate cancer cells (PC3). The IC_{50} was evaluated as 1.2 mM (NAMI-Pyr) and 8.2 mM (NAMIPytri) respectively. The increase of cytoxic effect is two order of magnitude greater than that of free complexes.

References

1. Kelland Nat. Rev. Cancer 2007, **7**:573–84.
2. E.Alessio Eur.J. Inorg. Chem 2017, 1549–1560,
3. B.M. Blunden, M.H. Stenzel J.Chem.Technol.Biotechnol. 2015, 90: 1177–1195.

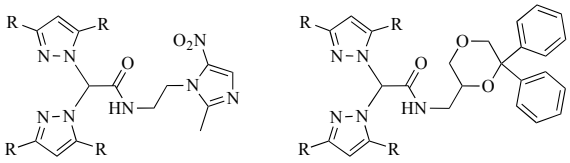
P20

Rational design and biological evaluation of novel conjugated heteroscorpionate ligands and related Copper(I/II) complexes

C. Santini[1], M. Pellei[1], L. Bagnarelli[1], C. Cimarelli[1], F. Del Bello[2], W. Quaglia[2], M.B. Morelli[3], C. Amantini[3], V. Gandin[4], C. Marzano[4]

1. School of Science and Technology, Chemistry Division, University of Camerino, Italy
2. School of Pharmacy, Medicinal Chemistry Unit, University of Camerino, Italy
3. School of Biosciences and Veterinary Medicine, University of Camerino, Italy
4. Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Italy

Polydentate nitrogen-containing donor ligands derived from poly(pyrazol-1-yl)methanes bearing organic functional groups on the bridging carbon have recently attracted considerable attention and their coordination chemistry towards main group and transition metals have been extensively studied [1]. Recently we designed and synthetized two carboxylated heteroscorpionate ligands (L^H, $[HC(CO_2H)(pz)_2]$ and L^{Me}, $[HC(CO_2H)(pz^{Me2})_2]$), and the related 5-nitroimidazole conjugated heteroscorpionate ligands named L^HMN and L^{Me}MN [2] (Fig. 1) by direct coupling of preformed side chain acid with 5-nitroimidazole. In particular the copper(II) complexes $(L^RMN)_2CuCl_2$ and the water soluble copper(I) complexes $[(L^RMN)Cu(PTA)_2](PF_6)$ (R = H or Me) have been prepared and evaluated for their cytotoxic activity towards a panel of several human tumour cell lines [3]. The ligands L^H and L^{Me} have also been functionalized with the potent NMDA receptor antagonist (6,6-diphenyl-1,4-dioxan-2-yl)methanamine, which showed a significant cytotoxic activity on MCF7 human breast cancer cell lines, highly expressing NMDA receptors [4], affording the conjugated derivatives L^HNMDA and L^{Me}NMDA (Fig. 1) used for the preparation of stable Cu(I/II) complexes. All the compounds were evaluated against a panel of human tumor cell lines derived from solid tumors. The research results suggest that these Cu(I/II) complexes might act through synergistic mechanisms of action due to the presence of the NMDA ligands and copper in the same chemical entity.



L^HMN: R = H
L^{Me}MN: R = Me

L^HNMDA: R = H
L^{Me}NMDA: R = Me

Figure 1

Acknowledgments: this work was supported by grants from the University of Camerino (Fondo di Ateneo per la Ricerca 2014-2015).

References

1. A. Otero, et al. ***Coord. Chem. Rev.*** **2013**, ***257***, 1806-1868.
2. M. Pellei, et al., ***Dalton Trans.*** **2011**, ***40***, 9877-9888.
3. C. Santini, et al., ***unpublished results.***
4. M. B. Morelli et al., ***unpublished results.***

Synthesis and structure of rare zwitterionic complexes involving the presence of $N_{(py)}MCl_3^-$ moieties (M = Pt^{II}, Pd^{II})

P21

E. Viola[1], M.P. Donzello[1], C. Ercolani[1], C. Rizzoli[2], A.B.P. Lever[3]

1. Dipartimento di Chimica, Università di Roma Sapienza, P.le Aldo Moro, 5 - 00185 Roma, Italy
2. Dipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale, Università degli Studi di Parma, Parco Area delle Scienze 17/A, I-43124 Parma, Italy
3. Department of Chemistry, York University, 4700 Keele St., Toronto, Ont. Canada M3J 1P3

The multifaceted modes of binding of metal ions by polyazine N donors such as 2,3-di(2-pyridyl) pyrazine (dpp) and derivatives carrying open chain or annulated ring substituents in 5,6 positions, have been recently reviewed.[1] For a variety of mononuclear metal derivatives, bidentate chelation involves both the N atoms of the vicinal 2-pyridyl rings ("py-py" coordination) or pyridine and pyrazine N atoms ("py-pyz" coordination). As shown by us, 2,3-dicyano-5,6-di(2-pyridyl)pyrazine, $[(CN)_2Py_2Pyz]$, largely used for the synthesis of porphyrazine macrocycles with potentialities as anticancer drugs, reacts with the reactants $[(C_6H_5CN)_2MCl_2]$ (M = Pt^{II}, Pd^{II}) at room temperature forming the mononuclear complexes $[(CN)_2Py_2PyzMCl_2]$.[2,3] The two complexes are isostructural and exhibit "py-py" coordination.

