



**FIRST CONFERENCE
OF THE ITALIAN
BIOINORGANIC
CHEMISTRY GROUP**

BOOK OF ABSTRACTS

SEPTEMBER 7-9, 2026

COMPLESSO DEI SS. MARCELLINO E FESTO
Conference Center of the University of Naples Federico II
NAPLES, ITALY



**Società
Chimica
Italiana**

Gruppo Tematico di
Chimica Bioinorganica

www.itabic26.unina.it



Welcome to the First Italian Bioinorganic Chemistry Conference ItaBIC26!

The Scientific and Organizing Committees are delighted to welcome you to the inaugural conference of the **Bioinorganic Chemistry Group** of the **Società Chimica Italiana (SCI)**, hosted by the University of Naples Federico II, in the historic setting of Naples, Italy. ItaBIC26 aims to bring together the Italian and international bioinorganic chemistry communities to discuss recent advances at the interface between **Inorganic Chemistry** and the **Life Sciences**, promoting scientific exchange, networking and new collaborations.

The scientific program features **three Plenary Lectures** delivered by internationally renowned scientists, **Thomas R. Ward** (University of Basel, Switzerland), **Franc Meyer** (Georg-August-Universität Göttingen, Germany), and **Gilles Gasser** (Chimie ParisTech, PSL University, France), together with **five Keynote Lectures** presented by distinguished experts: **Anabella Ivancich** (CNRS and Aix-Marseille University, France), **Fabio Carniato** (Università del Piemonte Orientale, Italy), **Gianantonio Battistuzzi** (Università di Modena e Reggio Emilia, Italy), **Ulf Hanefeld** (Delft University of Technology, The Netherlands), and **Emilia Sicilia** (Università della Calabria, Italy). The program is further enriched by **40 oral communications** and **more than 30 poster presentations**, offering a broad overview of the current and vibrant research activities in the field.

These three days will represent a valuable opportunity for scientific discussions and interactions among researchers working on the many aspects of **bioinorganic chemistry**, including metal ions in biology and medicine, metalloproteins and metalloenzymes, metal-based therapeutics, bioinspired catalysis, spectroscopy, computational approaches, and chemical biology.

The Organizing Committee gratefully acknowledges all invited speakers, participants, sponsors, and supporting organizations for their contribution to the success of this first edition. We look forward to welcoming you to Naples and to an inspiring meeting full of scientific exchange and collaboration.

The Scientific and Organizing Committees

Scientific and Organizing Committees

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The Venue

Located in the historic city centre of Naples, the Conference Center of the University of Naples Federico II is housed in the Complesso dei Santi Marcellino e Festo, a prestigious venue that blends cultural heritage with modern facilities.

The complex grew out of two Benedictine monasteries founded in the eighth and ninth centuries and rebuilt in their present form between the sixteenth and eighteenth centuries. Its frescoed hall, monumental staircase and cloister garden overlooking the Gulf are today part of the University of Naples Federico II, the oldest public university in the world in continuous operation, founded in 1224.

Largo San Marcellino 10, 80138 Naples, Italy



The conference hall



The cloister garden



The portico, where coffee breaks are served



The frescoed dome

Getting to Naples

By air

Naples International Airport (NAP, Capodichino) is about 7 km from the city centre. The centre is reached by taxi in 20–30 minutes, or by the Alibus shuttle, which runs every 20 minutes to Napoli Centrale and the port.

By rail

Naples is served by high-speed Frecciarossa and Italo services. Napoli Centrale station connects to metro lines 1 and 2 and to numerous bus routes.

By car

The A1 and A3 motorways serve the city. Traffic in the historic centre is restricted, so public transport or park-and-ride facilities are recommended.

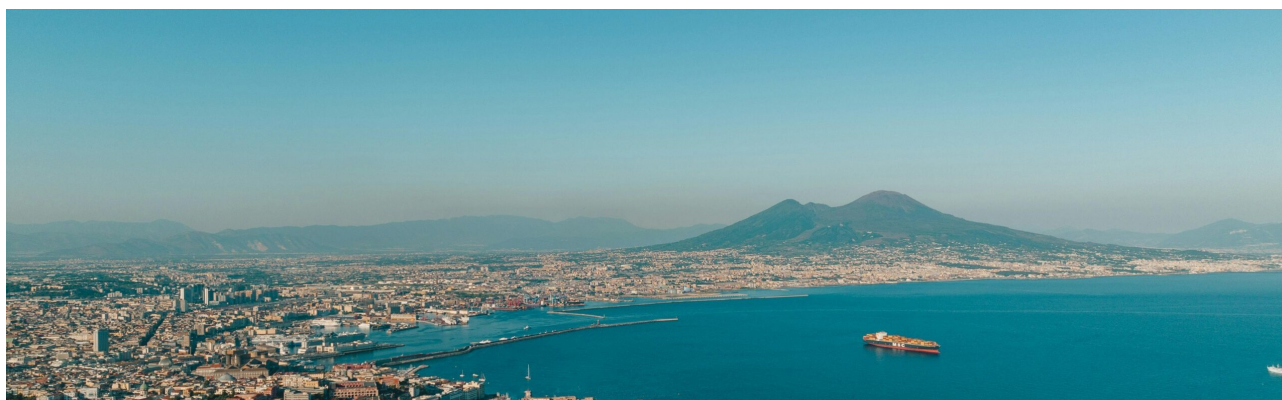
Reaching the venue

The Complesso dei Santi Marcellino e Festo is within walking distance of the city centre and is served by metro Line 1 (Dante or Museo stops). Taxis and ride-hailing services operate throughout the city.

Accommodation

Naples offers lodging across all budgets. The Centro Storico, Chiaia and Mergellina districts are the most convenient for the conference venue and for the city's main attractions. Early booking is strongly advised, as September is a busy season.

Preferential rates have been negotiated through the University of Naples Federico II at the Grand Hotel Oriente (Via Armando Diaz 44) and the Hotel Royal Continental (Via Partenope 38/44). Bookings are arranged through the Organizing Secretariat at ambralab@unina.it.



The Gulf of Naples and Vesuvius

Social Events

Welcome light aperitif

Participants are invited to a welcome light aperitif in the portico of the Complesso dei Santi Marcellino e Festo, following the first day's sessions. The same portico hosts the conference coffee breaks.

ItaBIC26 Social Dinner

The social dinner will be held on Tuesday 8 September 2026 at 20.30 at the Reale Yacht Club Canottieri Savoia, Banchina Santa Lucia 13 – Borgo Marinari, 80132 Naples. The club stands beside Castel dell'Ovo and offers a unique and elegant setting overlooking the Gulf of Naples.

Gentlemen are kindly requested to wear a jacket and tie.



Borgo Marinari



Castel dell'Ovo



General Information

Registration desk & conference secretariat

The registration desk is located at the entrance of the conference venue and remains open throughout the meeting. Participants can collect their conference materials and badges on arrival, and the staff will provide assistance and information on the scientific programme, the social events and general conference logistics. Members of the Organizing Committee will be available throughout the conference. For any question, please contact the Conference Secretariat at ambralab@unina.it.

Coffee breaks and lunches

Coffee breaks and lunches are included in the registration fee and will be served according to the scientific programme.

Attendance certificate

An attendance certificate and the payment receipt will be sent by email to all registered participants at the end of the conference.

Wi-Fi access

Complimentary Wi-Fi is available throughout the conference venue.

Network (SSID): ITABIC26

Password: Conference@26

Photography

Photographs and videos may be taken during the conference for promotional and social purposes. By attending, participants consent to the use of these images unless otherwise requested.

Social media

Participants are encouraged to share their conference experience using the official hashtag #ITABIC26.

Awards

The Organizing Committee is delighted to announce that Frontiers will support four awards dedicated to the best scientific contributions presented at the congress. Two Best Poster Presentation Awards and two Best Oral Presentation Awards will recognise excellence in scientific content, originality, presentation quality and communication effectiveness. Each award consists of a monetary prize, generously sponsored by Frontiers. Awardees are selected by the Scientific Committee and announced during the final session of the congress.

In addition, Frontiers will identify one selected contributor who will be offered the opportunity to submit a manuscript to Frontiers in Drug Discovery with publication fees waived. The manuscript will be subject to the journal's standard editorial and peer-review process.

Scientific Programme

Monday, September 7th, 2026

12:00	Registration
14:00 – 14:30	Welcome and Opening Ceremony

SESSION 1

Mechanistic Insight in Binding and Activity

Chairs: Michele Saviano and Marco Chino

14:30 – 15:00	[KL01] • Gianantonio Battistuzzi Università di Modena e Reggio Emilia, Italy Reduction thermodynamics to unravel the molecular factors influencing the E°' of redox metalloproteins
15:00 – 15:15	[*OC01] • Miriam Malagnini Aix-Marseille University Marseille, France Electrochemical characterization of <i>C. pasteurianum</i> hydrogenase II and four site-directed variants: catalysis and inhibition
15:15 – 15:30	[*OC02] • Mario Prejanò Università della Calabria Effect of distal aminoacidic mutations to Fe(III)/Fe(II) redox potential in human neuroglobin: insights from molecular modeling
15:30 – 15:40	[OC01] • Mirco Meglioli Università di Modena e Reggio Emilia Role of Distal Residues in Controlling the Interaction of Hydrogen Sulfide with Neuroglobin
15:40 – 15:55	[*OC03] • Chiara Bacchella Università degli Studi di Pavia The Many Faces of Metal Ions in Neurodegeneration
15:55 – 16:10	[*OC04] • Luigi Russo Università degli Studi della Campania "Luigi Vanvitelli" Mechanistic Insights into the Early Events of Prion Protein Pathogenic Conversion
16:10 – 16:40	Coffee Break

SESSION 2a

Natural and Artificial Metalloenzymes

Chairs: Angela Lombardi and Matteo Tegoni

16:40 – 17:25	[PL01] • Thomas R. Ward University of Basel and National Center of Competence in Research "Molecular Systems Engineering", Switzerland Artificial and Repurposed Metalloenzymes for in vivo New-to-Nature Catalysis Challenges and Opportunities
17:25 – 17:45	[GOC01] • Francesca Valetti Università di Torino Deciphering H-Cluster Protection Mechanisms in [FeFe]-Hydrogenases for the Design of Oxygen-Tolerant Catalysts
17:45 – 18:00	[*OC05] • Lorena Simunic Università degli Studi di Napoli Federico II Artificial metalloenzymes inspired by LPMOs for waste valorization
18:00 – 18:10	[OC02] • Roberta Russo Università degli Studi di Napoli Federico II Exploring the catalytic potential of a miniaturized heme enzyme in new-to-nature reactions
18:10 – 18:40	[KL02] • Ulf Hanefeld Biokatalyse, Afdeling Biotechnologie, Technische Universiteit Delft, HZ Delft, The Netherlands Versatility and Surprises with Manganese in Biocatalysis
19:00 – 21:00	Welcome Light Aperitif

Tuesday, **September 8th, 2026**

SESSION 2b

Natural and Artificial Metalloenzymes

Chairs: Flavia Nastri and Maria Elisa Crestoni

9:30 – 10:00	[KL03] • Anabella Ivancich French National Centre for Scientific Research (CNRS) and Aix-Marseille University Marseille, France De novo designed alpha-helical heme proteins as structural/functional models of bi-functional KatGs and cyt P450 peroxxygenases
10:00 – 10:15	[*OC06] • Federica Arrigoni Università degli Studi di Milano-Bicocca Multiscale Computational Insights into the Structure–Function Relationships of [FeFe]-Hydrogenases
10:15 – 10:25	[OC03] • Iago De Assis Modenez French National Centre for Scientific Research (CNRS) and Aix-Marseille University Marseille Probing Nϵ- and Nδ-histidine ligation in a de novo designed α-helical heme protein
10:25 – 10:35	[OC04] • Chiara Elena Palmiero Università degli Studi di Napoli Federico II MetalHawk 2.0: Beyond Octahedral Geometries with Neural Network Classification of Metal Sites
10:35 – 10:45	[OC05] • Alessia Procentese Università degli Studi di Napoli Federico II Design, synthesis, and characterization of a stimuli-responsive peptide-based hydrogel
10:45 – 10:55	[OC06] • Oluwasegun Eric Ajayi Università degli Studi di Siena Copper calling: Myxinidin and the ATCUN motif in metal binding
10:55 – 11:30	Coffee break and Poster Session

SESSION 3

Biocatalysis: Theoretical and Experimental Approaches

Chairs: Tiziana Marino and Roberto Fattorusso

11:30 – 11:50	[GOC02] • Luca Bertini Università degli Studi di Milano-Bicocca How Do Laccases Oxidize Recalcitrant Substrates? Insights from Classical and DFT Modeling
11:50 – 12:05	[*OC07] • Rachele Zunino Università degli Studi di Napoli Federico II QM/MM Investigation of O₂ Binding at the Binuclear Copper Active Site of Arthropod Hemocyanins: Insights Across Arthropod Lineages
12:05 – 12:20	[*OC08] • Rajesh Kushwaha University of Strasbourg Biologically Robust Copper(I) Photocatalysis Enables Oxidation of Endogenous Reductants under Aqueous Conditions
12:20 – 12:30	[OC07] • Jishnu Sai Gopinath Czech Academy of Sciences A Simple yet Efficient Model for Computing H-Atom Transfer Tunneling from Transition-State Properties
12:30 – 13:15	[PL02] • Franc Meyer Institut für Anorganische Chemie, Georg-August-Universität Göttingen, Germany Bioinspired Dicopper/Dioxygen Chemistry: New Intermediates, Electronic Structures, and Reactivities
13:15 – 14:30	Light Lunch and Poster Session

SESSION 4a

Metals in Medicine and Diagnostics

Chairs: Stefania Galdiero and Alessandro Pratesi

Saluti istituzionali di **Rossella Fasulo** (Presidente Ordine Regionale dei Chimici e dei Fisici della Campania)

14:30 – 15:00	[KL04] • Fabio Carniato Università degli Studi del Piemonte Orientale, Italy Novel Mn(II)- and Fe(III)-based probes as alternatives to conventional Gd(III) MRI contrast agents
15:00 – 15:20	[GOC03] • Luigi Messori Università degli Studi di Firenze Metal compounds as prospective antibacterial agents. Case Studies
15:20 – 15:35	[*OC09] • Thomas Scattolin Università degli Studi di Padova Gold(I)–NHC Complexes Bearing Non-Steroidal Anti-Inflammatory Drugs: An Innovative Synthetic Approach and Antitumor Activity
15:35 – 15:50	[*OC10] • Diego Di Girolamo Università degli Studi di Roma Tor Vergata NAM-Oriented In Silico Dermatokinetic Modeling of TiO₂ and Cu-Phthalocyanine Tattoo Pigments for Risk Assessment



1st Conference of the Thematic Group of Bioinorganic Chemistry

7-9 September 2026, Naples, Italy

15:50 – 16:00

[OC08] • **Simone Braccia** Università degli Studi di Napoli Federico II
Fe(III) coordination and membrane interaction drive the enhanced antimicrobial activity of a siderophore-peptide conjugate

16:00 – 16:30

Coffee Break and **Poster Session**

SESSION 4b

Metals in Medicine and Diagnostics

Chairs: Maria Pia Donzello and Riccardo Pettinari

16:30 – 16:45

[*OC11] • **Diego Tesauro** Università degli Studi di Napoli Federico II
Insights into on the behaviour of N-Heterocyclic Carbene (NHC) Gold(I) complexes targeting the Thioredoxin System

16:45 – 17:00

[*OC12] • **Lara Massai** Università degli Studi di Firenze
Metal-Based Anticancer Drugs Targeting Cytochrome c: Molecular Insights and Clinical Perspectives

17:00 – 17:15

[*OC13] • **Erika Ferrari** Università di Modena e Reggio Emilia
Charge Matters: A Sulfonated TACN Chelator Enabling Neutral and Stable Cu(II) Complexes for ⁶⁴Cu radiopharmaceuticals

17:15 – 17:30

[*OC14] • **Gina Elena Giacomazzo** Università degli Studi di Firenze
From Metal Complexes to Clinical Application: Ru(II)- and Os(II)-based Photosensitizers for PDT of Vulvar Intraepithelial Neoplasia

17:30 – 17:40

[OC09] • **Erika Stefano** Università del Salento
NMR-Based Metabolomic Approach revealed different response of Pancreatic Ductal Adenocarcinoma cells to [Pt(O,O'-acac)(γ-acac)(DMS)] and cisplatin treatment

17:40 – 17:50

[OC10] • **Lorenzo Risolo** Università del Piemonte Orientale
Fluoride Coordination in Metal Complexes: Thermodynamic, Kinetic and Structural Insights for Sensing and Diagnostic Applications

17:50 – 18:00

[OC11] • **Giulia Marcolli** Politecnico di Milano
Enhanced metal ion recognition with bispidine-based fluorinated chemosensors

20:30

Social Dinner

Wednesday, **September 9th, 2026**

SESSION 5

Metal-based drugs: Theoretical and Experimental Approaches

Chairs: Michele Benedetti and Giorgio Pelosi

9:30 – 10:00	[KL05] • Emilia Sicilia Università della Calabria, Arcavacata di Rende, Italy Computational insights on the anticancer activity of redox-activated Pt(IV) complexes
10:00 – 10:15	[*OC15] • Tiziano Marzo Università di Pisa Human Serum Albumin: A Hidden Player in the Success of Anticancer Metallodrugs
10:15 – 10:30	[*OC16] • Mauro Ravera Università del Piemonte Orientale An Unsymmetric Cisplatin-Based Pt(IV) Compound Containing 2-(2-Propynyl)Octanoate: A Coin With Many Faces
10:30 – 10:40	[OC12] • Giovanni Tonon Università di Venezia Harnessing Mesoionic Carbenes: Synthesis and Antiproliferative Activity of Novel Steroidal Metal Bioconjugates
10:40 – 10:50	[OC13] • Daniele Belletto Università della Calabria Passive diffusion of cisplatin and cisplatin-derived Pt(IV) prodrugs across a breast cancer plasma membrane: computational insights into the role of axial ligands
10:50 – 11:00	[OC14] • Alessia Dodaro Università della Calabria Advanced computational investigation of human Transferrin as a vehicle for metallodrugs absorption against cancer
11:00 – 11:30	Coffee break

SESSION 6

Metals in Medicine

Chairs: Daniela Marasco and Francesco Paolo Fanizzi

11:30 – 12:15	[PL03] • Gilles Gasser Chimie ParisTech, PSL University, CNRS Institute of Chemistry for Life and Health Sciences (i-CLeHS), France Metal Complexes for Medicinal Applications
12:15 – 12:25	[OC15] • Federica De Castro Università del Salento Sub-Lethal Stress vs Cytotoxic Threshold: Metabolic Rewiring of Neuroblastoma Cells Exposed to [Pt(η^1-C₂H₄OMe)(DMSO)(phen)]⁺ complex
12:25 – 12:35	[OC16] • Anna Maria Di Cosola Università degli Studi di Bari In vitro and ex vivo evaluation of dinuclear platinum–bisphosphonate complexes against prostate cancer bone metastasis models
12:35 – 12:45	[OC17] • Lorenzo Luciani Università di Camerino Carbazole-Based NHC Cu(I) And Au(I) Complexes As Anticancer Agents
12:45 – 12:55	[OC18] • Claudia Ghelarducci Università di Pisa Novel Pt(II) Complex-Peptide Conjugates for Targeted Anticancer Therapies: Synthesis, Characterization, and Bioactivity
12:55 – 13:10	[*OC17] • Damiano Cirri Università di Pisa Iodide in Gold and Platinum Anticancer Complexes: Reactivity Is Not Activity
13:10 – 13:30	[GOC04] • Annie Castonguay INRS, Institut national de la recherche scientifique, Canada Design of biologically active ruthenium-based organometallic complexes
13:30	Awards and Concluding Remarks

List of Posters

PO01	Anna Giorgio	Università degli Studi di Napoli, CNR, IBB
	Development of novel [99mTc][Tc(N)(PNP)]-labeled peptides for the diagnosis of $\alpha\text{V}\beta 3$ -positive cancers	
PO02	Mattia Fanelli	Università degli Studi di Firenze
	Deciphering the Mode of Action of Anticancer Gold Compounds via Shotgun Proteomics and Bioinformatics	
PO03	Erika Stefano	Università del Salento
	Study of [Pt(O,O'-acac)(γ -acac)(DMS)] and cisplatin anticancer activity on Pancreatic Ductal Adenocarcinoma cells	
PO04	Rossana Galassi	Università di Camerino
	New Details on the Anticancer Activity of Imidazolyl based Gold(I) Complexes	
PO05	Martina Aguanno	Università degli Studi di Firenze
	Advanced LC-MS strategies for the characterization of metal/protein adducts: methodological optimization and oncological applications	
PO06	Lorenzo Emiliano Imbò	Università degli Studi di Napoli Federico II
	Exploring Fe(III) coordination and membrane interaction of a siderophore-peptide conjugate: Enhancing synergistically the antimicrobial activity	
PO07	Francesca Fasano	Scuola Superiore Meridionale
	ATCUN-Mediated Copper Binding in Myxinidin	
PO08	Chiara Gabbiani	Università di Pisa
	Highly Cytotoxic Gold(I) Complexes Bearing Anthracenyl-Functionalized Phosphine Ligands	
PO09	Attilio Squadrini	Università di Parma
	Design and Antitumoral Evaluation of a Bioconjugable Copper(II)-Thiosemicarbazone Complex: ROS Targeting and Cytotoxicity in HT29 and A549 Cell Lines	
PO10	Dominga Rogolino	Università di Parma
	Thiohydrazones and their copper(ii) complexes as bioactive compounds	
PO11	Susanna Grasso	Sapienza Università di Roma
	Auranofin binding to uracil and thiouracils assayed by IRMPD spectroscopy	
PO12	Miriam Caviglia	Università di Camerino
	Copper and silver complexes as next-generation metallodrugs for the treatment of resistant cancers	
PO13	Valentina Ceccherini	Università degli Studi di Firenze
	Metal-Based Complexes as Emerging Antibacterial Agents: An Overview of Novel Design Strategies	
PO14	Andrea Angelucci	Sapienza Università di Roma
	Synthesis, physico-chemical properties and In Vitro studies of new porphyrazine complexes of the lanthanide series. Exploration of their potential applications in biomedicine	
PO15	Valentina Pecchioli	Università degli Studi di Firenze
	Exploring ferroptosis-related metabolomic signature of gold-based anticancer compounds: comparison with Erastin in A2780 ovarian cancer cells	
PO16	Vinay Kumar Srivastava	D.S College, Aligarh, India
	MoS ₂ Nanoparticles Derived from a Bioactive Pyrrolidine Dithiocarbamate Molybdenum(V) Complex	
PO17	Diego Di Girolamo	Università di Roma Tor Vergata
	The impact of cavitation treatments on optical properties, aggregation and toxicity of PG7 and PY14	
PO18	Jitka Pracharova	Palacký University Olomouc
	Antimetastatic Activity of a Novel (Arene)Ruthenium(II) Naphthopyran Complex in Metastatic Cancer Models	
PO19	Nicola Garofalo	Università del Salento
	Synthesis of Platinum(II) complexes with chelating amines: a greener approach using water/choline chloride-based deep eutectic solvents	
PO20	Chiara Santoni	Università Politecnica delle Marche
	Reducing chemoresistance in Triple-Negative Breast Cancer through PON2 silencing: FTIRM insights into response to combined therapy	

PO21	Martyna Kapica	University of Gdańsk, Poland
	Electrostatically-driven assembly of cationic lipopeptides with hexacyanoferrate anions: a thermodynamic and in silico study	
PO22	Matteo Tegoni	Università di Parma
	(The Power of) Vision3D: creating new virtual environments for 3D protein visualization and science dissemination	
PO23	Matteo Tegoni	Università di Parma
	Evolving SpyTag/SpyCatcher system into new artificial proteins	
PO24	Francesco Giaretto	Università di Torino
	Structural characterization of the chimeric enzyme CYP-SOX by pulsed EPR spectroscopy	
PO25	Hansol Kim	SoonChunHyang University
	Single-site hydrogen-bond modulation enhances catalytic ester hydrolysis in a Zn(II)-TPA scaffold	
PO26	Alessandra Esposito	Università degli Studi di Napoli Federico II
	Coupling Artificial Metalloenzymes with Photosensitizers for H ₂ Evolution	
PO27	Maria De Fenza	Università degli Studi di Napoli Federico II
	From nitrogen to sulfur ligation: reprogramming reactivity in miniaturized heme enzymes	
PO28	Luisa Curlacci	Università degli Studi di Bari
	Metal Binding Dynamics in Human Ctr1(1–25): A pH-Dependent Coordination Switch	
PO29	Domenico Loreto	Università degli Studi di Napoli Federico II
	Design, Synthesis and Characterization of a Zn(II)His ₃ Site in a Heterodimeric Three-Helix Bundle Scaffold	
PO30	Simone Molinaro	Università degli Studi di Napoli Federico II
	Artificial Type II copper proteins: a spectroscopic characterization	
PO31	Naveen Kumar	Università degli Studi di Napoli Federico II
	Oxidative biotransformation of lignin by a miniaturized heme-enzyme	
PO32	Concetta Avitabile	Istituto di Cristallografia- CNR
	Ruthenium Hexamine-Mediated Paper-Based PNA Biosensor for Pancreatic Ductal Adenocarcinoma Diagnosis	

Bioinorganic Chemistry in Medicine and Nanotechnology

Spectroscopic and computational methods

Natural and artificial metalloenzymes

Bioinorganic compounds in sensing and diagnostics



Plenary Lectures

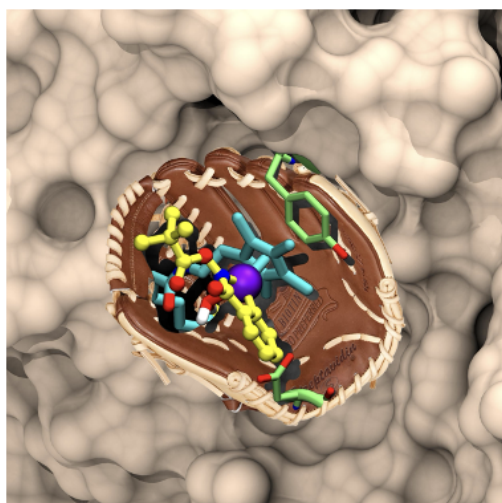
Artificial and Repurposed Metalloenzymes for in vivo New-to-Nature Catalysis Challenges and Opportunities

Thomas R. Ward^{1*}

¹Department of Chemistry, University of Basel and National Center of Competence in Research "Molecular Systems Engineering", Basel, Switzerland
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Artificial metalloenzymes (ArMs) have attracted increasing attention in the past two decades as attractive alternatives to either homogeneous catalysts or enzymes. ArMs result from anchoring a catalytically-competent abiotic metal cofactor within a host protein, see Figure. The resulting ArMs combine attractive features of both homogeneous- and bio-catalysts [1-3]. Within the group, we have chemo-genetically optimized the performance of ArMs for twenty different reactions.

Following a general introduction on the underlying principles of ArMs, this talk will highlight our recent progress towards engineering and evolving hybrid catalysts with an emphasis on new-to-nature transformations for whole-cell biocatalysis, including metal-catalyzed hydrogen atom transfer chemistry.



Reactions implemented:

Hydrogenation	Alcohol Oxidation
Transfer Hydrogenation	Sulfoxidation
Allylic Alkylation	Dihydroxylation
Suzuki Cross-Coupling	Peroxydation
C–H activation	Michael Addition
Enzyme Cascades	Hydroamination
Olefin Metathesis	Hydroxylation
Carbene Insertion	Cyclopropanation
Nitrene Insertion	Halogenation
H-Atom Transfer	CO ₂ -reduction

Figure Artificial metalloenzymes result from anchoring an organometallic catalyst within a protein scaffold. The resulting hybrid catalyst can be optimized by combining both chemical and genetic strategies.

References:

- [1] H. J. Davis, T. R. Ward, ACS Cent. Sci., 2019, 5, 1120.
- [2] F. Schwizer, Y. Okamoto, T. Heinisch, Y. Gu, M. M. Pellizzoni, V. Lebrun, R. Reuter, V. Köhler, J. C. Lewis and T. R. Ward, Chem. Rev. 2018, 118, 142.
- [3] Z. Zou, B. Higginson, T. R. Ward, Chem, 2024, 10, 2373.

Bioinspired Dicopper/Dioxygen Chemistry: New Intermediates, Electronic Structures, and Reactivities

Franc Meyer*

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For controlling the activation of O₂ and its subsequent coupled multielectron/multiproton transformations, some enzymes take advantage of the cooperative action of two (or more) proximate metal ions hosted within the protein active site. Understanding the functional principles of nature's sophisticated blueprints provides great inspiration for the development of novel bioinspired systems enabling oxidation/oxygenation catalysis with O₂. Metal ion spin states as well as spin state changes are important factors for determining the catalysts' reactivity and selectivity. This presentation will discuss spin state effects and spin dependent reaction trajectories in model systems of prominent coupled dicopper metalloproteins. Specifically, the presentation will show structural snapshots of the O₂ binding event relevant to biological type 3 dicopper sites; unusual interactions of Cu₂/O₂ intermediates with Lewis acids; proton- and redox-mediated interconversions between, and equilibria of, different Cu₂/O₂ species as well as a disentangling of PCET thermochemistry and kinetics; and catalytic substrate conversion by unusual ambiphilic peroxodicopper complexes.

References:

- [1] N. Kindermann et al., *J. Am. Chem. Soc.* **2017**, 139, 9831.
- [2] A. Brinkmeier et al., *J. Am. Chem. Soc.* **2021**, 143, 10361.
- [3] A. Brinkmeier et al., *J. Am. Chem. Soc.* **2021**, 143, 17751.
- [4] T. Lohmiller et al., *JACS Au* **2022**, 2, 1134.
- [5] C.-J. Spyra et al., *Angew. Chem. Int. Ed.* **2025**, 64, e202416022.
- [6] H.-T. Zhang, F. Meyer et al., unpublished work.

Metal Complexes for Medicinal Applications

Gilles Gasser^{1*}

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Metal complexes are currently playing a tremendous role in medicine [1]. For example, the platinum complex cisplatin and its derivatives oxaliplatin and carboplatin are employed in more than 50% of the treatment regimes for patients suffering from cancer!

Over the last years, our research group focused its attention on the development of novel metal complexes as imaging and therapeutic agents against cancer and parasitic diseases [2-5]. During this talk, we will present our latest results, including in vivo results, on these topics.

References:

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Keynote Lectures

Reduction thermodynamics to unravel the molecular factors influencing the E° of redox metalloproteins

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The strict control over the reduction potential (E°) of the redox centers of metalloproteins and metalloenzymes is essential for the functioning of the electron transport chains associated to bioenergetics and redox metabolism as well as for controlling the catalytic efficiency of redox metalloenzymes.

Significant insight into the molecular factors controlling the E° of the metal centers in electron transfer (ET) proteins and redox enzymes is provided by the enthalpic (ΔH°_{rc}) and entropic (ΔS°_{rc}) contributions to the reduction potential, obtained from the analysis of the temperature-dependence of E° [1].

Reduction enthalpy turns out to be related to ligation features in the first coordination sphere of the metal and weak binding and electrostatics in the surrounding matrix, whereas the entropic contribution is usually dominated by reduction-induced solvent-related molecular events [1], which exert a very limited effect on the reduction free energy (ΔG°_{rc}) due to the compensatory effects of the associated enthalpic terms (a phenomenology known as enthalpy-entropy compensation, EEC) [1-3].

As consequence, reduction entropy is much less important in determining the reduction potential of redox metalloproteins that it would appear from the raw thermodynamic data, exerting a real influence only when the metal site undergoes to reduction-induced protein-based changes in the accessible configurational microstates [1].

Therefore, in most cases the E° changes due to point mutations, ligand binding and charge changes have an ultimate enthalpic origin. Hence, they should be accounted for with coordination chemistry and electrostatics notions [1-4]. Only if they don't, protein-based entropic effects could play a role.

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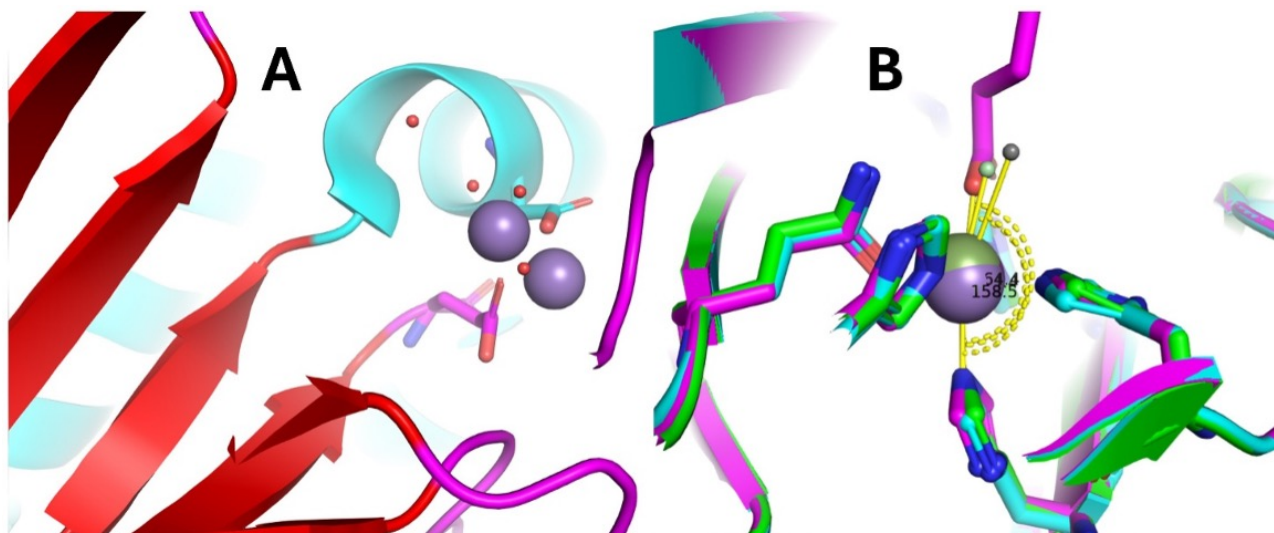
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Versatility and surprises with manganese in biocatalysis

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Enzymes are the basis of biocatalysis and about 35% of them are metalloenzymes. Manganese as bioavailable and earth abundant metal is one of the catalytically active metal ions. Manganese can act both as Lewis acid and redox catalyst. A surprising Lewis activity was found for the cupin identified in *Granulicella tundricola*. This hydroxynitrile lyase (HNL) [1], is only catalytically active if Mn has a distorted octahedral structure (**Figure 1B**) [2]. Even more remarkable is that in the pyruvate dependent aldolase from *Rhizorhabdus wittichii* RW1 (formerly called *Sphingomonas wittichii*; *Sw*HKA) the catalytically active metal can have two mutually exclusive metal binding sites (**Figure 1A**) [3,4].



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De novo designed alpha-helical heme proteins as structural/functional models of bi-functional KatGs and cyt P450 peroxxygenases

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Heme-containing proteins are versatile catalysts performing disproportionation of H₂O₂ (catalases [1]), substrates oxidation (peroxidases [2], bi-functional catalase-peroxidases [1]) and activation of inert C-H bonds/oxygenation reactions (cyt P450 monooxygenases [2]). Such versatility relies on the heme axial ligands (Tyr, His, Cys) and 2nd coordination sphere. The canonical Fe(IV)=O Por^{•+} catalytic intermediate shows concerted reactivity with specific Trp/Tyr sites. The Fe(IV)=O Trp[•] (or Tyr[•]) enables alternative catalysis such as anti-tuberculosis prodrug activation by KatGs [3a,b] or biomass bioconversion by lignin peroxidases [3c]. Our advantageous use of de novo designed heme proteins, that are artificial scaffolds capturing essential features of the heme active site in natural P450s and KatGs plus the required surrounding protein matrix, resulted in dimers of antiparallel alpha-helical dimers (with one heme per dimer, bound to His or Cys as a function of pH [4]), thus mimicking peroxidases/KatGs or cyt P450s, respectively, all in one single artificial metalloprotein. Specific heme coordination and environment/reactivity are assessed by EPR and resonance Raman spectroscopies. Modified peptide sequences altering the distal side of the thiolate heme or the pK_a of the Cys16 ligand, or introducing a Trp[•] site formed subsequently to the Fe(IV)=O Por^{•+}, will be discussed.

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Novel Mn(II)- and Fe(III)-based probes as alternatives to conventional Gd(III) MRI contrast agents

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Magnetic resonance imaging (MRI) is established as a powerful, noninvasive diagnostic tool, with its sensitivity significantly boosted by efficient contrast agents. While the majority of clinically approved agents currently utilize Gd(III) complexes due to their favorable electronic and magnetic properties, growing safety concerns regarding long-term gadolinium exposure, especially in patients with kidney impairment, have sparked intensive research into gadolinium-free alternatives. Among these emerging options, Mn(II) and Fe(III) complexes have drawn significant interest. In this project, two main examples of probes will be discussed. On one hand, a nanogel based on chitosan covalently functionalized with a bisamide derivative of t-CDTA is presented, which can effectively coordinate paramagnetic Mn²⁺ ions [1]. This probe offers several advantages: i) it provides MRI contrast seven times higher than typical monohydrated Gd³⁺-chelates at clinical field strengths; ii) it maintains high formulation stability over time at both pH 5 and 7.4, thereby preventing metal leaching and particle aggregation; and iii) it demonstrates favorable extravasation and accumulation properties. On the other hand, the project explores the synthesis and characterization of Fe(III)/gallic acid coordination nanoparticles coated with low molecular weight polyethylene glycol (PEG), designed to enhance second-sphere water interactions and boost relaxivity at clinical magnetic fields [2]. The ¹H NMR relaxometric behavior of these nanoparticles was thoroughly evaluated across a range of magnetic field strengths and temperatures and compared to similar systems. In conclusion, these Mn(II) and Fe(III) nanoproboscopes represent promising, safer, and high-performance alternatives to conventional gadolinium-based contrast agents for advanced clinical MRI.