It was also considered that the dpp monocation of formula $[(CN)_2Py(2\text{-}Mepy)Pyz]^+$ (Figure 1A), separated as iodide salt,[4] could be the appropriate dpp derivative able to promote the formation of Pt^{II} and Pd^{II} mononuclear complexes with a "py-pyz" mode of coordination. Surprisingly, reaction of the iodide salt $[(CN)_2Py(2\text{-}Mepy)Pyz](I)$ with appropriate Pt^{II} and Pd^{II} reagents leads to interesting new species of formula $[(CN)_2Py(2\text{-}Mepy)PyzMCl_3]\cdot CH_3CN$ (M = Pt^{II} and Pd^{II}) (see Figure 1B for the Pt^{II} compound). The two species, found isostructural by X-ray work, are rare examples of zwitterionic Pt^{II} and Pd^{II} complexes typically presenting the anionic moiety $N_{(py)}MCl_3^-$, widely studied by IR and UV-Vis spectra and examined by DFT methods (paper submitted).

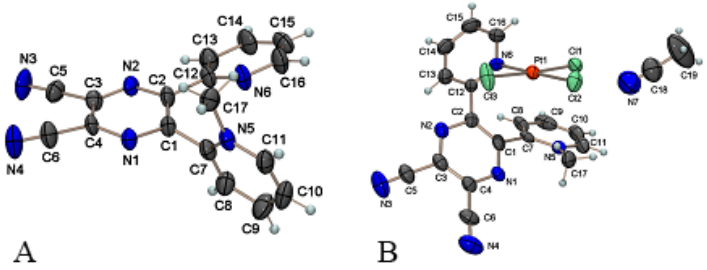


Figure 1

References

1. B. Floris, M.P. Donzello, C. Ercolani, E. Viola, Coord. Chem Rev., 347 (2017) 115.
2. M.P. Donzello, E. Viola, X. Cai, L. Mannina, C. Rizzoli, G. Ricciardi, C. Ercolani, K.M. Kadish, A. Rosa, Inorg. Chem. 47 (2008) 3903.
3. X. Cai, M.P. Donzello, E. Viola, C. Rizzoli, C. Ercolani, K.M. Kadish, Inorg. Chem. 48 (2009) 7086.
4. C. Bergami, M.P. Donzello, C. Ercolani, F. Monacelli, K.M. Kadish, C. Rizzoli, Inorg. Chem. 44 (2005) 9852.

P22

Tetrapyrazinoporhyrazines with externally pending octacarboranthiolate groups. A route to potential bimodal PDT/BNCT anticancer drugs

E. Viola, M P. Donzello, C. Ercolani

Dipartimento di Chimica, Università di Roma Sapienza, P.le Aldo Moro, 5 - 00185 Roma, Ital

In our previous studies we focused on the synthesis, physicochemical chatacterization and potentialities as anticancer agents in photodynamic therapy (PDT) of a series of neutral mononuclear tetrapyrazinoporphyrazines (TPyzPzs) carrying externally 2-pyridyl rings ([Py_8TPyzPzM]; Figure 1A, M = bivalent metal center), from which multinuclear and multicationc species were also prepared (1 and refs. therein). It was established that most of the species examined, having centrally Zn^{II}, Mg^{II} and Pd^{II}, show in DMF solution relevant photoactivity for the generation of singlet oxygen, $^1O_2$, the most active cytotoxic agent in PDT, with measured moderate-to-high quantum yield values (Φ_Δ = 0.4-0.6). For symmetrical octacationic Zn^{II} TPyzPzs and related low-symmetry hexacationic macrocycles, carrying peripherally one *cis*-platin-like functionality of the type $N_{2(py)}PtCl_2$, proved active in PDT, it was observed their capability to interact with different forms of DNA (G-quadruplex and dsDNA), thus prefigurating bi-multimodal anticancer potentialities.