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Computational insights on the anticancer activity of redox-activated Pt(IV) complexes

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The accidental discovery of the cytotoxic activity of cis-diamminedichloridoplatinum (II), or cisplatin, and its approval by FDA in 1978 changed the course of the modern chemotherapy and inspired the synthesis of many platinum-based compounds to solve various issues of toxicity and limitations associated with the original cisplatin. However, as many of these designed and tested drugs/prodrugs continue to be plagued by an array of side effects and DNA damage repair-inducing drug resistance, a great deal of attention has been devoted to the search for alternative strategies able to overcome such well-known shortcomings. Here, two possible alternatives are examined: a) the introduction of structural changes with the synthesis of six-coordinate Pt(IV) complexes proposed as inert prodrugs, activated by reduction for the release of active Pt(II) anticancer agents [1]; b) shifting of target focus from double stranded DNA to DNA of other configurations, such as G-quadruplexes [2]. The outcomes of both quantum-mechanical DFT calculations and Molecular Dynamics (MD) simulations aimed at examining the behaviour of octahedral Pt(IV) prodrugs and the mode of interaction of Pt(II) complexes with non-canonical G-quadruplex DNAs (Figure 1) are illustrated.

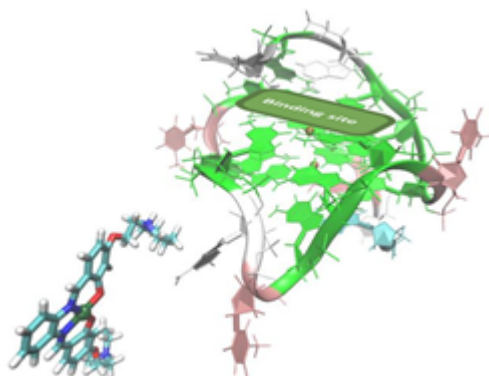


Figure 1 – Starting arrangement of the MD recognition process for an investigated Pt(IV) complex.

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Gold Oral Communications

Deciphering H-Cluster Protection Mechanisms in [FeFe]-Hydrogenases for the Design of Oxygen-Tolerant Catalysts

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[FeFe]-hydrogenases are efficient biocatalysts for hydrogen turnover, owing to the unique organometallic H-cluster. Understanding how the surrounding protein matrix controls the reactivity of this cofactor is essential for developing robust biomimetic systems. The oxygen-tolerant [FeFe]-hydrogenase CbA5H from *Clostridium beijerinckii* [1] provides a unique model to investigate how first- and second-coordination sphere interactions modulate the chemical properties of the H-cluster and protect it from oxidative damage. The PRIN 2022 funded MORF project combined protein engineering, spectroscopy, electrochemistry and DFT calculations to elucidate the molecular basis of oxygen tolerance and transfer it to oxygen sensitive enzymes.

Mutagenesis studies demonstrated that residues A419, M393, I424, and A425, located within the inner (4 Å) and outer (8 Å) interaction spheres of the diiron subsite, significantly modulate catalysis [2]. Additional residues involved in conformational switching (L364, P386, A561) were associated with oxygen tolerance [3], enabling the discovery of two new [FeFe]-hydrogenases that display oxygen resistance similar to CbA5H despite sharing only ~75% sequence identity. The results further revealed a key role of the monomer–dimer equilibrium in regulating activity, suggesting dimer-interface engineering as a promising strategy for future optimization.

DFT calculations complemented the experimental studies, providing atomistic insight into the electronic consequences of O₂-dependent morphing and active-site modifications, in particular on the role of conserved Cys367, by predicting the effect of replacing it with Aspartate or Selenocysteine.

Gain-of-function variants of the oxygen-sensitive hydrogenase CrHydA1 were obtained through only two amino acid substitutions, whose protective effects were stabilized by ET domains in the MAIA chimeric scaffold.

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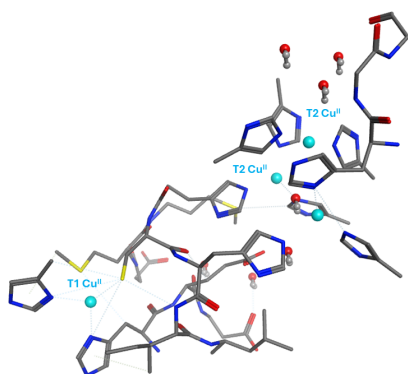
How Do Laccases Oxidize Recalcitrant Substrates? Insights from Classical and DFT Modeling

Luca Bertini^{1*}, Lara Callea², Carla Orlando¹, Giole Fumagalli¹, Federica Arrigoni¹, Francesca Persico¹, Mattia Fossati¹, Andrea Fasano¹, Jacopo Vertemara¹, Giuseppe Zampella¹, Luca De Gioia¹, Claudio Greco²cond Author^{1,2}, Third Author¹

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Laccases are multicopper oxidases capable of catalyzing the oxidation of a wide range of organic substrates through long-range electron transfer to the T1 copper site. While fungal high-redox-potential laccases are known to efficiently oxidize phenolic compounds, increasing evidence suggests that both fungal and low-potential bacterial laccases may also act on highly recalcitrant substrates, including polycyclic aromatic hydrocarbons (PAHs) and synthetic polymers such as polyethylene. The molecular determinants governing substrate recognition, binding, and oxidation in these systems, however, remain poorly understood. Here, we present a computational investigation of substrate binding and oxidation by bacterial and fungal laccases using a multiscale approach combining classical molecular modeling and density functional theory (DFT) calculations. Classical simulations were employed to characterize substrate recognition and identify productive binding modes within the enzyme environment, while DFT cluster models of the catalytic site were used to explore electron-transfer and oxidation mechanisms. A set of substrates, including phenolic compounds, PAHs, and polyethylene model molecules, was examined to elucidate the structural and electronic factors controlling reactivity. Particular attention was devoted to the interaction of substrates with the T1 copper site and to the thermodynamic and kinetic feasibility of the initial oxidation step. The calculations reveal how substrate-dependent binding modes, electronic coupling, and local active-site interactions modulate oxidation efficiency across different laccase families. These results provide new molecular-level insight into the catalytic versatility of multicopper oxidases and contribute to understanding their potential application in the degradation and valorization of persistent aromatic and polymeric materials.



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Metal compounds as prospective antibacterial agents. Case Studies

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Due to their significant chemical diversity, metal compounds are attracting increasing interest from the scientific and medical communities as a potential source of new antimicrobial agents [1]. This is in response to the growing issue of antibiotic resistance. However, the development of metal compounds for use as antimicrobial agents typically involves traditional drug discovery procedures, which are often costly, time-consuming and risky. Here, we demonstrate how a few well-established drug discovery strategies can be successfully and conveniently applied to antimicrobial metal compounds, particularly gold compounds [2]. This accelerates the clinical translation of new treatments. Specifically, we discuss cases of drug repurposing and drug combinations, using a few examples from our ongoing collaboration with Giovanna Batoni's research group in Pisa [3,4].

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Design of biologically active ruthenium-based organometallic complexes

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Our research program aims at creating innovative metal-based therapeutics that could potentially overcome problems associated with existing chemotherapies. This presentation will focus on different aspects of a promising class of anticancer, antimicrobial and antifungal metal-based compounds, notably Ru(II) organometallic complexes, and the influence of structural transformations on their biological properties. We are particularly interested in the design of ruthenium complexes that include biologically active ligands in their structure, leading to drug candidates that display a considerable activity via multiple modes of action, simultaneously. We also aim at developing novel strategies for the delivery of ruthenium complexes that include moieties with the unique ability to undergo reversible cycloaddition reactions with cell-penetrating/targeting agents. This talk will provide an overview of our most recent findings.



Star Oral Communications

Electrochemical characterization of *C. pasteurianum* hydrogenase II and four site-directed variants: catalysis and inhibition

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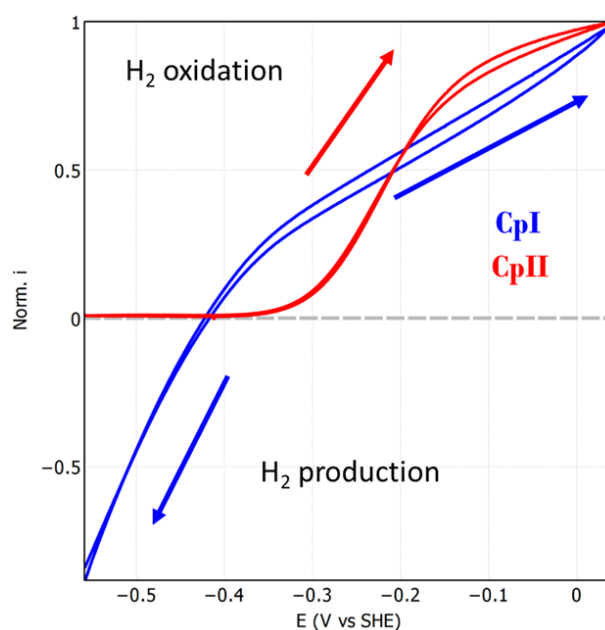
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FeFe-hydrogenases are amazing catalysts for bio-hydrogen production, thanks to a unique highly conserved active site called H-cluster. These enzymes show a wide variety of properties, proving that structural elements located far away from the active site play a role in tuning the catalysis. Understanding these molecular mechanisms is crucial to design new enzymes with specific features, to be employed for H₂ technologies.

Clostridium pasteurianum hydrogenases I and II are perfect examples of how two homologous enzymes can catalyse very different reactions: *Cpl* is bidirectional (it can both produce and oxidise H₂), reversible (no large driving force is required to obtain a reaction) and quite sensitive to O₂ inhibition. On the other side, *CplI* is almost unidirectional for H₂ oxidation, irreversible, and shows a peculiar resistance to O₂ exposure [1].

With the aim to find the molecular reasons behind the different catalytic properties of these two enzymes, four *CplI* variants were created changing four residues in “hot” positions (close either to the active site or to other iron-sulfur clusters) to the ones found in *Cpl*. Wild-type enzymes and variants were characterized using protein film electrochemistry, a powerful technique that allows to study the catalysis of redox enzymes by monitoring the activity at the electrode as an electric current. Some variants made *CplI* more similar to *Cpl*, while others interestingly had the opposite effect. S73A variant gave a surprising effect when exposed to O₂, making *CplI* react like *Cpl*, thus allowing us to elaborate a general model describing the reaction with O₂ [2].

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Effect of distal aminoacidic mutations to Fe(III)/Fe(II) redox potential in human neuroglobin: insights from molecular modeling

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Human neuroglobin (hNeuro) is an heme-dependent enzyme involved in the intracellular signaling, protection of cells from apoptosis and/or by reducing the ferric cytochrome-c released in the cytosol [1]. All these functions require a strict control over the redox state of the heme iron, therefore the understanding of the molecular factors controlling the E° value of the Fe(III)/Fe(II) couple is relevant for the physiological role of neuroglobin.

In the current presentation, the contribution to the control of Fe(III)/Fe(II) redox potential from distal amino acid residues has been investigated in the framework of molecular dynamics (MD) simulations, focusing on single-mutant systems (hNeuro-Y44A, hNeuro-Y44F, hNeuro-K67A), double-mutants containing models (hNeuro- C46A/C55A) and triple-mutants containing systems (hNeuro-Y44A/C46A/C55A, hNeuro-Y44F/C46A/C55A and hNeuro-K67A/C46A/C55A), in comparison with wild type enzyme. Analysis of structural behaviours from MD well compared to the experimental results, providing atomistic details that impact on the rationalization of hNeuro's reactivity and physiological role.

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The Many Faces of Metal Ions in Neurodegeneration

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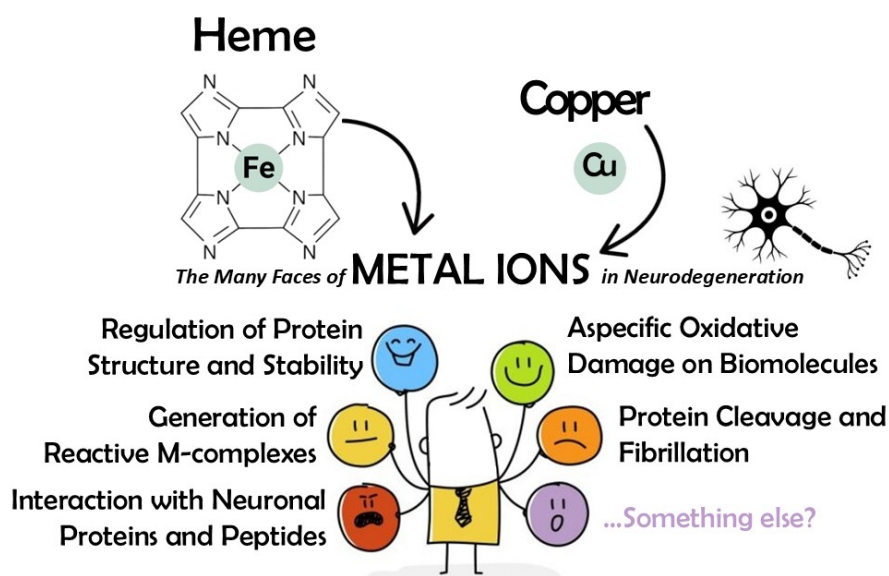
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Transition metal ions are indispensable for life, supporting a broad range of biological functions including oxygen transport, energy metabolism, redox regulation and enzymatic catalysis. Yet, the same chemical properties that make these molecules essential can become detrimental when their homeostasis is compromised.¹ Altered copper and heme metabolism has emerged as a common feature of several oxidative stress-related pathologies, such as neurodegenerative disorders, vascular diseases, cancer, etc.

A major challenge in this field is understanding how these reactive species interact with biomolecular targets and how such interactions influence protein structure, aggregation, and toxicity. Proteins associated with neurodegeneration, including amyloid- β peptides, tau, and prion proteins, are particularly relevant because of their ability to bind metal ions and undergo profound conformational changes. These interactions may not only modulate protein assembly pathways, but also generate new redox-active complexes capable of promoting oxidative stress.

Our research focuses on deciphering the molecular basis of heme- and copper-mediated processes in biologically relevant peptide and protein systems. By combining structural, spectroscopic, and reactivity studies, we investigated the nature of metal-binding sites and the consequences of complex formation on protein/peptide stability. Special attention was devoted to understanding how metal-induced structural rearrangements affect aggregation, solubility, and redox activity.²⁻⁴

Despite considerable progress, the mechanisms linking metal dysregulation, protein misfolding, and oxidative damage remain far from being fully understood; anyway, the possibility that metal ions can influence protein assemblies through yet-unrecognized mechanisms opens new avenues for investigation.



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Mechanistic Insights into the Early Events of Prion Protein Pathogenic Conversion.

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The aberrant misfolding and aggregation of native proteins into oligomers and fibrils are central to the pathogenesis of numerous neurodegenerative disorders [1,2]. Among these, Prion Diseases - or transmissible spongiform encephalopathies - are driven by the conformational conversion of the native cellular prion protein (PrP^C) into misfolded oligomeric or fibrillar species (PrP^{Sc}) that accumulate in the brain. Experimental evidence increasingly demonstrates that transient, intermediate misfolded conformations serve as the key drivers of this aggregation cascade. Recently, a high-resolution description of a β -sheet-enriched intermediate state (β -PrPI) detected during the folding mechanism of the pathological human prion protein HuPrP(90-231) has been reported [3]. NMR data revealed that, within the regions spanning the native two β -sheets and the first α -helix, β -PrPI samples conformations with a pronounced propensity to expand the β -sheet architecture relative to the native state, without compromising the stability of the remaining α -helix [3]. Here, we illustrate the molecular mechanism by which this on-pathway β -PrPI intermediate induces amyloid fibril formation through the assembly of transient oligomeric species (β -PrPI(O)). Additionally, we provide a high-resolution characterization of the dynamic equilibrium between the native HuPrP(90-231) form and these soluble, NMR-invisible β -PrPI(O) species involved in the early stages of fibrillation. Our data indicate that the N-terminal region of the protein within these oligomeric states exhibits remarkable structural similarities to mature fibrils [4] at the very inception of prion fibrillation. Overall, this study outlines a definitive structural trajectory for the initial steps of PrP^C conversion, uncovering promising structural hot spots for targeted therapeutic intervention in prion diseases.

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Artificial Metalloenzymes inspired by LPMOs for waste valorization

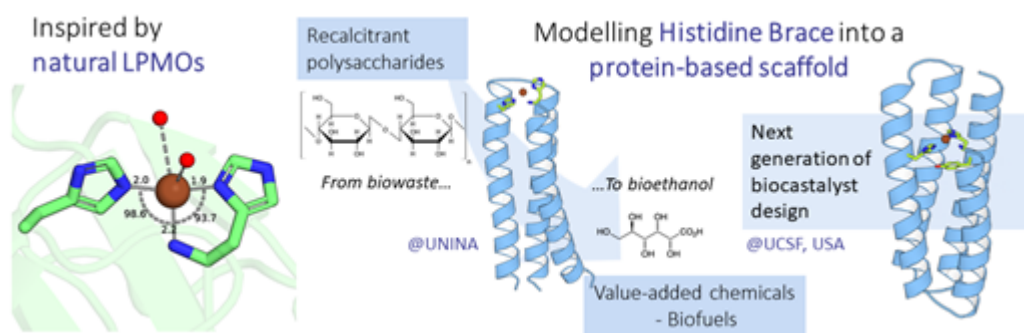
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Bioinorganic chemistry offers innovative strategies for addressing global sustainability challenges, particularly through the conversion of biomass waste into valuable chemical products [1]. Lytic polysaccharide monooxygenases (LPMOs) exemplify this potential, catalyzing oxidative depolymerization of recalcitrant polysaccharides found in biomass. For performing this task, they employ a peculiar type 2 copper center involving the Histidine Brace (HB) coordination motif [2]. *De novo* protein design is a powerful approach for the development of artificial peptide-based biocatalysts that are both spectroscopic and functional mimics of LPMOs [3-4]. In this context, at AMBRA Lab, we engineered the HB motif into small, stable α -helical scaffolds [5], yielding miniLPMO and dHisB (designed Histidine Brace) models. The latter is a three-helix bundle that reproduces key spectroscopic features of native LPMOs and oxidizes model substrates. Modifications to the HB, including methylation and acetylation, were further introduced to probe how changes in copper coordination affect metal binding and reactivity. Building on the knowledge gathered through dHisB model, a collaboration with the DeGrado Lab (UCSF) led to the design of a new generation of LPMO mimics. These designs were aimed at (i) enhancing carbohydrate binding through an extended substrate-binding surface; (ii) introducing a tyrosine residue in proximity of the copper center to recapitulate the second coordination shell of most LPMOs; (iii) reformulate the structure as a single protein chain amenable to crystallization. Together, these analogues represent a step forward in developing structurally characterized biocatalysts inspired by LPMOs that combine the histidine-brace active site with robust peptide scaffolds.



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Multiscale Computational Insights into the Structure–Function Relationships of [FeFe]-Hydrogenases

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[FeFe]-hydrogenases are among the most efficient biological catalysts for hydrogen turnover and represent key systems for understanding the molecular principles of biological dihydrogen production and activation [1]. Their reactivity originates from the H-cluster, a unique organometallic iron-sulfur active site bearing unusual CO and cyanide ligands and finely tuned for proton-coupled electron transfer. However, catalysis is not determined by the active site alone: accessory iron-sulfur clusters, when present, and the surrounding protein matrix play a crucial role in controlling electron and proton transfer, substrate access, redox properties, and catalytic bias [2].

A central question in [FeFe]-hydrogenase chemistry is how this complex molecular framework responds to different functional conditions, particularly exposure to molecular oxygen. Although most [FeFe]-hydrogenases are rapidly inactivated by molecular oxygen, selected enzymes display reversible oxygen-protective behaviour through mechanisms that differ across organisms and enzyme variants. Understanding how these protective strategies arise requires connecting active-site chemistry with long-range electron transfer, gas diffusion, protein-controlled dynamics, and the electronic properties of oxygen-protected states.

In this context, computational approaches based on quantum chemistry, hybrid QM/MM techniques, molecular dynamics, and data-driven methods provide powerful complementary insights to experiment. Here, we highlight selected recent studies showing how such approaches can help address open mechanistic questions in [FeFe]-hydrogenases, including the role of Fe–S clusters in electron transfer, substrate and molecular oxygen diffusion pathways, and the still elusive mechanisms of active-site chemistry [3] [4].

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QM/MM Investigation of O₂ Binding at the Binuclear Copper Active Site of Arthropod Hemocyanins: Insights Across Arthropod Lineages

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Hemocyanin (Hc) is a copper-containing protein responsible for the reversible binding and transport of molecular oxygen in arthropods and mollusks [1,2]. Beyond respiration, Hc participates in several immune-related and redox processes, highlighting its multifunctional biological role [3]. Its active site consists of a type-3 dicopper center, where each copper ion is coordinated by three histidine residues. Oxygen binding occurs through reversible coordination of O₂ between the two copper atoms and is accompanied by significant structural rearrangements.^{4,5}

Although the structure and oxygen-binding mechanism of Hc have been extensively investigated experimentally, computational studies have largely focused on the hemocyanin of *Limulus polyphemus* [6,7]. Consequently, the molecular determinants governing oxygen affinity across arthropod lineages, particularly in relation to adaptation from marine to terrestrial environments, remain poorly understood.

Herein, we present a comparative computational investigation of O₂ binding in Hcs from representative arthropod species. Molecular dynamics simulations combined with QM/MM calculations were employed to characterize both the deoxy and oxy states of the binuclear copper active site. The results reveal substantial variability in oxygen-binding energetics across species. Oxygenation is consistently associated with contraction of the Cu–Cu distance and formation of a peroxide-like O₂ adduct. Furthermore, second-sphere interactions, including hydrogen-bonding networks and local solvent organization, emerge as key factors modulating oxygen affinity and stabilizing the oxygenated state.

These findings provide new atomistic insights into the structure–function relationships of arthropod hemocyanins and advance our understanding of the molecular mechanisms underlying the evolutionary adaptation of respiratory proteins.

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Biologically Robust Copper(I) Photocatalysis Enables Oxidation of Endogenous Reductants under Aqueous Conditions

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Earth-abundant Cu(I) complexes are attractive photoredox catalysts for chemical biology. Yet, their application in physiologically relevant environments remains fundamentally constrained by two major challenges: (i) intrinsic ground-state instability caused by disproportionation, aerobic oxidation, and rapid demetallation by intracellular thiols/metallothionein; (ii) poor excited-state performance arising from pseudo-Jahn–Teller-induced flattening of the ³MLCT state [1,2]. Herein, we report a series of substituted phenanthroline-based homoleptic Cu(I) complexes, **Cu1–Cu3**, with systematically varied aryl substituents that were designed to simultaneously enforce tetrahedral geometry, sterically shield the Cu(I) centre, and create a hydrophobic microenvironment around the metal [3].

These complexes display exceptional robustness under biologically relevant conditions. UV–Vis spectroscopic analyses confirmed that Cu1–Cu3 (60 μM) remain fully intact in aqueous HEPES buffer (pH 7.4) in the presence of physiological glutathione (1 mM), excess L-methionine (1 mM), and even metallothionein (60 μM), the principal intracellular Cu(I) sink, demonstrating remarkable resistance to thiol-mediated ligand exchange and metal sequestration. Critically, this ground-state stability does not compromise photocatalytic performance. Under blue-light irradiation, Cu1–Cu3 generate both singlet oxygen and superoxide radical anion, indicating both Type I/II pathways. Beyond this, these complexes also efficiently induced photoredox catalysis of four key endogenous reductants, i.e, NADH, ascorbate, glutathione, and cysteine. Scavenger experiments establish that NADH oxidation proceeds predominantly via direct excited-state electron transfer. The most active complex, Cu3 presented turnover frequencies approaching those of the benchmark [Ru(bpy)₃]²⁺ system. Collectively, this work contributes to resolve the often-perceived incompatibility of Cu(I) photocatalysts' biological stability and photocatalytic activity, and establishes a rational design framework for earth-abundant intracellular photoredox catalysts.



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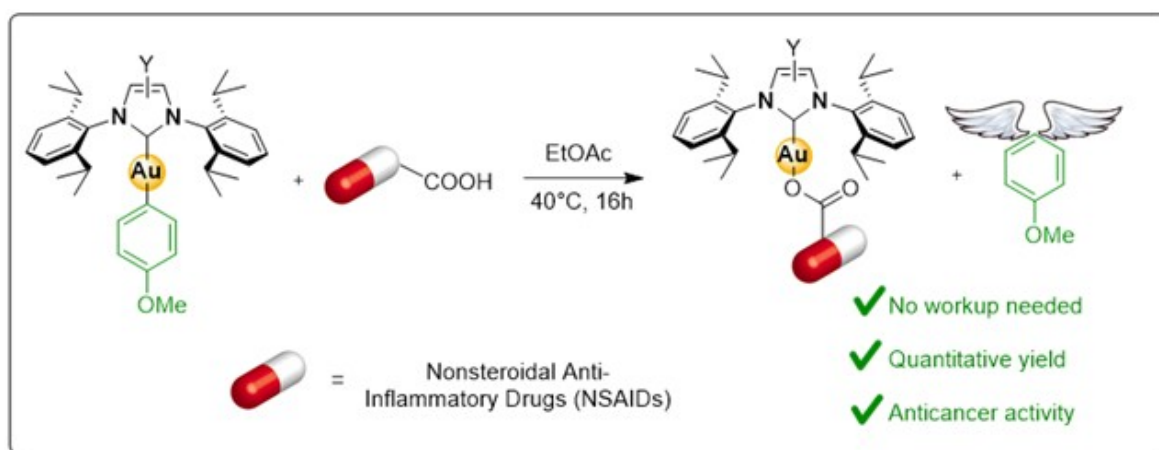
Gold(I)–NHC Complexes Bearing Non-Steroidal Anti-Inflammatory Drugs: An Innovative Synthetic Approach and Antitumor Activity

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Gold-based compounds, and in particular N-heterocyclic carbene (NHC) gold complexes, have attracted considerable attention over the past decade because of their remarkable cytotoxic effects against cancer cells, making them promising candidates for anticancer drug development.¹ Various approaches have been investigated to improve both their therapeutic efficacy and selectivity. Among these, the combination of gold complexes with biologically active molecules, including nonsteroidal anti-inflammatory drugs (NSAIDs), has emerged as a valuable strategy. Gold complexes are known to inhibit thioredoxin reductase (TrxR), thereby promoting oxidative stress and activating multiple pathways leading to cell death.^{1,2} The presence of NSAID moieties, which exhibit their own pharmacological activity, can further potentiate the biological effects of these systems. In particular, hybrid gold–NSAID derivatives have shown encouraging results against cancer stem cells (CSCs),³ suggesting their potential utility as innovative anticancer agents.

Despite their promising biological properties, the preparation of Au(I)–NSAID complexes generally involves laborious multistep synthetic protocols, often requiring toxic solvents and silver-mediated intermediates, which inevitably generate silver-containing waste. The unique reactivity of NHC–Au(I)–aryl species, a well-established class of compounds in homogeneous catalysis, offers an attractive alternative for the synthesis of NHC–Au(I)–NSAID derivatives. Through a simple one-step transformation carried out in environmentally benign solvents and without the need for silver reagents, these compounds can be obtained more efficiently and sustainably. This methodology therefore represents a greener and more practical route toward the development of this promising family of anticancer gold complexes.



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NAM-Oriented In Silico Dermatokinetic Modeling of TiO₂ and Cu-Phthalocyanine Tattoo Pigments for Risk Assessment

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The development of reliable *in silico* methodologies for the risk assessment of persistent dermally deposited particles is emerging as a major challenge within New Approach Methodologies (NAMs) [1]. Current regulatory frameworks still lack mechanistic dermatokinetic models capable of describing the long-term fate, transport, and accumulation of insoluble pigments within skin-associated tissues. Tattoo inks represent a relevant case study, as they are intentionally deposited into the dermis, may persist for decades, and migrate toward lymph nodes and potentially distal organs. In this work, TiO₂ and Cu-phthalocyanine pigments were selected as representative systems to develop a mechanistically grounded physiologically based pharmacokinetic (PBPK) framework for dermatokinetic risk assessment.

A multi-compartment dermal PBPK model was developed using a differential equation architecture aligned with PK-Sim/MoBi environments and incorporating nano-specific processes, including phagocytic saturation kinetics, lymphatic transport, lymph node trapping, and long-term particle persistence. Model parameterization was supported through systematic literature and database analysis collecting ADME-relevant descriptors such as particle size, surface charge, protein interactions, biopersistence, and evidence of systemic distribution. Simulations reproduced key dermatokinetic features reported for tattoo pigments, including progressive migration from the dermal compartment to regional lymph nodes and prolonged tissue retention. Under tattoo-relevant exposure scenarios, TiO₂ showed predicted lymph node accumulation of 0.8–3.2% of the deposited dose within 12 weeks, while Cu-phthalocyanine pigments exhibited higher fractional lymphatic transfer. The proposed framework demonstrates the potential of PBPK-based *in silico* methodologies for NAM-oriented dermatokinetic risk assessment and provides a mechanistic strategy for integrating physicochemical descriptors, *in vitro* data, and simulated tissue exposure.

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Insights into on the behaviour of N-Heterocyclic Carbene (NHC) Gold(I) complexes targeting the Thioredoxin System

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Thioredoxin (Trx) and Thioredoxin Reductase (TrxR) enzymes are essential constituents of the Trx system involved in the cellular redox regulation network. This mitochondrial apparatus, in recent years, has been recognized as an important modulator of tumor growth; hence specific inhibitors are developed to target TrxR/Trx for cancer treatment [1,2]. Trx and TrxR redox active sites are characterized by the presence, respectively, of two cysteine (WCGPCK) at the N-terminus and by a selenol thiol motif (GCUG, where U=SeCys) at the C-terminus. Both Cys and SeCys are Lewis soft base therefore Au(I) based compounds show high affinity for these targets. Several studies have revealed that many cytotoxic gold compounds, such as N-heterocyclic carbene (NHC)-gold(I) complexes, are potent thioredoxin reductase (TrxR) inhibitors [3]. But many other pathways have been supposed to be altered by gold coordination to protein targets. In this context, we selected and synthesized two (NHC)₂-gold(I) complexes (Figure 1), able to cross mitochondrial membrane, and examined by mass spectrometry their interaction with Trx in comparison with the Au(I) drug Auranofin. The cytotoxic properties were tested on Huh7 hepatocellular carcinoma (HCC) cells, and MDAMB-231 triple-negative breast cancer (TNBC) in order to gather new evidence on possible target of gold complexes. Our results highlight the potential of both NHC-Gold complexes in cancer treatment and demonstrated that the two complexes showed different mechanisms of action, either dependent or independent on TrxR1 inhibition.

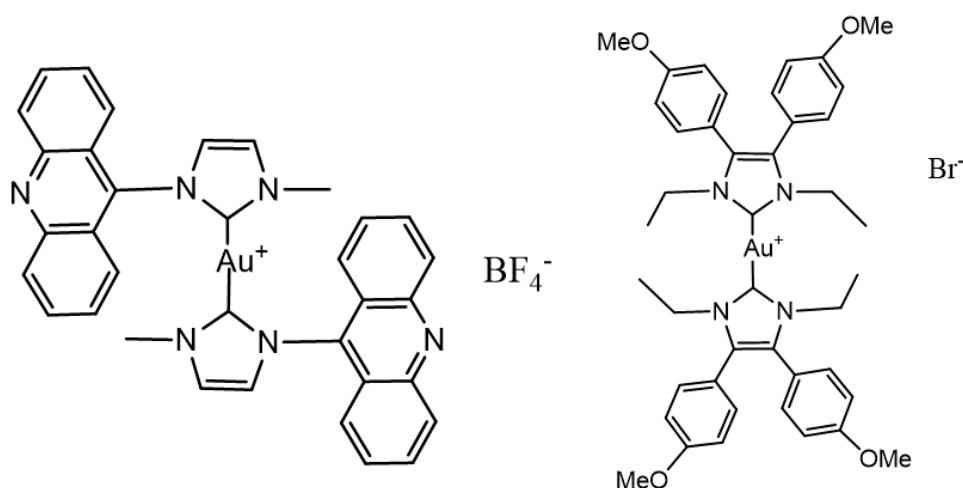


Figure 1: Chemical structures of two (NHC)₂-gold(I) complexes

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Metal-Based Anticancer Drugs Targeting Cytochrome c: Molecular Insights and Clinical Perspectives

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The binding of a metal-based drug to a target protein can alter both the protein conformation and function. Platinum-based drugs are widely used in chemotherapy, while gold-based drugs have emerged as a new class of anticancer compounds [1,2]. Both families exert cytotoxic effects through protein binding: gold compounds primarily target these biomolecules, whereas protein binding represents a secondary target for platinum-based drugs. However, their molecular mechanism of action is not yet fully understood.

Cytochrome c (Cyt c) plays a proapoptotic role triggered by binding with cardiolipin (CL), a mitochondrial membrane phospholipid. The formation of Cyt c-CL complex is an essential step in the apoptotic pathway that induces non-native states with enhanced peroxidase activity, and subsequent release of Cyt c into the cytosol to activate apoptosis processes [3]. Due to this proapoptotic role, this protein represents a compelling target for anticancer metal-based drug candidates [4]. Given the ability of platinum and gold compounds to form stable adducts with Cyt c, we characterized the molecular interactions between selected metal-based drugs and this protein using a combination of biophysical approaches. High resolution mass spectrometry (MS) probed the formation and stoichiometry of Cyt C metallodrugs adducts; Circular Dichroism (CD) monitored change in the secondary structure, while UV-Vis electronic absorption provided information on the electronic structure of the porphyrin within the protein pocket. These findings provide valuable insights into the metalation mechanisms of these complexes with Cyt C, contributing to the rational identification of metal-based drugs capable of modulating apoptotic pathways.

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Charge Matters: A Sulfonated TACN Chelator Enabling Neutral and Stable Cu(II) Complexes for ⁶⁴Cu radiopharmaceuticals.

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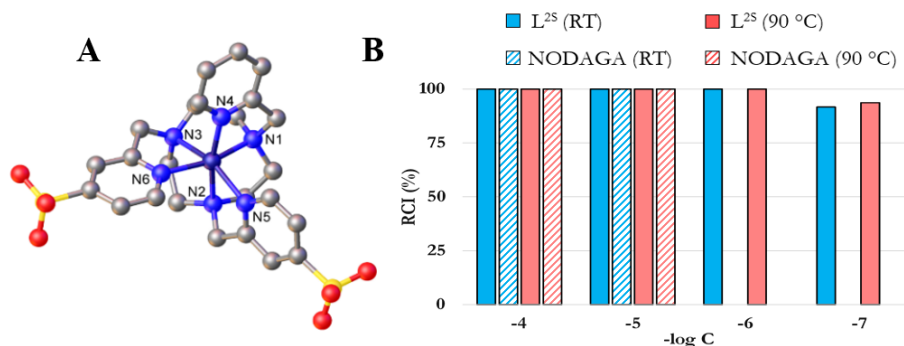
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The positron-emitting copper radioisotopes - i.e. copper-61 (⁶¹Cu, $t_{1/2}$ = 3.33 h), copper-64 (⁶⁴Cu, $t_{1/2}$ = 12.7 h), and the beta-emitter copper-67 (⁶⁷Cu, $t_{1/2}$ = 2.58 d) - form an attractive theranostic set that is gaining prominence in nuclear medicine [1]. The development of copper(II) chelating agents combining rapid complexation at room temperature, high thermodynamic stability, and robustness under reducing conditions remains a central challenge in advancing copper-based radiopharmaceuticals. The here reported novel sulfonated TACN-based ligand, no1py2pyS (L^{2S}) was designed to provide high aqueous solubility, neutral complex charge, and strong Cu(II) affinity. The Cu(II) complex ($[CuL^{2S}]$) formed rapidly under acidic (1 M HCl) and physiological (PBS, pH 7) conditions and remained stable across a wide pH range (0-12), even under a highly acidic environment (5 M HCl). DFT calculations revealed two diastereoisomeric forms with a negligible free energy difference (0.04 kcal mol⁻¹), suggesting significant population of both forms at room temperature. X-ray crystallography validated the DFT structure, revealing macrocyclic and pendant arm coordination (N_6 donor set) and sulfonate-mediated copper bridging. Cyclic voltammetry demonstrated quasi-reversible redox behaviour, a reduction potential ($E_{1/2}$ = -614 mV vs Ag/AgCl) well below the physiological range and a negligible risk of demetallation. Finally, radiolabeling studies with [⁶⁴Cu]Cu²⁺ showed quantitative incorporation (>99%) under mild conditions (pH 4.5, RT, 10 min) at low concentration (10⁻⁶ M), and high stability in human serum for up to 2 h. Taken together, these findings identify L^{2S} as a promising platform for the development of copper-based radiopharmaceuticals.



A. TPSSH-D3-optimized structures of the $[CuL^{2S}]$ isomer $\Delta(\lambda\lambda\lambda)$.

B. Concentration- and temperature-dependent [⁶⁴Cu]Cu²⁺ radiochemical incorporation (RCI, %) of L^{2S} and NODAGA at pH 4.5.

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From Metal Complexes to Clinical Application: Ru(II)- and Os(II)-based Photosensitizers for PDT of Vulvar Intraepithelial Neoplasia

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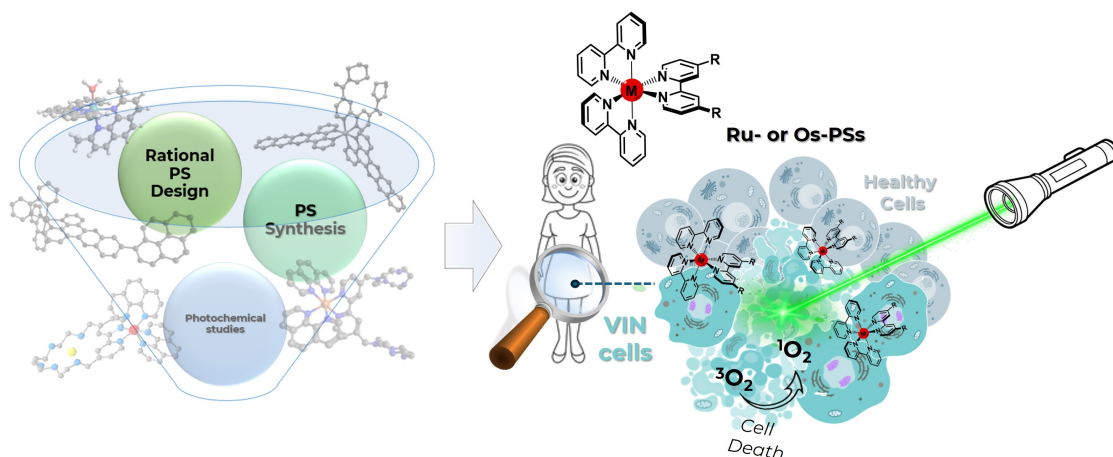
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Photodynamic Therapy (PDT) is a minimally invasive therapeutic approach that overcomes key limitations of conventional anticancer treatments, including systemic toxicity and poor tissue selectivity. Ru(II)- and Os(II)-polypyridyl complexes (RPCs and OPCs) have emerged as promising photosensitizers (PSs) owing to their exceptional photochemical and photophysical properties, structural tunability, and efficient ROS generation upon light irradiation [1]. [2],

Our research focuses on the rational design, synthesis, and characterization of novel RPCs and OPCs tailored for PDT applications. By modulating the coordination sphere and ligand architecture, we aim to develop photoactive metal-based systems with enhanced phototherapeutic efficacy, improved stability, and optimized biological performance. Particular attention has been devoted to structure–property relationships governing light absorption, excited-state behavior, and ROS generation, with the goal of identifying next-generation PSs active under clinically relevant irradiation conditions.