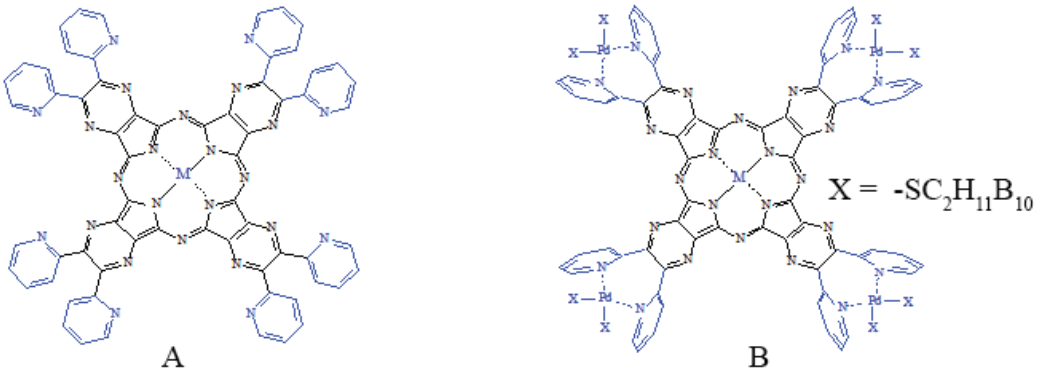


Figure 1

In an extension of our work on new TPyzPzs it was thought interesting to open additional perspectives of application in a bimodal anticancer therapy including studies on Boron Neutron Capture Therapy (BNCT). For this purpose new homo/heteropentanuclear tetrapyrazinoporphyrazines with high boron content, having externally pending octacarboranthiolate groups, formulated as [{$Pd(SC_2H_{11}B_{10})_2$}$_4$$Py_8$TPyzPzM] (M = $Mg^{II}(H_2O)$, Zn^{II}, Pd^{II}) (Figure 1B) have been synthesized and characterized. Their behavior as active species in PDT in DMF solution is a promising preliminary feature for potential application of these compounds as bimodal PDT/BNCT anticancer drugs.

References

1. a) M. P. Donzello, C. Ercolani, V. Novakova, P. Zimcik, P.A. Stuzhin. ***Coord. Chem. Rev.*** **2016**, *309*, 107; b) V. Novakova, M.P. Donzello, C. Ercolani, P. Zimcik, P.A. Stuzhin. ***Coord. Chem. Rev.*** **2018**, in press, doi..org/10.1016/j.ccr.2018.01.015.

Novel alanyl-based Pt(II) complexes: synthesis, characterization and antiproliferative activity

P23

D. Capasso[1,2], G. M. Rozza[3], D. Musumeci[3], S. Di Gaetano[4], C. Platella[3], C. Riccardi[3], F. Moccia[3], G. N. Roviello[4], D. Montesarchio[3]

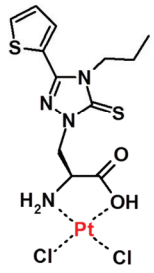
1. CESTEV, University of Naples Federico II, Napoli, Italy;
2. Department of Pharmacy, University of Naples Federico II, Napoli, Italy;
3. Department of Chemical Sciences, University of Naples Federico II, Napoli, Italy;
4. Institute of Biostructures and Bioimaging - CNR, Napoli, Italy.

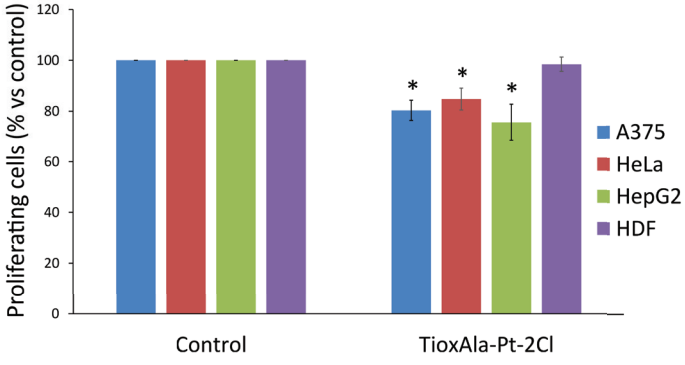
The application of inorganic chemistry to medicine is producing novel therapeutic metal complexes with an impact on medical practice. Advances in biocoordination chemistry are crucial for improving the design of novel metal complexes with enhanced therapeutic efficacy and reduced toxic side effects.[1]

It was recently established a structural motif of (O,S) bidentate ligands bound to a Pt(II) metal center which is effective against various cancer cell lines, and an overall picture of the binding properties of this class of compounds with defined DNA model systems were reported.[2] Furthermore, the synthesis of complexes of platinum(II) with amino acids derivatives produced also compounds with interesting properties.[3]

Here we report our studies on the synthesis, characterization and biological activity of new Pt complexes based on an amino acid derivative of L-alanine containing both a thiophene and triazolyl thione moieties.

The obtained complexes were characterized by NMR, MALDI-TOF and UV-vis spectroscopy. Furthermore, their biological activity in terms of antiproliferative effects towards several cancer cell lines was evaluated.