As a translational application, these compounds are being investigated for the treatment of *Vulvar Intraepithelial Neoplasia* (VIN), a premalignant lesion frequently associated with *human papillomavirus* (HPV) infection and characterized by high recurrence rates and risk of progression to invasive *Vulvar Squamous Cell Carcinoma* (VSCC). VIN represents an ideal clinical target for PDT, as light delivery can be accurately localized in gynaecological lesions [3].



The lack of effective conservative treatments underscores the urgent need for selective, tissue-sparing strategies capable of controlling symptoms while preventing cancer progression [4].

We are therefore exploring RPCs and OPCs as next-generation PSs for an effective, painless, and tissue-sparing treatment of VIN, improving patients' quality of life, reducing disease recurrence, and preventing the onset of VSCC.

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Human Serum Albumin: A Hidden Player in the Success of Anticancer Metalloodrugs

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Human Serum Albumin (HSA) is a major determinant of the biological fate of anticancer metalloodrugs, although the consequences of drug–protein association remain incompletely understood. Here, HSA adducts of cisplatin, oxaliplatin, and auranofin were investigated to establish whether albumin functions as a carrier, reservoir, or inactivator.

Bioconjugates were prepared under controlled conditions and characterized by ESI-MS and ICP-OES. Cisplatin and oxaliplatin showed extensive binding to HSA, resulting in high levels of metalation (ca. 70–100%), whereas auranofin displayed lower metal incorporation (ca. 46%), consistent with more selective coordination.

Biological evaluation in A2780 and HCT116 cancer cells revealed marked differences among the adducts. Albumin conjugation completely abolished the cytotoxic activity of the platinum drugs, while the auranofin–HSA adduct retained significant antiproliferative effects. Uptake and stability studies under acidic and reducing conditions showed that platinum remains tightly bound to HSA, limiting intracellular release, whereas partial release of the gold fragment occurs in cells [1].

Overall, albumin binding acts as a functional inactivator for platinum drugs but as a modulatory reservoir for gold compounds, highlighting the metal-dependent nature of protein–metallodrug interactions and their relevance for metallodrug design.

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An unsymmetric cisplatin-based pt(IV) compound containing 2-(2-propynyl)octanoate: a coin with many faces

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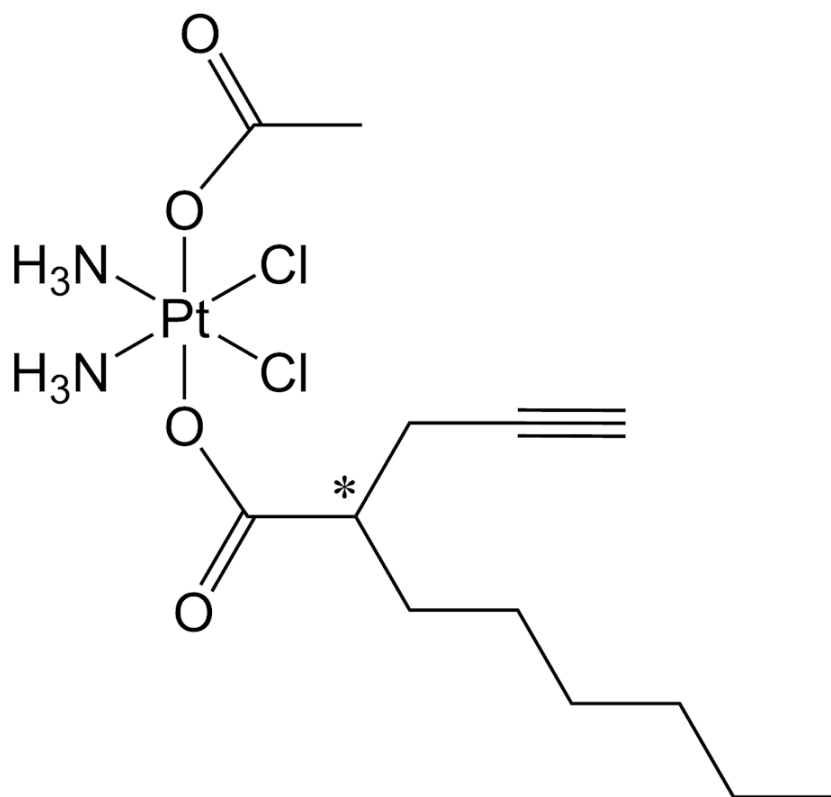
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The (OC-6-44)-acetatodiamminedichlorido(2-(2-propynyl)octanoato)platinum(IV), **PtAcPOA**, was extensively evaluated for its biological properties. The high antiproliferative potency against cancer cells of this prodrug is mainly due to its high cellular accumulation and synergism between the DNA-damaging cisplatin and the histone deacetylase inhibitor (2-propynyl)octanoato, POA, both released after intracellular reduction of **PtAcPOA** [1]. But is that all? In the last eight years it has been demonstrated that **PtAcPOA** can be involved in several different and interlinked cell mechanisms, some of them potentially able to explain why the title compound is not simply a boosted cisplatin, but there is more than meets the eye [2]- [5]. The activation of several programmed (cancer) cell death mechanisms induced by **PtAcPOA** and their importance in modulating pathological processes and pharmacological resistance will be discussed.



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Iodide in Gold and Platinum Anticancer Complexes: Reactivity Is Not Activity

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The introduction of iodide in gold- and platinum-based anticancer complexes represents a seemingly minor structural modification that, in fact, induces profound changes in chemical behavior. From a coordination chemistry perspective, the metal–iodide bond is stronger and less labile than the corresponding metal–chloride bond, leading to reduced hydrolysis rates and lower reactivity toward nucleophilic biomolecules.

On this basis, a significant loss of biological activity would be expected. However, experimental evidence points to a different scenario. In platinum systems, the iodo analogues of cisplatin and oxaliplatin retain notable in vitro cytotoxicity, showing protein interactions and, in some cases, the ability to overcome resistance mechanisms. More broadly, the introduction of iodide alters activation pathways, introducing mechanisms that do not rely solely on halide dissociation [1, 2].

A similar paradigm emerges in gold(I) complexes, in which the replacement of thioglucose moiety of Auranofin with iodide significantly affects drug properties, yet the biological activity is often preserved. This suggests that, also for gold compounds, reduced reactivity does not necessarily translate into reduced efficacy, and that alternative activation pathways or target interactions may play a relevant role [3, 4].

These findings highlight that the relationship between chemical reactivity and biological activity in metallodrugs is not straightforward. Reduced iodide lability may enhance stability under physiological conditions and modulate solution speciation, ultimately favoring effective delivery to biological targets prior to activation.

In this context, systematic comparisons between iodide and other established ligands in gold and platinum complexes provide a powerful framework to reassess established paradigms.

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Oral Communications

Role of Distal Residues in Controlling the Interaction of Hydrogen Sulfide with Neuroglobin

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Neuroglobin (Ngb) is a 151-aminoacid monomeric globin discovered in 2000 in mammalian neurons [1]. A key feature of Ngb is its bis-histidyl 6-coordinated heme *b*, in which His64 and His96 are distal and proximal ligands respectively. Moreover, the presence of an intramolecular disulfide bridge, between Cys46 and Cys55, increases exogenous ligand affinity in oxidizing conditions, by weakening the Fe-His64 bond through cavity conformational rearrangements [1]. Ngb still draws attention due to its neuroprotective role under oxidative stress conditions and neurodegenerative diseases [1].

Although is commonly known as a toxic gas, recently H₂S has been recognized as an endogenous neuromodulator implicated in neurological, cardiovascular, and metabolic disorders [2]. Heme proteins can bind sulfide triggering redox processes. Specifically, Ngb interacts with H₂S and undergoes heme reduction concomitantly to slow conversion of sulfide to S₂O₃²⁻. The His64Ala substitution enhances the interaction [3].

Using a combination of spectroscopic techniques (UV-Vis, Resonance Raman) and stopped flow kinetics, we explored the role of key residues in the distal pocket region (His64, Lys67) in controlling H₂S binding to Ngb and the properties of corresponding Fe(III)-S adducts. H-bonding exerts no significant effect on the iron-bound sulfide, indicating that sulfide stabilization in Ngb is rather due to aromatic ring electrostatic interaction [4]. Moreover, formation of the Fe(III)-S Ngb adducts was followed by that of sulfheme-containing species, featuring covalent modification of the tetrapyrrole ring, as observed for other heme proteins [5]. Experimental data will be discussed in relation to the protein function and the structure of its active site.

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Exploring the catalytic potential of a miniaturized heme enzyme in new-to-nature reactions

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Artificial heme-enzymes (ArHEs) are among the most efficient and versatile biocatalysts reported to date [1]. They can overcome the catalytic boundaries of natural heme-enzymes through two levels of tunability. Protein scaffold modifications alter the steric and electronic environment surrounding the metal center, modulating active site hydrophobicity, substrate access and first/second-sphere interactions [2]. Changes to the metalloporphyrin influence the redox properties of the metal and the stability of catalytic intermediates [2]. ArHEs can thus improve the catalytic properties of heme-enzymes, while steering reactivity toward "new-to-nature" transformations [3]. These reactions include carbene transfer processes, enabling the formation of abiological C–X bonds (X = C, N, Si, etc.) [3].

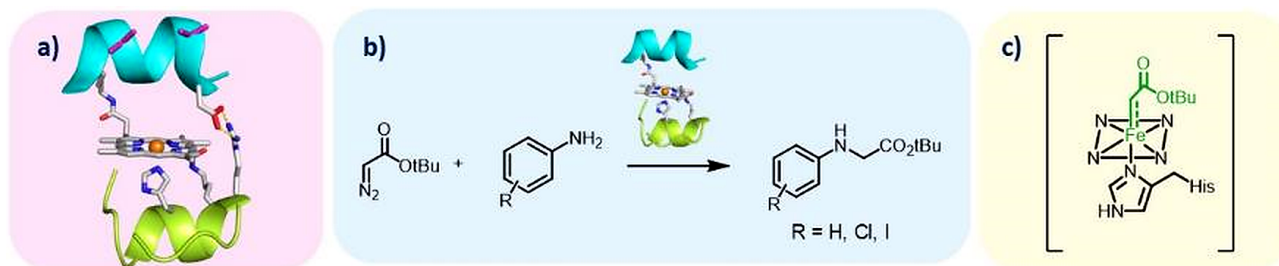


Figure 1. a) Molecular model of Fe-MC6*a; b) Fe-MC6*a-catalyzed N-H insertion of aniline and its derivatives; c) chemical structure of the iron-carbenoid intermediate.

Among ArHEs, miniaturized heme-enzymes named mimochromes (MCs), consists of a minimal scaffold composed of two α -helical peptides linked to a deuteroporphyrin IX [2]. Among them, MC6*a (Fig.1a) has exhibited robustness, efficiency and highly catalytic versatility, displaying different reactivities depending on the nature of the metal ion: from peroxidase and peroxygenase activity of the Fe and Mn, complexes, respectively, to hydrogenase and CO₂ reductase activities of the Co complex [4,5]. Based on this catalytic promiscuity, we set out to expand the range of MC6*a reactivities to include carbene-transfer reactions. Fe-MC6*a catalyzes the N–H insertion of aniline and its derivatives with TON values up to 3,000 (Fig.1b) and with no detected side products. Spectroscopic studies have identified the putative iron-carbenoid intermediate (Fig.1c) as the key catalytic species. Fruitful for mechanistic studies, porphyrin structure modifications are being devised to alter the reactivity of the iron-carbenoid intermediate while expanding the substrate scope of the system.

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Probing N ϵ - and N δ -histidine ligation in a de novo designed α -helical heme protein

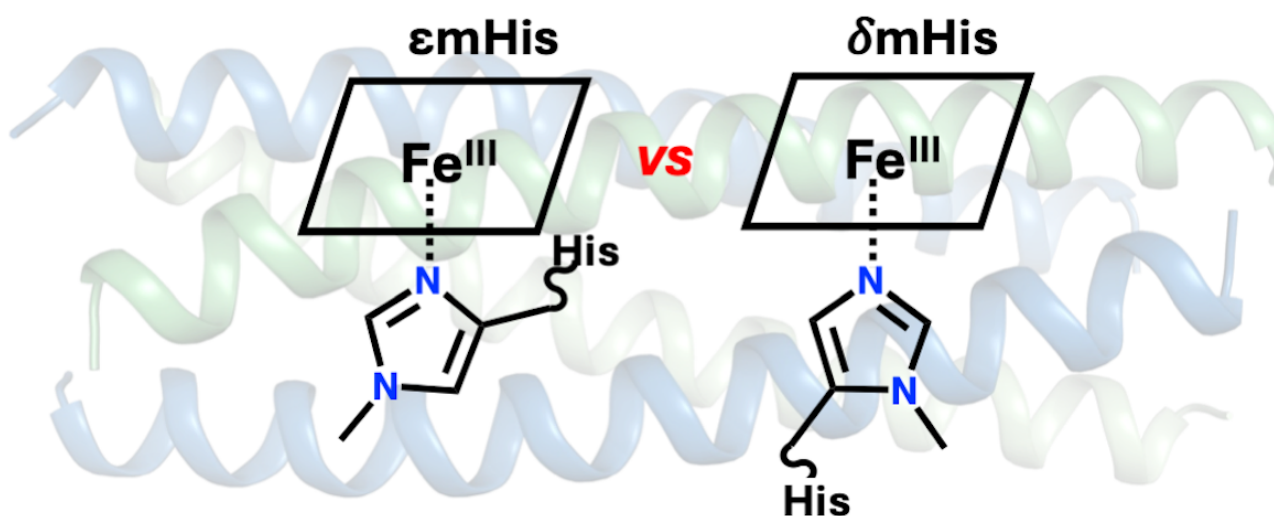
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Enzymes with active sites involving histidine (His) selectively utilize either ϵ - or δ -nitrogen (N ϵ or N δ) of the imidazole ring for coordination and catalysis. In heme-containing proteins, axial ligation occurs predominantly through N ϵ , often accompanied by H-bonding to the noncoordinating N δ that enhances electron donation [1]. In contrast, N δ ligation is rare, raising questions whether N ϵ coordination is intrinsically required for heme binding and function or merely reflects evolutionary selection. His with methylated N ϵ or N δ (ϵ mHis or δ mHis) provides a powerful means to address this question, simultaneously altering the ligand's electronic and steric properties [2,3]. However, systematic evaluation of these ligation modes in proteins remains challenging [4]. Here, we employed a previously studied coiled coil, GRW-L16CL30H [5] in complex with heme, to compare N ϵ - or N δ -coordination to the His axial ligand. Incorporation of ϵ mHis and δ mHis enabled selective control of the coordination mode. Characterization using UV-vis electronic absorption, Electron Paramagnetic Resonance, and resonance Raman spectroscopies revealed distinct electronic structures for the two types of ligations and allowed assignment of the coordination mode in the parental peptide. Functional studies showed that His ligation geometry influences heme binding, peroxidase activity, and the pH-induced His-to-Cys heme coordination. Accordingly, both N ϵ or N δ of His resulted in axial ligation to the heme and reactivity in the GRAND de novo heme proteins. N ϵ coordination promotes stronger heme binding and enhanced peroxidase activity. These findings establish relationships between His coordination and heme reactivity and highlight the utility of de novo design for probing fundamental structure-function relationships in metalloproteins.



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MetalHawk 2.0: Beyond Octahedral Geometries with Neural Network Classification of Metal Sites

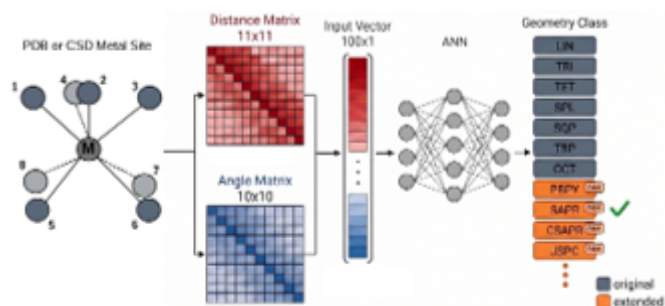
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The chemical properties of metal complexes are strongly dependent on the number and geometrical arrangement of ligands coordinated to the metal center. Accurate and fast classification of coordination number (CN) and geometry is a key prerequisite for large-scale annotation of structural databases and for training more advanced machine learning models targeting metal-based compound discovery. We previously introduced MetalHawk [1], a machine learning approach for simultaneous classification of metal site CN and geometry through artificial neural networks trained on the Cambridge Structural Database (CSD), achieving balanced accuracy of 96.51% across seven geometry classes spanning CN from 2 to 6. Here we present MetalHawk 2.0, a substantially extended version that expands classification to CN=10 and covers the full range of coordination environments observed in transition metal and f-block chemistry.



Building on the solid methodological foundation of the original model, MetalHawk 2.0 incorporates a new large-scale CSD dataset classified using Continuous Shape Measures, an expanded geometry class set, and a refined training strategy to handle the increased complexity and class diversity. The approach retains the speed and accuracy that characterize MetalHawk, while enabling classification of the higher coordination numbers typical of lanthanide and heavy metal compounds. MetalHawk 2.0 represents a significant step toward a generalized tool for automated annotation of metal site structural properties, with direct applications in metalloprotein analysis, coordination chemistry, and the data-driven design of novel metal-based compounds.

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Design, synthesis, and characterization of a stimuli-responsive peptide-based hydrogel

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Peptide-based hydrogels are a versatile class of biomaterials whose properties can be programmed through sequence design and controlled supramolecular assembly. In this work, we report the rational design and characterization of a new series of metal-responsive α -helical hydrogelating peptides, called hDF. The designed peptides form staggered heterotetrameric coiled-coil assemblies in which metal coordination and hydrophobic interactions cooperate to promote higher-order fibrillar organization and hydrogel formation. The first hDF1 construct confirmed the design feasibility but showed unintended amorphous aggregation, prompting the development of a second-generation hDF2 series. hDF2-A2 and hDF2-B were synthesized after design optimization and investigated by Circular Dichroism (CD) spectroscopy, inverted-vial tests, a creep-tracking mechanical test, and scanning electron microscopy (SEM). CD analyses confirmed predominantly α -helical conformations and revealed peptide–peptide interactions on mixing, together with metal-dependent structural stabilization. Zn(II) promoted ordering of hDF2-B alone, whereas Co(II) supported hydrogel formation in the mixed system under neutral pH conditions. The mechanical creep test ranked the resulting gels by stiffness, showing that hydrogel rigidity depends jointly on peptide composition and on metal stoichiometry. Together, these results support a hydrogel formation mechanism in which complementary peptide design and metal coordination act cooperatively.

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Copper calling: Myxinidin and the ATCUN motif in metal binding

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Metal-binding motifs offer an interesting way to develop peptides with improved biological activity. In addition to their use in developing specific drugs, metal-binding motifs can improve the efficacy of antimicrobial peptides, providing a new weapon against antimicrobial resistance. Amino-terminal copper (ATCUN) binding motifs, involved in the formation of reactive oxygen species (ROS) upon metal binding, are part of the mechanism of action of many naturally occurring antimicrobial peptides (AMPs) [1]. The interaction of ATCUN sequences with copper ions produces stable metal-peptide complexes with nuclease and protein cleaving activities, causing lysis through oxidative damage generated during copper redox cycling [2]. Beyond metal transport, this motif shows promise for incorporation into rationally designed peptide therapeutics with increased antimicrobial potency [3]. Among naturally occurring AMPs, Myxinidin (GIHDILKYGKPS) is a membrane-active peptide isolated from hagfish mucous secretions and previously studied by our research team [4,5]. It contains the ATCUN motif GIH, indicating a dual mechanism of action: membrane disruption and metal-mediated oxidative damage. In this study, we researched the Cu(II) binding ability of Myxinidin using UV/Vis spectrophotometry and Circular Dichroism (CD). To understand structure–activity relationships, we created a family of Myxinidin analogues ranging from the minimal “GIH” motif to the full-length peptide. Their ability to bind Cu(II) and the geometric arrangement of copper were determined by UV/Vis spectroscopy, with CD providing supporting structural data. We also evaluated how physicochemical factors affect metal coordination under different pH conditions relevant to therapeutic environments. The functional consequence of copper binding was assessed using the ascorbate oxidation assay, providing insight into ROS

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A Simple yet Efficient Model for Computing H-Atom Transfer Tunneling from Transition-State Properties

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Hydrogen atom abstraction (HAA) reactions are ubiquitous in biological and synthetic chemistry, ranging from enzymatic C–H bond activation to alkane functionalization [1]. They commonly proceed via hydrogen-atom transfer (HAT) or proton-coupled electron transfer (PCET) pathways, with reaction rates often strongly influenced by hydrogen tunneling, as evidenced by large kinetic isotope effects (KIEs). Despite its importance, the connection between tunneling and the electronic and vibrational structure of transition-metal-mediated HAA reactions remains incompletely understood.

Here, we present a compact transition-state-based framework that links hydrogen tunneling to fundamental properties of the reactive vibrational mode obtained from density functional theory calculations. Analysis of representative transition-metal HAT and PCET reactions reveals a strong correlation between tunneling contributions and the fraction of reactive-mode kinetic energy localized on the transferring hydrogen atom. This relationship provides a simple mechanistic picture of how reactive-mode delocalization govern tunneling. Building on this insight, we derive an analytical expression for the tunneling correction factor with explicit temperature dependence. Combined with conventional transition-state theory, the framework enables quantitative prediction of H/D KIEs and their thermal dependence. Comparisons with semiclassical tunneling models and experimental data show that the approach captures the essential features of hydrogen tunneling while maintaining conceptual simplicity and computational efficiency.

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Fe(III) coordination and membrane interaction drive the enhanced antimicrobial activity of a siderophore-peptide conjugate

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Iron acquisition is essential for bacterial survival and proliferation within the host. Among bacterial strategies to overcome iron limitation, siderophore secretion is one of the most efficient. These low-molecular-weight chelators bind Fe(III) with high affinity and promote its uptake through dedicated transport systems, supporting pathogen growth in iron-restricted environments.

In this context, hybrid molecules able to limit iron availability while exerting direct antimicrobial activity represent a promising therapeutic approach. We recently designed a siderophore-inspired peptide conjugate composed of an antimicrobial peptide sequence, a flexible bio-linker of optimized length, and a terminal hydroxamate-based chelating unit [1]. This modular architecture was conceived to combine membrane-active antimicrobial properties with Fe(III)-binding capability, potentially generating a synergistic antibacterial effect [2].

This study aimed to assess whether the peptide retained its structural and functional properties after conjugation with the chelating moiety and to investigate its interaction with membrane models mimicking Gram-negative bacterial membranes. Fluorescence assays and circular dichroism analyses were used to evaluate membrane interaction and peptide conformational behaviour, confirming that the conjugated molecule preserves its ability to interact with membrane-mimicking systems.

Fe(III)-coordination properties were further investigated by UV-Vis spectroscopy and paramagnetic NMR experiments. Spectrophotometric analyses allowed the determination of complexation parameters, including the binding constant and the number of coordination sites, while paramagnetic NMR provided additional evidence of Fe(III) interaction with the hydroxamate-containing region.

Overall, these findings show that combining an antimicrobial peptide with an iron-chelating unit generates a multifunctional molecule able to integrate membrane perturbation and iron sequestration, offering a promising strategy against Gram-negative [3].

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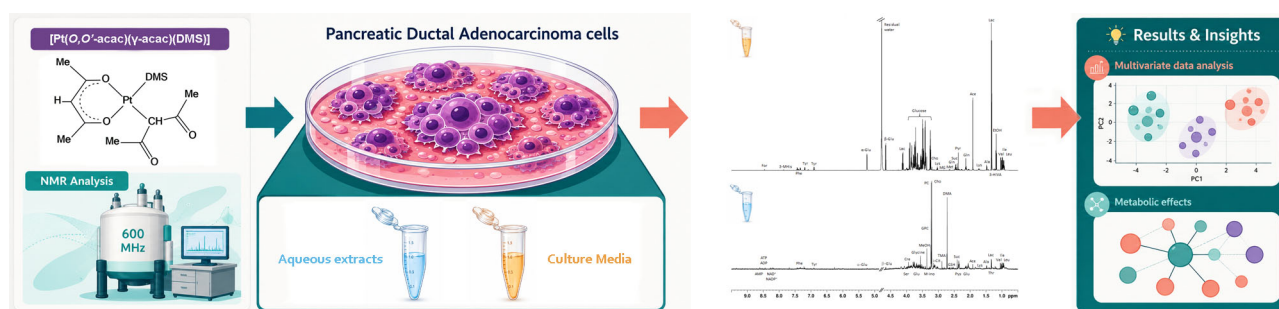
NMR-Based Metabolomic Approach revealed different response of Pancreatic Ductal Adenocarcinoma cells to [Pt(O,O'-acac)(γ-acac)(DMS)] and cisplatin treatment

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The β-diketonate metal complexes represent a well-known and versatile class of chelating coordination compounds that continues to attract considerable interest due to their reactivity and chemical properties [1,2]. About twenty years ago, the platinum(II) complex [Pt(O,O'-acac)(γ-acac)(DMS)] (Ptac2S; acac = acetylacetonate; DMS = dimethyl sulfide) was synthesized and showed promising anticancer properties [2]. Several studies demonstrated its notable antitumor activity across different cancer types, both in vitro and in vivo, mainly through the activation of mitochondrial apoptotic pathways and autophagy. Moreover, Ptac2S appears to exert its anticancer activity primarily through non-genomic targets, displaying a mechanism of action distinct from that of conventional cisplatin [3,4].

In this work, we aimed to evaluate the cytotoxic effects of Ptac2S on two poorly differentiated pancreatic ductal adenocarcinoma (PDAC) cell lines, MIA PaCa-2 and PANC-1. Since Ptac2S showed stronger cytotoxic and anticolonogenic effects in MIA PaCa-2 cells compared with cisplatin, a ¹H NMR-based metabolomic approach was chosen to investigate the intracellular and extracellular metabolic profiles of treated MIA PaCa-2 cells. Consistently with our previous findings, pyruvate metabolism was confirmed as one of the main pathways altered by Ptac2S. Moreover, a marked alteration of glycine-serine metabolism and a critical downregulation of choline metabolism were also observed in MIA PaCa-2 cell line. Overall, these results highlight a distinct metabolic response induced by Ptac2S compared with conventional cisplatin, supporting the hypothesis of a different mechanism of action for this β-diketonate platinum(II) complex [4].



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Fluoride Coordination in Metal Complexes: Thermodynamic, Kinetic and Structural Insights for Sensing and Diagnostic Applications

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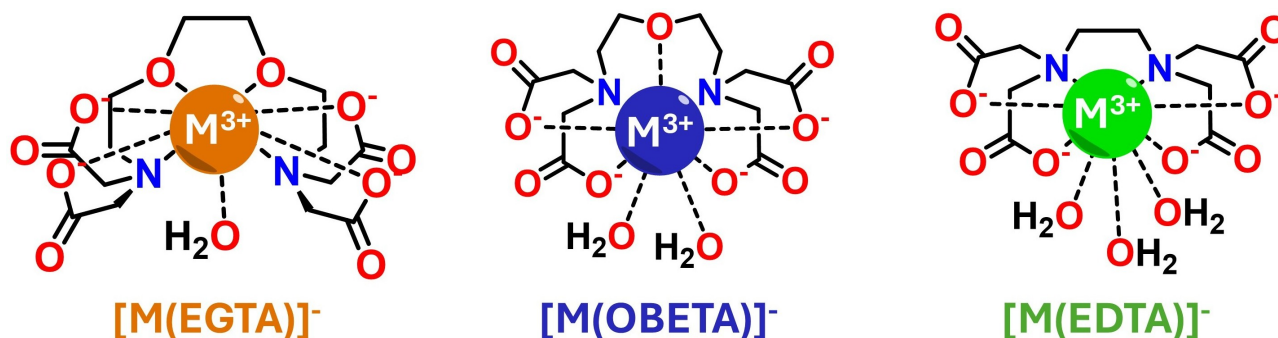
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Anion recognition by metal complexes represents a challenge in coordination chemistry, with major implications in diagnostic and sensing fields [1]. Recently, research attention has focused on the fluoride anion, which plays a fundamental role in medical imaging, such as chemical exchange saturation transfer (CEST) and positron emission tomography (PET) [2].

In this work, we investigated the fluoride binding to metal complexes of paramagnetic Gd^{3+} and its diamagnetic analogue Y^{3+} with a series of polyaminocarboxylate ligands with different structures and hydration states (i.e. EGTA, OBETA, EDTA).



Scheme: Chemical structures of the metal complexes under investigation ($M^{3+} = Gd^{3+}, Y^{3+}$).

By combining low-resolution 1H NMR relaxometry with high-resolution ^{19}F NMR spectroscopy, we demonstrated that F^- can displace one or more inner-sphere water molecules, leading to the formation of ternary adducts and dimeric structures [3,4]. The latter are generally challenging to observe in solution [5]. The proton relaxation enhancement (PRE) method was employed to determine the association constants, while ^{19}F NMR line-shape analysis elucidated the fluoride exchange dynamics, showing that an associative mechanism is typically preferred by bis-hydrate complexes. Complementary DFT calculations supported our proposed structures, accurately reproducing ^{19}F NMR chemical shifts and J_{Y-F} coupling constants.

These findings enhance our understanding of the thermodynamic, kinetic, and structural properties behind fluoride coordination. Notably, this multi-technique approach can also be applied to investigate biologically relevant interactions between NMR-active inorganic anions and macromolecular systems, such as metalloproteins with paramagnetic centres. Ultimately, this methodology directly supports the rational design of next-generation anion-sensitive molecular probes and high-performance contrast agents for medical imaging.

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Enhanced metal ion recognition with bispidine-based fluorinated chemosensors

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One of the major challenges for medical, environmental and pharmaceutical applications is the reliable and specific detection of analytes in complex mixtures. Proton Nuclear Magnetic Resonance (¹H-NMR) is often employed for this, because it is a powerful analytical technique to study molecular and atomic-level organization. However, its interpretation can be challenging due to signal overlap and low selectivity [1]. To address this issue, chemosensing systems use specific molecular interactions to generate distinguishable signals and simultaneously detect multiple species [2]. In this context, using ¹⁹F-labeled molecular probes for the coordination of analytes can be a powerful tool, as it generates unique ¹⁹F-NMR signals with minimal background interference [1]. Additionally, metal-chelating fluorinated probes represent advanced materials designed for dual-mode imaging or stimuli-responsive theranostics [3]. In this work, bispidines were selected as a scaffold for metal chelation thanks to their rigid framework, conformational adaptability and multiple nitrogen donor atoms. Mannich reaction was employed to introduce both ¹⁹F-labelled probes (such as F, CF₃ and OCF₃) and additional nitrogen atoms to enhance coordination. Two types of scaffolds were then prepared: bidentate bispidines via a one-pot reaction, and tetradentate bispidines via a multi-step one. These compounds were tested to evaluate their ability to form coordination complexes with different metal salts, and the best-suited ones were tested for three possible applications: recognition of organic molecules in solution, studies of coordination competition between different metal salts and evaluation of ligand extraction capacity with two-phase mixtures.

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Harnessing Mesoionic Carbenes: Synthesis and Antiproliferative Activity of Novel Steroidal Metal Bioconjugates

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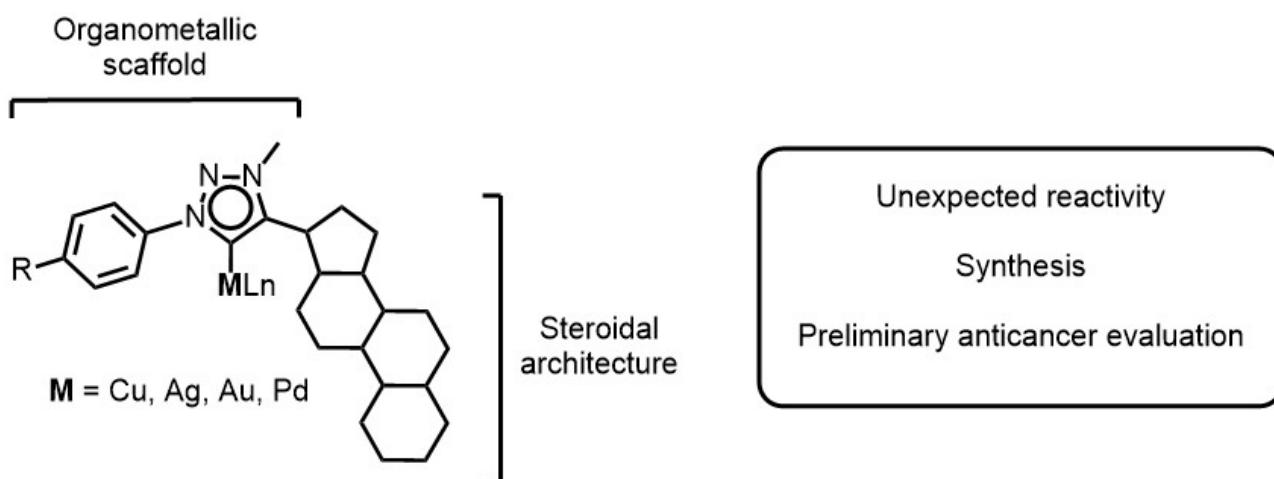
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Bioconjugation is a powerful strategy in modern drug discovery, enabling the fusion of cytotoxic and targeting payloads to create next-generation chemotherapeutics. While steroid scaffolds are widely valued for their diverse medicinal properties, their potential as carriers for organometallic anticancer agents remains largely untapped [1]. Organometallic moieties offer unique electronic and structural properties [2]; coupling them directly to a steroidal backbone can synergistically enhance lipophilicity, membrane permeability, structural rigidity, and targeted delivery.

Herein, we report the synthesis and biological evaluation of a novel class of steroid-conjugated organometallic complexes (featuring Cu, Ag, Au, and Pd). Intriguingly, initial complexation attempts with the native steroidal scaffold revealed unexpected reactivity. This prompted strategic structural modifications of the steroid core, enabling the successful development of a 1,2,3-triazole-based mesoionic carbene system conjugated to the hormone scaffold.

Following the optimization of the reaction conditions, the modified steroids were efficiently functionalized via Copper-Catalyzed Alkyne-Azide Cycloaddition (CuAAC) and subsequently methylated to yield 1,2,3-triazolium salts. These served as versatile precursors, affording highly stable bioconjugated metal chemotherapeutics.

We evaluated the antiproliferative activity of these novel complexes across a comprehensive panel of tumoral and non-tumoral cell lines. By systematically varying complex geometry, overall charge, substituents, and auxiliary ligands, we established detailed structure-activity relationships (SAR). Ultimately, this work introduces a highly modular and promising platform for the development of steroid-based metallodrugs for cancer therapy.



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Passive diffusion of cisplatin and cisplatin-derived Pt(IV) prodrugs across a breast cancer plasma membrane: computational insights into the role of axial ligands

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Pt(II)-based anticancer agents' clinical effectiveness is often compromised by issues including systemic toxicity, drug resistance, and inefficient cellular uptake. In response to these limitations, Pt(IV) complexes have attracted growing attention as potential prodrugs, showing greater kinetic stability and reduced reactivity compared to their Pt(II) counterparts [1]. After entering cancer cells, intracellular reducing agents convert Pt(IV) complexes into the corresponding active Pt(II) forms. A crucial factor governing their reduction, membrane permeability and their overall biological profile is the nature of their axial ligands. In the present in-silico investigation, biased Molecular Dynamics simulations have been applied to explore the permeation of cisplatin (cisPt) and three related Pt(IV) derivatives containing hydroxido (OH) and/or acetato (OAc) axial ligands, namely cisPt(OH)₂, cisPt(OAc)(OH), and cisPt(OAc)₂, across a realistic membrane model of human breast cancer. Free-energy profiles identified the hydrophobic membrane core as the main obstacle to drug permeation. Complexes bearing acetato ligands exhibited lower permeation energy barriers and stronger interactions with polar headgroups and hydrophobic tails. By contrast, hydroxido derivatives tend to maintain hydration, forming hydrogen bond networks. Interestingly, both cisPt and cisPt(OH)₂ preserved partly their hydration shell even while crossing the lipid bilayer, whereas the acetato derivatives gradually establish contacts with membrane components. cisPt(OAc)(OH) in experimental observations demonstrated a particularly favourable accumulation profile, suggesting that mechanisms other than passive diffusion may also contribute to its internalization. The study provides insights on the pivotal role of Pt(IV) prodrugs axial ligands in membrane permeation and intracellular accumulation, supporting the rational design of more efficient platinum-containing anticancer therapeutics.

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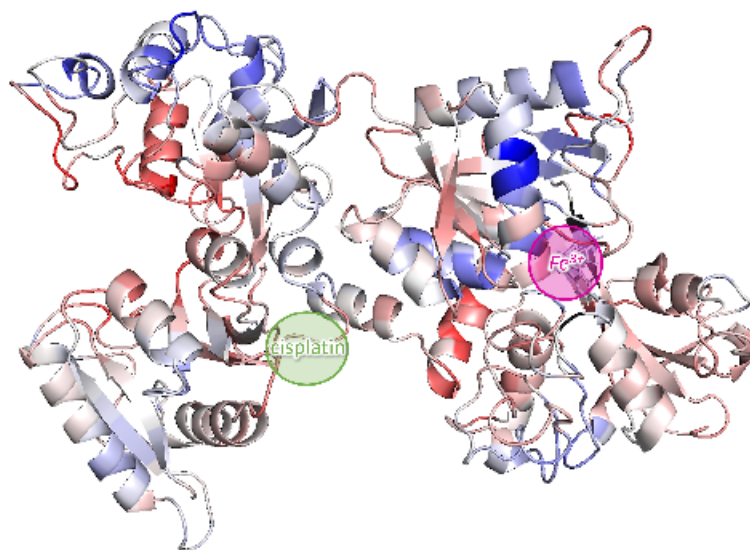
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Advanced computational investigation of human Transferrin as a vehicle for metallodrugs absorption against cancer.