References

1. Dasari S. and Tchounwou P. B., Eur J Pharmacol. **2014**; 740: 364–378.
2. Mügge C., Musumeci D., Michelucci E., Porru F., Marzo T., Massai L., Messori L., Weigand W., Montesarchio D., J Inorg Biochem. **2016**; 160: 198-209.
3. B.T.i Khan , S. V. Kumari ,G N. Goud *J Coord Chem* **2006**, 12, 19-25

P24

Bulk fill composites finishing procedures: conversion degree and microhardness

E. Giorgini,[1], C. Conti[2], S. Sabbatini[2], G. Tosi[2]

1. Dipartimento Scienze della Vita e dell'Ambiente, Università Politecnica delle Marche, Ancona, Italy
2. Dipartimento Scienze e Ingegneria della Materia, dell'Ambiente ed Urbanistica, Università Politecnica delle Marche, Ancona, Italy

The polymerization of a dental composite affords crosslinked networks between monomers making the composite hard. In the formation of these crosslinked networks, conversion degree (DC), and microhardness (VMH) of restorative materials assume great importance in their success and clinical longevity. The aim of this study was to analyse the effects of new polishing procedures on two bulk composites (Estelite Bulk-Fill Flow, EBFF, Tokuyama, and One Bulk Fill Restorative, OBFR, 3M ESPE) at two different times. Ten samples of each composite were cured; five samples were immediately polished (t0), while the other ones were polished after 24 hours (t24). For each sample, DC and VMH values were evaluated by using a Spectrum GX1 spectrometer (Perkin Elmer), a Micro-Hardness tester (Leitz) and a Scanning Electron Microscope SEM (Gemini, Zeiss). At t0, both tested materials presented statistically different DC and VMH ($p<0.05$) before and after polishing treatments, with OBFR always showing higher values with respect to EBFF. In addition, after 24 hours all OBFR samples reached the same DC values, suggesting that polishing treatments do not affect the final degree of polymerization (Table 1). For both composites, at t0, VMH values of polished samples were higher than unpolished ones. Polishing treatments carried out after 24 hours showed only a tiny improvement of VMH (Table 2). In conclusion, for both materials, DC values showed a time dependent response, not so much affected by polishing treat- ments. Conversely, for OBFR, VMH was improved when samples were polished immediately after curing.

	t0		t24	
	Pre Polishing	Post Polishing	Pre Polishing	Post Polishing
OBFR	78.01 ± 4.13 a	90.9 ± 3.20 b		88.43 ± 6.17 b
	81.01 ± 1.69 a		82.87 ± 1.79 c	84.78 ± 6.25 b,c
	60.23 ± 2.41 a	67.17 ± 1.39 b		62.93 ± 2.18 b
EBFF	59.94 ± 1.49 a		62.92 ± 2.49 b	63.40 ± 3.67 b

Table 2. VMH evaluations of One Bulk Fill Restorative and Estelite Bulk-Fill Flow

	t0		t24	
	Pre Polishing	Post Polishing	Pre Polishing	Post Polishing
OBFR	81.70 ± 2.63 a	89.57 ± 3.62 b		92.48 ±4.02 b
	82.84 ± 1.92 a		91.78 ± 1.48 b	91.96 ± 2.62 b
EBFF	69.68 ± 3.90 a	74.88 ± 2.06 b		91.73 ± 5.21 c
	68.49 ± 3.09 a		95.53 ± 4.01 c	94.21 ± 2.43 c

Table 1. DC evaluations of One Bulk Fill Restorative and Estelite Bulk-Fill Flow

References

1. De Souza G ***et al.***. Correlation between clinical performance and degree of conversion of resin cements: a literature review. J Appl Oral Sci 2015;23:358–368.
2. Monterubbianesi ***et al.*** Spectroscopic and Mechanical Properties of a New Generation of Bulk Fill Composites. Front Physiol 2016;7:652.
3. Trogolo JA, Rajan K. Near surface modification of silica structure induced by chemical/mechanical polishing. J Mater Sci 1994;29:4554–4558.