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Human serum transferrin (hTF) is a pivotal transport glycoprotein in iron metabolism, it facilitates iron transport throughout the systemic circulation. Structurally, hTF is a bilobal monomer consisting of an N-lobe and a C-lobe connected by a linker sequence, each capable of binding and transporting Fe³⁺. In the bloodstream, hTF exists in different states: apotransferrin (~40%), diferric transferrin (~27%), and the C-lobe (~11%) or N-lobe (~23%) monoferric states, depending on systemic iron saturation [1]. Once it is recognized by the transferrin receptor (TfR) and successfully internalized, the iron ions are released at the endosome's acidic pH. The presented research is guided by two evidences: first, TfR overexpression in tumor cells which provides higher iron supply, driving cellular proliferation [2]; second, hTF ability to bind metallodrugs like cisplatin, a notorious antineoplastic drug, in different sites of Fe³⁺, thereby acting as a vehicle for cellular absorption [1]. Thus, transferrin is potentially a new target to treat some malignancies, such as solid tumours. Through the application of extensive molecular dynamics simulations and advanced computational tools, we have investigated the structural behaviour of hTF in its different states of crescent complexity (apotransferrin, C-lobe monoferric transferrin, Transferrin:cisplatin, C-lobe monoferric Transferrin:cisplatin), in order to gain deeper atomistic insights on the binding region of iron ion such as in that of cisplatin where Met256 (N-lobe) and Met499 (C-lobe), are involved [1]. Our results show the effect of Fe³⁺ and cisplatin binding respect to the apoprotein in terms of conformational rearrangements, functional for protein recognition and absorption.



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Sub-Lethal Stress vs Cytotoxic Threshold: Metabolic Rewiring of Neuroblastoma Cells Exposed to [Pt(η^1 -C₂H₄OMe)(DMSO)(phen)]⁺ complex

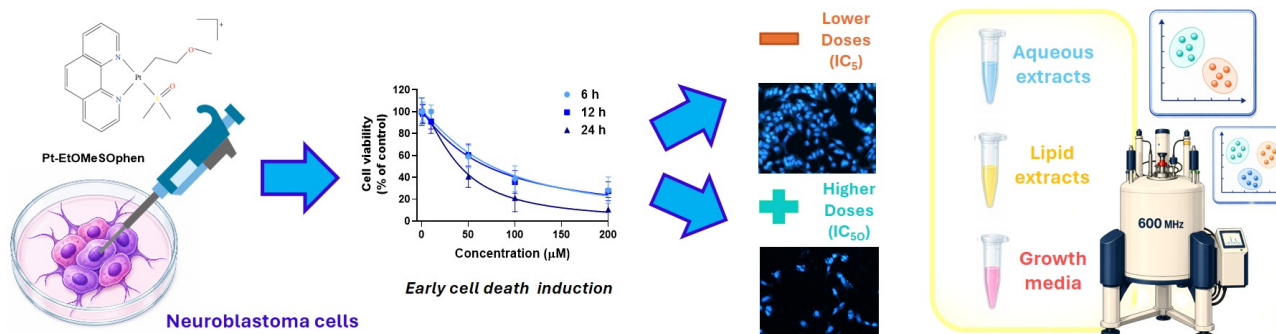
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Neuroblastoma is one of the most common pediatric solid tumors, and high risk cases still show poor prognosis despite therapeutic advances, highlighting the need for new anticancer strategies [1].

The new platinum(II) complex [Pt(η^1 -C₂H₄OMe)(DMSO)(phen)]⁺ (phen=1,10-phenanthroline), named Pt-EtOMeSphen, has demonstrated potent antitumor and antimetastatic activity in SH SY5Y neuroblastoma cells, and previous NMR based metabolomics at IC₅₀ concentrations revealed early metabolic perturbations, including alterations in glutathione metabolism, which suggested cytosolic targets [2-4].

This study applies a ¹H-NMR based metabolomic approach to characterize the dose dependent metabolic response of SH SY5Y cells to Pt EtOMeSphen by comparing cytotoxic (IC₅₀) and sublethal ($\approx$ IC₅) exposures. Assessing sublethal drug effects enables the detection of primary biochemical events while minimizing metabolic signatures associated with widespread cell death. This approach is suited to identify early biomarkers, sublethal adaptive responses, and redox related mechanisms that may precede the cell death process. Sublethal dosing also better reflects the possible in vivo drug distribution, where heterogeneous vascularization often results in tumor regions exposed to suboptimal concentrations. By integrating metabolic profiles across low and cytotoxic doses, this work determined the metabolic signatures induced by Pt EtOMeSphen providing a comprehensive understanding of its mechanism of action.



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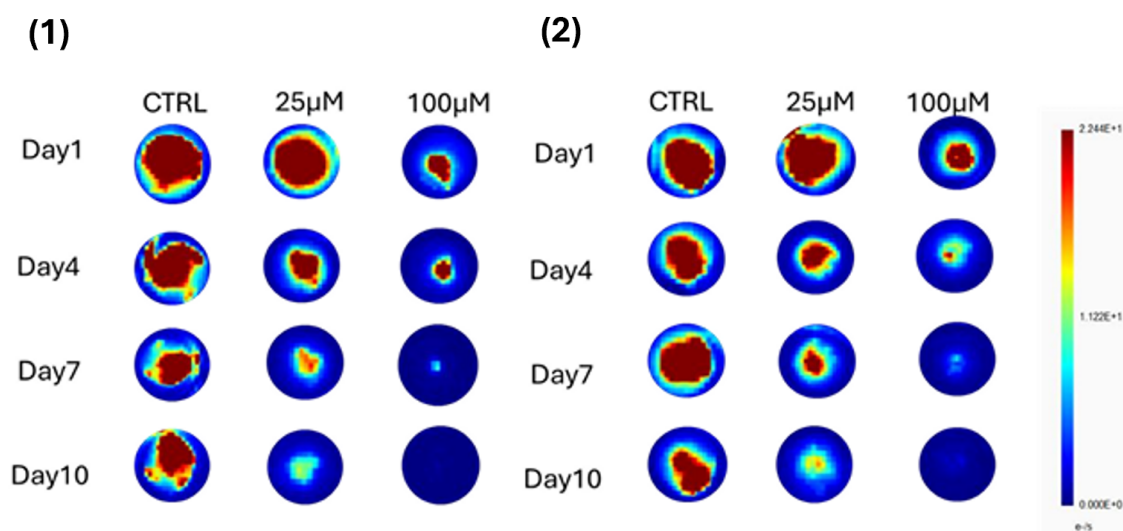
In vitro and ex vivo evaluation of dinuclear platinum–bisphosphonate complexes against prostate cancer bone metastasis models

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Bone metastases are a major clinical challenge in advanced prostate cancer and remain difficult to treat because conventional platinum drugs, although highly effective, lack bone selectivity and cause dose-limiting systemic toxicity [1,2]. Here, we assessed two dinuclear platinum(II)–bisphosphonate complexes, $[\{\text{Pt}(1\text{R},2\text{R-DACH})\}_2(\text{PAM})]^+$ (1; PAM = pamidronate) and $[\{\text{Pt}(1\text{R},2\text{R-DACH})\}_2(\text{ZOLE})]^+$ (2; ZOLE = zoledronate), designed to combine platinum-mediated cytotoxicity with the bone-seeking properties of bisphosphonates [3]. Their anticancer activity was compared with cisplatin and oxaliplatin in human PC3 prostate cancer cells, first in conventional 2D cultures and then in a more clinically relevant ex vivo human bone model. In 2D assays, cells were treated under continuous exposure or 24 h exposure schedules at 25 and 100 μM ; viability was quantified by AlamarBlueTM, while DAPI staining provided morphological evidence of cytotoxicity. Compound 2 showed the most pronounced and reproducible activity, approaching the effect of cisplatin. To evaluate drug response in a bone-like metastatic microenvironment, standardized human bone discs containing 2 mm defects were seeded with PC3 cells and monitored over 10 days by bioluminescence imaging. Both compounds significantly reduced tumor cell viability within bone tissue, with compound 1 producing the strongest ex vivo response. Overall, these results support dinuclear Pt–bisphosphonate complexes as promising bone-targeted metal-based anticancer agents for metastatic prostate cancer.



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CARBAZOLE-BASED NHC Cu(I) AND Au(I) COMPLEXES AS ANTICANCER AGENTS

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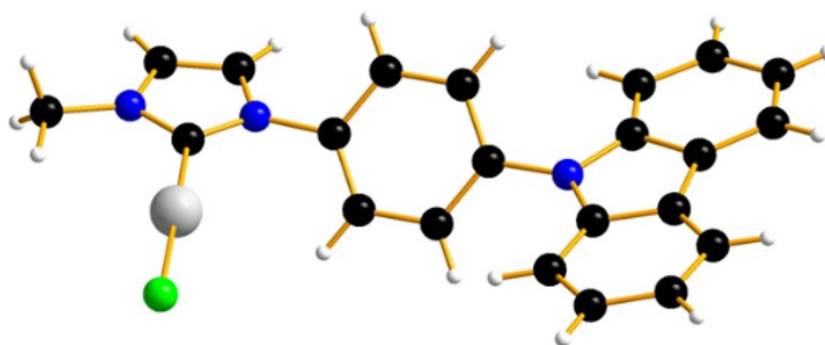
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Carbazoles are a class of natural nitrogen-containing organic compounds that have attracted considerable attention in medicinal chemistry because of their broad applications as antimicrobial, anti-inflammatory, and anticancer agents [1]. Their cytotoxic effects have been associated with DNA intercalation, inhibition of some DNA-dependent enzymes such as topoisomerases and telomerase, modulation of cyclin-dependent kinases and estrogenic receptors, interference with the JAK/STAT signalling pathway, and induction of cell-cycle arrest and apoptosis [1-3]. Several carbazole-based synthetic drugs have reached clinical use, including alectinib and midostaurin. Moreover, newer derivatives such as Carbazole Blue (CB) have shown selectivity against breast cancer cells by targeting aberrant DNA replication and repair processes, while preserving normal healthy cells [3]. Furthermore, a recent promising approach to improve anticancer efficacy involves the integration of carbazole scaffolds into ligands for metal-based complexes, particularly Au(I)-NHC complexes [4]. This strategy demonstrates the potential to overcome drug resistance while also aiding in the development of effective drugs against some aggressive subtypes of breast cancer [5]. In this study, novel Cu(I) and Au(I) complexes with carbazole-conjugated NHC ligands have been synthesized and fully characterized. In Figure 1, the X-ray diffraction crystal structure of 1-(4-(carbazol-9-yl)phenyl)-3-methyl-imidazol-2-yl)gold(I) chloride shows the carbazole scaffolds in the NHC molecular frame. The synthesized gold(I) complexes displayed optimal stability in solutions and were tested against cancer cell lines, including MDAMB-231 and SKBR3 cancer cells. Notably, all tested complexes exhibited strong anticancer activity (in the low micromolar range) and were more active than their respective organic NHC ligands.



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Novel Pt(II) Complex-Peptide Conjugates for Targeted Anticancer Therapies: Synthesis, Characterization, and Bioactivity

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Platinum-based anticancer agents remain central to the treatment of many human malignancies; however, their clinical use is often limited by poor selectivity and the emergence of intrinsic or acquired resistance [1]. In this context, drug targeting and delivery (DTD) strategies have been developed to improve therapeutic outcomes by exploiting ligands that selectively recognize biomarkers overexpressed on cancer cell surfaces, thereby enhancing drug accumulation and uptake while reducing systemic toxicity [2]. Among targeting agents, peptides are particularly attractive due to their biocompatibility and high receptor affinity, although cytotoxic metal-peptide conjugates are still relatively underexplored [3]. In this work, novel Pt(II) complexes were synthesized and conjugated in solution phase to tumor-targeting peptide sequences. The platinum scaffold was rationally designed to include a chelating ligand bearing an activatable carboxyl group, enabling selective amide bond formation with peptide N-terminal amine. Additionally, suitable leaving groups were incorporated to generate reactive species upon hydrolysis, capable of interacting with DNA and inducing antiproliferative effects [4]. Peptides with known cell-penetrating and homing properties toward colorectal (HCT-116) and triple-negative breast (MDA-MB-231) cancer cell lines [5] were synthesized via microwave-assisted solid-phase techniques and characterized by RP-UHPLC-MS. The resulting bioconjugates were fully characterized and evaluated *in vitro*, and their cytotoxicity was compared with that of the corresponding Pt(II) precursors to assess the impact of peptide targeting. To improve aqueous solubility, hydroxypropyl- β -cyclodextrin (HP- β -CD) was employed as a carrier. Interaction profiles with biologically relevant models, including human serum albumin and single-stranded oligonucleotides, were investigated by HR-ESI-MS to explore reactivity and potential distribution, before and after conjugation.

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Poster Presentations

Development of novel $[^{99m}\text{Tc}][\text{Tc}(\text{N})(\text{PNP})]$ -labeled peptides for the diagnosis of $\alpha\text{V}\beta 3$ -positive cancers

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RGDechi is a bifunctional chimeric peptide composed of a cyclic RGD-containing pentapeptide covalently linked by a spacer to an echistatin domain [1]. This peptide can selectively modulate $\alpha\text{V}\beta 3$ function and its antiangiogenic activity, antiadhesive, antiproliferative, and pro-apoptotic effects on human malignant melanoma cells were demonstrated.

RGDechi can be considered a good candidate as a non-invasive diagnostic tracer in tumor imaging [1,2]. ^{99m}Tc ($t_{1/2}=6.02$ h and $E_{\gamma}=140$ keV) is the workhorse radionuclide in Nuclear Medicine for SPECT imaging applications. To prepare the $[^{99m}\text{Tc}]$ -tagged RGDechi derivative peptides, the labeling approach, which involved the use of the $[^{99m}\text{Tc}][\text{Tc}(\text{N})(\text{PNPn})]^{2+}$ -system (PNP=bis-phosphino-amine), was investigated [3]. By exploiting this technology, both the molecular weight and lipophilicity of the radiolabeled peptides were easily modified by varying substituents of the P atoms of PNP in $[^{99m}\text{Tc}][\text{Tc}(\text{N})(\text{PNPn})]$ scaffold; this allows for a fine modulation of their stability and pharmacological properties. Taking advantage of the $[^{99m}\text{Tc}][\text{Tc}(\text{N})(\text{PNPn})]$ technology, a Cys residue was coupled to the side chain of the Lys1, obtaining RGDechi-Cys analogues. This residue was selected as a bifunctional chelating agent, to allow the coordination to the $[^{99m}\text{Tc}][\text{Tc}(\text{N})(\text{PNPn})]$ -synthon, through the negative sulfur and the neutral nitrogen atoms, affording the final monocationic complex. Moreover, a spacer between the peptide recognition sequence and the radioactive probe was introduced to evaluate its influence on the peptide activity. The cellular uptake and internalization studies of the obtained radiolabeled peptides were performed, confirming the selectivity for $\alpha\text{V}\beta 3$ -positive cancer cells and their potential use for the diagnosis of $\alpha\text{V}\beta 3$ -positive cancers.

The project was funded by AIRC IG2020 (ID24528).

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Deciphering the Mode of Action of Anticancer Gold Compounds via Shotgun Proteomics and Bioinformatics

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Proteomics represents a powerful approach for elucidating the mechanisms of action of anticancer metallodrugs. In this study, shotgun proteomics was employed to investigate the proteomic impact of auranofin and two gold carbene compounds on A2780 ovarian cancer cells. Over 8,000 proteins were identified and quantified, and drug-induced alterations were systematically interpreted through relevant bioinformatics tools.

Auranofin exhibited a markedly distinct proteomic signature compared to the two gold carbene compounds. It strongly activates the NRF2 pathway, producing notable effects on glutathione, thioredoxin, NADPH, and iron metabolism, ultimately leading to cancer cell death. These features clearly indicate ferroptosis as the predominant mechanism of auranofin-induced cell death [1]. In contrast, the gold carbene compounds did not induce glutathione dysregulation or ferroptosis; instead, they directly damaged mitochondria and caused severe endoplasmic reticulum (ER) stress, thereby triggering apoptosis [2]. This overall picture was strongly supported by a series of independent biochemical determinations.

Thus, despite sharing a reactive mononuclear gold(I) centre, auranofin and the two gold carbene compounds exert their antiproliferative effects through profoundly different modes of action, depending on the nature of the gold ligands. These findings may carry important implications for the therapeutic application of gold compounds in cancer treatment.

Overall, this study emphasises the vital role of proteomics and bioinformatics in elucidating the distinct cellular pathways regulated by multitarget gold drugs, and in evaluating their biological and mechanistic significance.

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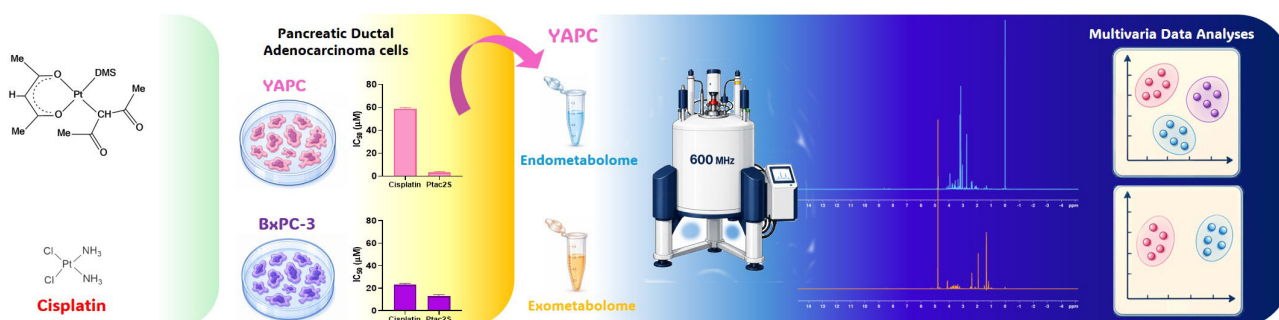
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Study of [Pt(O,O'-acac)(γ-acac)(DMS)] and cisplatin anticancer activity on Pancreatic Ductal Adenocarcinoma cells

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies and remains poorly responsive to conventional chemotherapy. Platinum-based drugs are included in therapeutic regimens for selected PDAC patients, but their efficacy is often limited by intrinsic or acquired resistance [1,2]. In this context, novel platinum compounds with alternative mechanisms of action may represent promising anticancer candidates. Here, we investigated the *in vitro* anticancer activity of the β-diketonate platinum(II) complex [Pt(O,O'-acac)(γ-acac)(DMS)] (Ptac2S) [3] in two PDAC cell lines, YAPC and BxPC-3, and compared its effects with those of cisplatin. Cytotoxic and clonogenic studies showed that both platinum compounds induced dose- and time-dependent cytotoxic effects and anti-clonogenic potential. Interestingly, YAPC cells displayed a markedly higher sensitivity to Ptac2S, compared to cisplatin. Based on the pronounced response of YAPC cells to Ptac2S, a ¹H NMR-based metabolomic approach was applied to investigate drug-induced metabolic alterations in both aqueous cell extracts and recovered culture media. Multivariate analysis revealed a clear separation among untreated, Ptac2S-treated and cisplatin-treated YAPC cells, indicating distinct metabolic signatures [4]. While Ptac2S mainly affected metabolites related to energy metabolism, amino acid homeostasis and organic acid balance, cisplatin treatment seemed to be associated with alterations in purine-related metabolites and choline derivatives. These findings, together with previous data obtained in another PDAC cell line, MIA PaCa-2, highlight distinct and partially cell line-dependent metabolic perturbations induced by Ptac2S and cisplatin, suggesting different modes of action of the two platinum compounds.