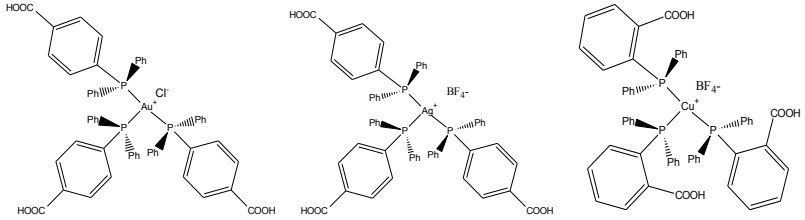
Synthesis and characterization of poly-phosphane coinage metals complexes and study on the protein ligation and catalysis

P25

R. Galassi[2] , S. Pucciarelli[1], **V. Gambini,** [1] **M. Tilio,**[1] **A. Burini**[2]

1. School of Biosciences and Veterinary Medicine, University of Camerino, Via Gentile III da Varano, Camerino 62032.
2. School of science and Technology, University of Camerino, Via Sant'Agostino, 1, Camerino 62032

A series of coinage metals centered poly-phosphane complexes has been synthesized and characterized under photophysical, chemical and biochemical aspects also in combination with a protein. Poly-phosphane metal complexes possess many properties in the field of luminescence,[1] catalysis, [2] chemo sensing, [3] and of anticancer activity [4]. In this study phosphane ligands containing the carboxylic functional group in ortho or para position of PPh_3 have been used. The introduction of this polar group has the double aim either to make more hydrophilic the complexes and to tune the binding ability of the phosphane. In the case of gold(I) complexes, the poly-phosphine compound have been studied in comparison with the corresponding [bis-triphenylphosphine-gold(I)chloride], where the carboxylic group is absent, to evaluate the influence of its presence in the photopysical properties as well as on the interaction with dihydrofolate reductase, a protein involved in cell proliferation, DNA duplication and many other biological functions [5]. Affinity constants have been estimated through quenching of fluorescence studies and inhibition constants have been evaluated through rate constant determination of the reduction of dihydrofolate (H_2F) to tetrahydrofolate (H_4F) with reduced nicotinamide adenide dinucleotide phosphate (NADPH) as hydride donor. The tests highlighted a catalytic activity of the gold(I) compounds versus the H_2F, which is the substrate of the enzyme. A strong effect of the enzyme on the luminescence properties of the gold(I) complexes have been observed. A coinage metals homolog series have been also evaluated as antiproliferative agent by in vitro MTT tests.



Scheme. Schematic view of a homolog series of coinage metals complexes under study.

References

1. R. Edward, T. Tiekink, J. G. Kang, ***Coord. Chem. Rev.*** **2009**, 253, 1627-1648
2. David J. Gorin, Benjamin D. Sherry, and F. Dean Toste, ***Chem. Rev.*** **2008,** 108, 3351–3378
3. X. He, V. W. Yam, ***Coord. Chem. Rev.*** **2011**, 2111-2123
4. R. Galassi, A.Burini, O. Camille Simon, A. Dolmella, D. Micozzi, S. Vincenzetti, S. Pucciarelli ***Dalton Trans.***, **2015**, 44, 3043-3056 DOI: 10.1039/C4DT01542H

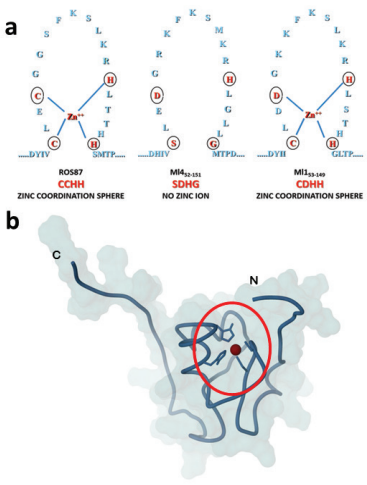
P26

Metal ions: influences on protein structure, folding mechanism and self-association propensity

G. Malgieri[1], G. D'Abrosca[1], L. Russo[1], V. Sivo[1], F. Russo[1], I. Baglivo[1], D. Milardi[2], P. V. Pedone[1], R. Fattorusso[1] , C. Isernia[1]

1. Department of Environmental Science and Technologies, Biological and Pharmaceutical, University of Campania – Luigi Vanvitelli, Via Vivaldi, 43-81100 Caserta (Italy).
2. Institute of Biostructures and Bioimaging-CNR, Viale A. Doria 6, 95125 Catania (Italy).

Using three isostructural proteins of the prokaryotic zinc finger family as model systems (the proteins $Ml4_{52\text{-}151}$ lacking zinc binding and $Ml1_{53\text{-}149}$ and Ros87 that bind a structural metal ion), our research is designed to contribute to the knowledge about the detailed mechanisms by which metal ions, both endogenous or exogenous, perturb proteins structure and function, folding mechanism and self-association propensities.



Coordination spheres. (a) Circles indicate the positions corresponding to the coordination residues in Ros87 and $Ml1_{53\text{-}149}$. $Ml4_{52\text{-}151}$ does not bind the structural Zn^{2+}. (b) The globular fold of Ros87; the circle evidences the Zn^{2+} coordination sphere.

The prokaryotic zinc finger domain[2] shows a ββββαα globular fold that, while including a ββα motif similar to the eukaryotic domain, is stabilized by an extensive hydrophobic core of 15 amino acids and uses different combinations of amino acids to coordinate the structural metal ion when present.

We will discuss how metal substitution, with different metal ions[3], can influence structure and function of this domain and how the metal recruitment can modify the folding pathway of these relatively small domains, control conformational accessibility to aggregation-prone states and change aggregation kinetics.

Our findings both complement and extend previous results obtained for different eukaryotic zinc fingers[4], suggesting that metal substitution in these motifs may be of relevance to toxicity and/or carcinogenicity mechanisms.

While these model domains have little direct disease-relevance, implications of our findings should be of broad general interest as many disease-relevant proteins bind metal ions, which could similarly influence their structures, folding pathways and aggregation.

References

1. M. Palmieri, G. Malgieri, L. Russo, I. Baglivo, S. Esposito, F. Netti, A. Del Gatto, I. de Paola, L. Zaccaro, P.V. Pedone, C. Isernia, D. Milardi, R. Fattorusso, J Am Chem Soc, vol. 135, 2013, pp. 5220-5228.
2. G. Malgieri, L. Russo, S. Esposito, I. Baglivo, L. Zaccaro, E.M. Pedone, B. Di Blasio, C. Isernia, P.V. Pedone, R. Fattorusso, PNAS, vol. 104, Issue 44, 2007, pp. 17341-17346
3. G. Malgieri, M. Palmieri, S. Esposito, V. Maione, L. Russo, I. Baglivo, I. De Paola, D. Milardi, D. Diana, L. Zaccaro, P.V. Pedone, R. Fattorusso, C. Isernia, Metallomics, vol. 6, Issue 1, 2014, pp. 96-104
4. G. Malgieri, L. Zaccaro, M. Leone, E. Bucci, S. Esposito, I. Baglivo, A. Del Gatto, L. Russo, R. Scandurra, P.V. Pedone, R. Fattorusso, C. Isernia, Biopolymers, vol. 95. Issue 11, 2011, pp. 801-810.

Protein Metalation by Metal Based Drugs

P27

L. Messori[1], A. Pratesi[1], T. Marzo[1,2], L. Massai[1], A. Merlino[3]

1. Laboratory of Metals in Medicine (MetMed), Department of Chemistry "U. Schiff", University of Florence, Via della Lastruccia 3, 50019 Sesto Fiorentino, Italy
2. Department of Chemistry and Industrial Chemistry (DCCI), University of Pisa, Via Moruzzi, 13, 56124 Pisa, Italy
3. Department of Chemical Sciences, University of Naples Federico II Via Cintia, 80126, Napoli (Italy) and CNR Institute of Biostructure and Bioimages Via Mezzocannone 16, 80100, Napoli (Italy)

Interactions of metal-based drugs with proteins and consequent adduct formation ("protein metalation") play a crucial role in governing the mechanism of action of several anticancer agents and in determining their overall toxicological profile. Through a novel investigative strategy grounded on the combined use of electrospray ionization mass spectrometry (ESI MS) and biological macromolecule X-ray crystallography we show that it is possible to elucidate in depth the metalation process of small model proteins; a number of instructive examples are provided. More recently, this investigative approach has been extended to bigger proteins such as human serum albumin and horse spleen ferritin, with encouraging results. Overall, metalation of proteins produced by anticancer metallodrugs can be disclosed in the molecular detail. The next challenging step in this kind of research is the identification of metalated proteins within complex mixtures of biological relevance.

Elenco dei partecipanti

Accardo Antonella	Dipartimento di Farmacia, Università degli studi di Napoli "Federico II", Napoli
Agonigi Gabriele	Dipartimento di Chimica e Chimica Industriale, Università di Pisa,
Ambrosio Luigi	Istituto per i Polimeri, Compositi e Biomateriali, Consiglio Nazionale delle Ricerche, Napoli
Arnesano Fabio	Dipartimento di Chimica, Università degli Studi di Bari "Aldo Moro", Bari
Attanasio Francesco	Istituto di Biostrutture e bioimmagini, Consiglio Nazionale delle Ricerche, Catania
Barbanente Alessandra	Dipartimento di Chimica, Università degli Studi di Bari Aldo Moro, Bari
Baroncelli Riccardo	Dipartimento di Chimica "Ugo Schiff", Università degli Studi di Firenze, Firenze
Bartoli Jennifer	Dipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale, Università degli studi di Parma, Parma
Bellia Francesco	Istituto di Biostrutture e bioimmagini, Consiglio Nazionale delle Ricerche, Catania
Benedetti Michele	Dipartimento Scienze e Tecnologie Biologiche ed Ambientali, Università del Salento, Lecce
Biancalana Lorenzo	Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Pisa
Bisceglie Franco	Dipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale, Università degli Studi di Parma, Parma
Biver Tarita	Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Pisa
Calvanese Luisa	Dipartimento di Farmacia, Università degli Studi di Napoli "Federico II", Napoli
Canil Giovanni	Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Pisa
Capasso Domenica	CESTEV , Università degli studi Napoli , Napoli
Caporale Andrea	Istituto di Biostrutture e Bioimmagini, Consiglio Nazionale delle Ricerche, Napoli
Carcelli Mauro	Dipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale, Università di Parma, Parma
Caruso Viviana C.L.	Dipartimento di Scienze Chimiche, Università degli Studi di Catania, Catania
Ciofi Lorenzo	Dipartimento di Chimica Ugo Schiff, Università degli studi di Firenze, Sesto Fiorentino
Cirri Damiano	Dipartimento di Chimica Ugo Schiff, Università degli Studi di Firenze, Sesto Fiorentino
Coletta Massimiliano	Dipartimento di Scienze Cliniche e Medicina Traslazionale, Università di Roma Tor Vergata, Roma
Conti Carla	Dip. di Scienze e Ingegneria della Materia, dell''Ambiente ed Urbanistica, Università Politecnica delle Marche, Ancona
Crestoni Maria Elisa	Dipartimento di Chimica e Tecnologie del Farmaco, Università di Roma La Sapienza, Roma
Cucci Lorena	Dipartimento delle Scienze Chimiche, Università di Catania, Catania
Dacarro Giacomo	Dipartimento di Chimica, Università di Pavia, Pavia
Dalla Via Lisa	Dipartimento di Scienze del Farmaco, Università degli Studi di Padova, Padova
D'Auria Gabriella	Dipartimento di Farmacia, Università degli studi di Napoli "Federico II", Napoli
De Castro Federica	DiSTeBA, Università del Salento, Lecce
De Luca Luca	Istituto di Biostrutture e Bioimmagini, Consiglio Nazionale delle Ricerche, Napoli
De Zorzi Rita	Dipartimento di Scienze Chimiche e Farmaceutiche, Università degli Studi di Trieste, Trieste
Del Gatto Annarita	Istituto di Biostrutture e Bioimmagini, Consiglio Nazionale delle Ricerche, Napoli
Di Gaetano Sonia	Istituto di Biostrutture e Bioimmagini, Consiglio Nazionale delle Ricerche, Napoli
Diaferia Carlo	Dipartimento di Farmacia, Università degli studi di Napoli "Federico II", Napoli
Donzello Maria Pia	Diartimento di Chimica, Università degli Studi di Roma "La Sapienza" , Roma
Esposito Alfonso	CESTEV - Centro Di Servizi Di Ateneo, Università di Napoli "Federico II", Napoli
Fabrizi de Biani Fabrizia	Dipartimento Di Biotecnologie, Chimica E Farmacia, Università Di Siena
Facchetti Giorgio	Dipartimento di Scienze Farmaceutiche, Università degli Studi di Milano, Milano
Falanga Annarita	Dipartimento di Farmacia, Università degli studi di Napoli "Federico II", Napoli
Falcigno Lucia	Dipartimento di Farmacia, Università degli studi di Napoli "Federico II", Napoli
Falini Giuseppe	Dipartimento di Chimica "Giacomo Ciamician", Università di Bologna Alma Mater Studiorum, Bologna
Fanizzi Francesco Paolo	Dipartimento di Scienze e Tecnologie Biologiche ed Ambientali, Università del Salento, Lecce
Fornarini Simonetta	Dipartimeto di Chimica e Tecnologie del Farmaco, Università degli Studi di Roma La Sapienza, Roma
Gabbiani Chiara	Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Pisa
Galassi Rossana	Scuola di Scienze e Tecnologie, Università di Camerino, Camerino (MC)
Galdiero Stefania	Dipartimento di Farmacia, Università degli studi di Napoli "Federico II", Napoli
Giorgini Elisabetta	Dipartimento DISVA, Università Poltecnica delle Marche, Ancona

Guarra Federica	Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Pisa
Hyeraci Mariafrancesca	Dipartimento di Scienze del Farmaco , Università degli Studi di Padova, Padova
Isernia Carla	DiSTABiF, Università della Campania L. Vanvitelli, Caserta
La Mendola Diego	Dipartimento di Farmacia, Università di PIsa, Pisa
Lombardi Lucia	Dipartimento di Farmacia, Università degli studi di Napoli "Federico II" , Napoli
Malgieri Gaetano	DiSTABiF, Università della Campania L. Vanvitelli, Caserta
Marasco Daniela	Dipartimento di Farmacia, Università degli studi di Napoli "Federico II", Napoli
Marchetti Fabio	Dipartimento di Chimica e Chimica Industriale (DCCI), Università di Pisa, Pisa
Margiotta Nicola	Dipartimento di Chimica, Università degli Studi di Bari Aldo Moro, Bari
Marvelli Lorenza	Dipartimento di Scienze Chimiche e Farmaceutiche, Università di Ferrara, Ferrara
Marzo Tiziano	Dipartimento di Chimica e Chimica Industriale (DCCI), Università di Pisa, Pisa
Massai Lara	Dipartimeto di Chimica "Ugo Schiff", Università degli studi di Firenze, Sesto Fiorentino
Messori Luigi	Dipartimento di Chimica "Ugo Sciff", Università Firenze, Sesto Fiorentino (FI)
Monsù Scolaro Luigi	Dipartimento di Chimica Inorganica, Chimica Analitica e Chimica Fisica, Università degli studi di Messina, Messina
Montalbano Serena	Dipartimento di scienze chimiche, della vita e della sostenibilità ambientale, Università degli studi di Parma, Parma
Morelli Giancarlo	Dipartimento di Farmacia, Università degli studi di Napoli "Federico II", Napoli
Musumeci Domenica	Dipartimento di Scienze Chimiche, Università degli studi di Napoli Federico II, Napoli
Naletova Irina	Dipartimento delle Scienze Chimiche, Università degli Studi di Catania, Catania
Nardella Maria Incoronata	Dipartimento di Chimica, Università degli Studi di Bari Aldo Moro, Bari
Natile Giovanni	Dipartimento di Chimica, Università degli Studi di Bari Aldo Moro, Bari
Oliveri Valentina	Dipartimento di Scienze Chimiche, Università degli Studi di Catania, Catania
Osella Domenico	Dipartimento di Scienze e Innovazione Tecnologica, Università del Piemonte Orientale, Alessandria
Pallavicini Piersandro	Dipartimento di Chimica, Università degli studi di Pavia, Pavia
Pappalardo Giuseppe	Istituto di Biostrutture e Bioimmagini, Consiglio Nazionale delle Ricerche, Catania
Pedone Carlo	Napoli
Pedone Emilia Maria	Istituto di Biostrutture e Biommagini , Consiglio Nazionale delle Ricerche, Napoli
Pellei Maura	Dipartimento DISVA, Università Poltecnica delle Marche, Ancona
Pelosi Giorgio	Dipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale, Università degli studi di Parma, Parma
Pirone Luciano	Istituto di Biostrutture e Bioimmagini, Consiglio Nazionale delle Ricerche, Napoli
Pisani Michela	SIMAU, Univerità Politecnica delle Marche, Ancona
Pratesi Alessandro	Dipartimeto di Chimica "Ugo Schiff", Università degli studi di Firenze, Sesto Fiorentino
Rangone Beatrice	Dipartimento di Scienze e Innovazione Tecnologica, Università del Piemonte Orientale
Ravera Mauro	Dipartimento di Scienze e Innovazione Tecnologica, Università del Piemonte Orientale
Rimoldi Isabella	Dipartimento delle Scienze Farmaceutiche, Università degli Studi di Milano, Milano
Rizzarelli Enrico	Dipartimento di Scienze Chimiche, Università degli studi di Catania, Catania
Rogolino Dominga	Dipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale, Università degli studi di Parma, Parma
Sabbatini Simona	SIMAU, Università Politecnica delle Marche, Ancona
Santini Carlo	Scuola di Scienze e Tecnologie - Sez. Chimica, Università di Camerino, Camerino (MC)
Satriano Cristina	Dipartimento delle Scienze Chimiche, Università degli Studi di Catania, Bari
Saviano Michele	Istituto di Cristallografia, Consiglio Nazionale delle Ricerche, Bari
Sbardella Diego	Scienze Cliniche e Medicina Traslazionale, Università di Roma Tor Vergata, Roma
Scopelliti Michelangelo	Dipartimento di Fisica e Chimica (DiFC), Università degli Studi di Palermo, Palermo
Tesauro Diego	Dipartimento di Farmacia, Università degli studi di Napoli , Napoli
Vecchio Graziella	Dipartimento di Scienze Chimiche, Università di Catania, Catania
Venditti Iole	Department of Sciences, Roma Tre University of Rome, Roma
Viola Elisa	Dipartimento di Chimica, Università di Roma La Sapienza , Roma
Zaccaro Laura	Istituto di Biostrutture e Biommagini , Consiglio nazionale dele ricerche, Napoli
Zangrando Ennio	Dipartimento delle Scienze Chimiche, Università di Trieste, Trieste

Elenco degli autori

CIRPEB

Società Chimica Italiana
Divisione di Chimica Inorganica

CESTEV
Centro di Servizio di Ateneo per le Scienze e Tecnologie per la Vita
Università degli Studi di Napoli Federico II

Consiglio Nazionale delle Ricerche

CIRC MSB