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New Details on the Anticancer Activity of Imidazolyl based Gold(I) Complexes

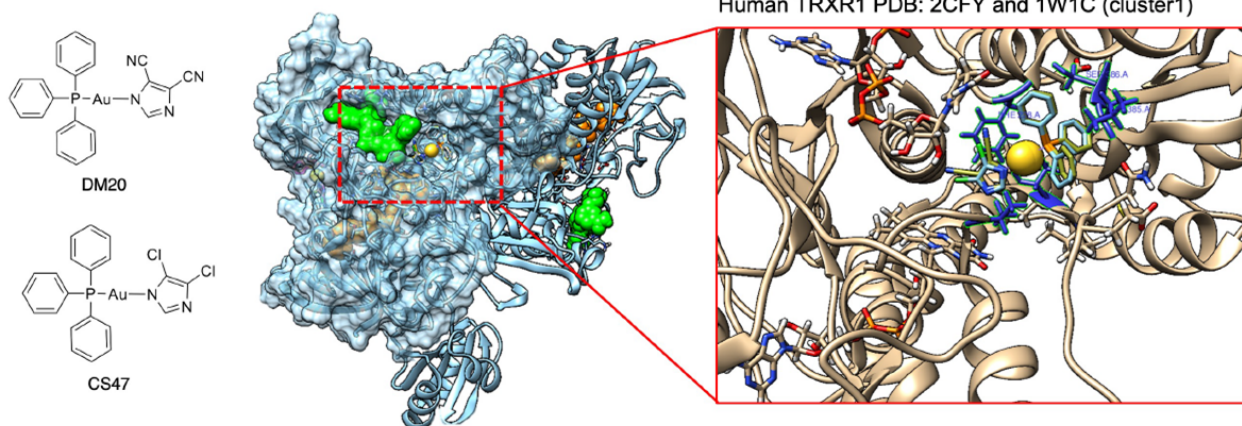
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Gold(I) complexes featuring heterocycles, such as imidazoles, are recognized for their potent anticancer properties across various cancer cell lines [1]. The renewed interest in Auranofin as an anticancer agent has resulted in extensive research into gold(I) compounds. In particular, several imidazolyl/phosphane gold(I) compounds have demonstrated activity against a wide range of cancer cells, including those resistant to cisplatin (e.g., C13* cancer cells) [2]. These compounds also exhibit fewer severe side effects and a favorable selectivity index between healthy and diseased cells. The proposed mechanism of action suggests that thioredoxin reductase is the primary molecular target, although our research has identified multiple potential targets [3]. Given this context, the efficacy of new gold(I) imidazolyl compounds and an understanding of their mechanisms of cellular activity remain significant areas of interest in bioinorganic chemistry [4]. In this context, our efforts are in the synthesis of likely active hybrid imidazolyl gold(I) compounds and in the studies aimed at exploiting the likely mechanisms of action, finely tuned by molecular structures and conjugated molecules. In this communication, the activity of new hybrid imidazolyl/carbazole gold(I) compounds and the results on well-known imidazolyl gold(I) compounds, such as the 4,5-dichloro- and 4,5-dicyanoimidazol-2-yl-gold(I) triphenylphosphane, will, be discussed.

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Advanced LC-MS strategies for the characterization of metal/protein adducts: methodological optimization and oncological applications.

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Understanding the interactions between metallodrugs and biomolecules is essential for elucidating the molecular mechanisms underlying the pharmacological activity of metal-based compounds. This work investigates the interactions of selected gold(I) and platinum(II) complexes, as potential anticancer agents [1], with biologically relevant protein targets, aiming to assess their binding affinity, selectivity, and competitiveness. The metal complexes examined include the FDA-approved platinum drugs cisplatin and oxaliplatin, alongside the gold compounds auranofin and the monocarbene complex [Au(NHC)Cl]. Human serum albumin, superoxide dismutase I, carbonic anhydrase I, cytochrome c, and ribonuclease A were selected as model proteins.

The experimental approach combined high-resolution electrospray ionization mass spectrometry (ESI-MS) [2] and high-performance liquid chromatography–mass spectrometry (HPLC-MS). These techniques enabled the characterization of proteins in their native state and the monitoring of metalloprotein adduct formation under controlled incubation conditions. Initial analyses focused on the identification of the principal molecular species and post-translational modifications of the native proteins, followed by metalation studies to evaluate the kinetics and extent of protein–metal interactions. Competitive binding experiments involving multiple protein targets were also performed and analyzed by HPLC-MS.

The results demonstrate a pronounced affinity of gold(I) complexes for proteins containing accessible thiol groups, leading to the formation of stable adducts and, in some cases, high protein-to-metal stoichiometries. In contrast, platinum(II) compounds exhibited lower selectivity and generated a broader range of metalated species. Overall, this work provides valuable experimental insights into the biological behavior of metal-based drugs and supports the development of more selective metal-based anticancer agents.

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Exploring Fe(III) coordination and membrane interaction of a siderophore-peptide conjugate: Enhancing synergistically the antimicrobial activity

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Bacteria have developed various methods to acquire iron, a crucial nutrient for their growth, from mammalian cells. One prominent strategy is the secretion of siderophores, small high-affinity iron chelators that facilitate the uptake of iron(III) from the extracellular environment. These siderophores sequester iron ions from human tissues, fluids and cells, transferring them into bacterial cells via specialized porins. The conjugation of antimicrobial peptides (AMPs) with iron chelators represents a promising approach to reducing iron availability, triggering bacterial death, and enhancing the overall effectiveness of AMPs. Recently, we designed a multi-block molecule featuring an antimicrobial peptide, whose efficacy has been gradually improved through specific sequence modifications. This molecule also incorporates a flexible bio-linker, optimized in length, and terminates in a hydroxyamide unit, a potent metal chelator [1]. Consequently, the molecule integrates two components that work synergistically to combat infection. To assess whether the peptide unit retains its structural integrity and antimicrobial activity despite the addition of a long tail, and to characterize its interaction with bio-membrane models mimicking Gram-negative membranes, we conducted fluorescence-based experiments and circular dichroism studies. These investigations supported our design, which effectively combines two distinct components. Iron(III) paramagnetic NMR spectroscopy and ultraviolet-visible spectroscopy validated the peptide's chelating activity and binding affinity. Spectrophotometric methods were employed to determine the complexation parameters, including Michaelis constant (K) and the number of binding sites, which were corroborated by the iron (III) paramagnetic NMR data. Our results demonstrate that integrating antimicrobial properties with iron-trapping capabilities is effective for treating infections caused by Gram-negative pathogens [2].

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ATCUN-Mediated Copper Binding in Myxinidin

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The amino-terminal copper-binding motif (ATCUN; H₂N-AA1-AA2-His) is a conserved sequence known for its ability to coordinate Cu(II) ions and produce reactive oxygen species (ROS) [1] [2]. This redox activity contributes to both metal transport and the antimicrobial properties of several peptides [1] [2]. Myxinidin (GIHDILKYGKPS), an antimicrobial peptide found in the mucus of hagfish, contains the ATCUN sequence Gly-Ile-His [3] [4]. To clarify the role of this motif, we analysed the copper-binding behaviour of myxinidin and a series of truncated analogues, starting from the minimal GIH motif and extending to the full-length peptide.

Spectroscopic techniques, including UV-Vis, electron paramagnetic resonance (EPR) and circular dichroism (CD), were employed to investigate binding stoichiometry, the coordination environment and pH dependence. In parallel, we assessed the ability of the Cu-peptide complexes to generate ROS through the ascorbate oxidation assay.

Our findings demonstrate that myxinidin efficiently binds Cu(II) through its ATCUN motif, forming redox-active complexes that enhance ROS production. These results suggest that copper coordination is an additional mechanism supporting the antimicrobial activity of myxinidin.

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Highly Cytotoxic Gold(I) Complexes Bearing Anthracenyl-Functionalized Phosphine Ligands

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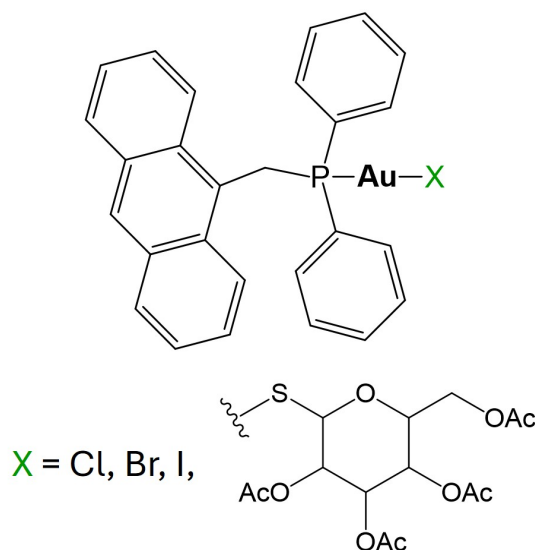
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Auranofin (AF), approved in 1985 for the treatment of rheumatoid arthritis, has also demonstrated promising anticancer activity [1], prompting extensive investigations of gold-based compounds as potential chemotherapeutic agents [2]. In this work, a panel of four novel gold(I) complexes was developed and characterized. All compounds feature the same anthracenyl-functionalized phosphine ligand, while differing in the second ligand coordinated to gold: three complexes bear a halide (Cl, Br, or I), whereas the fourth incorporates the thiosugar moiety of auranofin. The anthracenyl group was introduced to promote possible interactions with nucleic acids and to act as a fluorescent probe for future confocal microscopy studies, while the phenyl substituents were expected to enhance lipophilicity and cellular uptake.

All compounds were synthesized and fully characterized, and their solubility and stability under physiological-like conditions were evaluated. Biological studies performed on several cancer cell lines and one non-tumoral cell line revealed marked antiproliferative activity, with IC₅₀ values in the low micromolar range after only 24 h of exposure. Notably, the compounds were able to overcome cisplatin resistance in ovarian cancer cells, highlighting their potential as alternative metal-based anticancer agents.

To gain insight into their mechanism of action, interactions with natural DNA and Cathepsin B, a protease frequently overexpressed in cancer, were investigated. The results provide valuable structure–activity relationship information within this family of gold(I) compounds and support their further development as promising anticancer candidates.



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Design and Antitumoral Evaluation of a Bioconjugable Copper(II)-Thiosemicarbazone Complex: ROS Targeting and Cytotoxicity in HT29 and A549 Cell Lines

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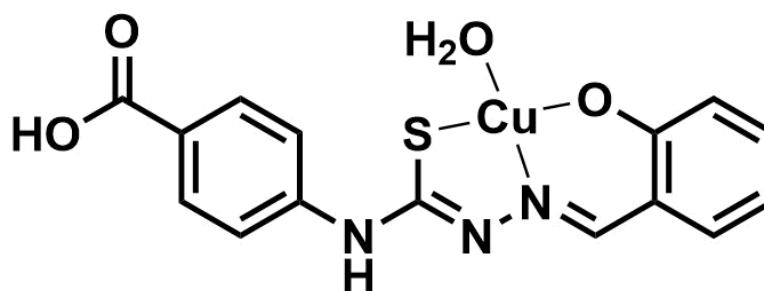
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Thiosemicarbazones are compounds characterized by a broad range of biological activities, with a particular relevance for their anticancer potential [1]. In this study, we synthesized a thiosemicarbazone bearing a carboxy group to improve its aqueous solubility and enable bioconjugation with peptides, thereby enhancing selectivity toward cancer cells. The anticancer activity of thiosemicarbazones is closely related to their ability to modulate reactive oxygen species (ROS), chemically reactive molecules generated during cellular metabolism, especially as byproducts of aerobic respiration. Although ROS play essential physiological roles, excessive ROS accumulation can trigger cellular apoptosis, and despite being extensively investigated, remains a promising strategy for cancer therapy [2].

On this basis, we synthesized a metal complex with copper(II) with our bioconjugable thiosemicarbazone. The ligand was prepared starting from 4-aminobenzoic acid, with the thiosemicarbazide as intermediate (also characterized by SC-XRD). Since the use of trifluoroacetic acid is a common cleavage method in peptide synthesis, a study of its stability in the presence of trifluoroacetic acid was carried out. The metal complex is characterized by IR, ESI-MS, elemental analysis, UV-Vis studies (Titrations, Job Plot, Stability in 24 hours), CV, EPR, DLS. We also performed DFT studies on the geometry of the metal center. Eventually, we performed UV-Vis studies of interactions with ROS (DPPH, H₂O₂, OH⁻) and with biomolecules (DNA, albumin) via circular dichroism and fluorescence spectroscopy.

Cytotoxic assays on cancer cell lines HT29 and A549 showed a remarkable activity of the metal complex, supporting the high potential of this compound for antitumoral application.



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Thiohydrazones and their copper(ii) complexes as bioactive compounds

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Thiohydrazones and their metal complexes constitute a class of bioactive compounds [1,2,3]. The traditional procedure for the synthesis of aromatic thiohydrazides involves the use of highly toxic and hazardous reagents, such as carbon disulfide and hydrazine [4,5]; therefore, a different protocol was applied, involving thionation with Lawesson's reagent of a carboxylic acid.

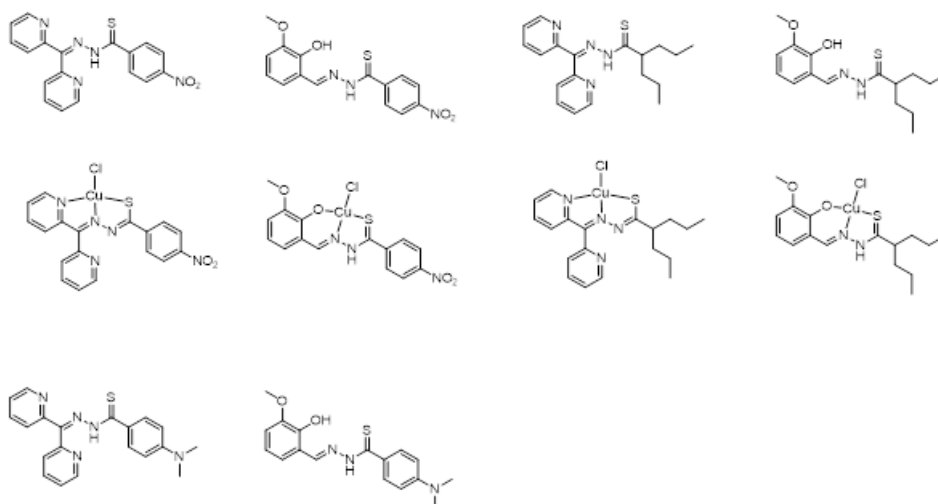


Figure 1. Chemical structures of the novel thiohydrazones and Cu(II) complexes.

[6] Two aromatic precursors were chosen with the aim of studying the effects of an electron donating and an electron-withdrawing group in position 4 of the phenyl ring can have on both the reactivity and the anticancer activity of the related thiohydrazones. The obtained 4-(dimethylamino)benzothiohydrazide, 4-nitrobenzothiohydrazide and 2-propylpentanethiohydrazide were used to synthesize novel thiohydrazones (Figure 1). Two different carbonyl precursors were employed: ortho-vanillin and di(2-pyridyl)ketone. The ligands were used to synthesize novel copper(II) complexes (Figure 1). The resulting complexes were characterized by means of FT-IR spectroscopy, mass spectrometry and elemental analysis. The assessment of the anticancer properties of the new ligands and of their copper(II) complexes are ongoing.

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Auranofin binding to uracil and thiouracils assayed by IRMPD spectroscopy

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Since the clinical approval of cisplatin for cancer treatment, targeting of nucleobases to disorder DNA/RNA structure has significantly inspired medicinal inorganic chemistry. In the context of repositioning strategy, the leading gold(I) compound Auranofin (AF) has been included in clinical search for antitumor candidates [1]. Alike most of gold(I) complexes, AF selectively binds to sulfur and selenium-containing proteins, including glutathione peroxidase and thioredoxin reductase (TrxR) [2]. AF acts as an exemplary prodrug, whose activation releases the [(Et₃)Au]⁺ fragment, the effective pharmacophore [3]. The potential interaction with (poly)nucleotides, a still less explored frontier, has prompted the exploration of dicarbene gold(I) adducts as G4 stabilizers with associated antitumor properties. In continuation of our current interest in gathering a structural characterization of metal-drug adducts with prime targets [4], in the present study, we report a joint experimental and quantum chemical computational survey of [(Et₃P)Au (L)]⁺ ions generated by electrospray ionization of a mixture of AF and four nucleobases L, i.e. uracil (U), and its thioderivatives, 2-thiouracil (2SU), 4-thiouracil (4SU) and 2,4-dithiouracil (24dSU), established as minor components of transfer-RNA. The [(Et₃P)Au (L)]⁺ complexes have been assayed by tandem mass spectrometry, IR ion spectroscopy (IRMPD). With this multimethodological approach, we intend to explore how thio-substitution may affect the tautomeric equilibria of (thio)uracils, possibly contributing to the therapeutic efficacy of the drug.

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Copper and silver complexes as next-generation metallodrugs for the treatment of resistant cancers

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The development of metal-based therapeutics with improved selectivity and efficacy remains a major challenge in medicinal inorganic chemistry. In this context, novel copper(I), copper(II), and silver(I) complexes supported by *N,O*-donor ligands functionalized with the bioactive molecules amantadine and memantine were designed, synthesized, and characterized to investigate their potential anticancer activity. The new synthesized copper compounds displayed remarkable antiproliferative activity against glioma cell lines, exhibiting IC₅₀ values significantly lower than cisplatin and reduced toxicity toward non-tumoral cells. Mechanistic studies revealed that the metal center plays a crucial role, promoting ROS generation and mitochondrial dysfunction, as evidenced by mitochondrial depolarization and altered intracellular distribution. Furthermore, the cytotoxic activity of these compounds was effectively inhibited by the Cu chelator tetrathiomolybdate, confirming the essential role of copper in their mechanism of action. Building on these promising results and aiming to assess the influence of the metal center on the pharmacological profile of the complexes, the same ligand design strategy was extended to the synthesis of silver(I) complexes. The resulting amantadine-functionalized silver(I) complexes were biologically evaluated, showing significant cytotoxicity against pancreatic cancer cells in both two and three-dimensional culture models. Their activity was associated with efficient intracellular accumulation and inhibition of thioredoxin reductase, resulting in disruption of cellular redox homeostasis and increased oxidative stress. Overall, these findings highlight the potential of rationally designed copper and silver complexes as a new generation of metallodrugs, capable to overcome limitations associated with conventional platinum-based chemotherapy and offering promising opportunities for the treatment of resistant malignancies.

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Metal-Based Complexes as Emerging Antibacterial Agents: An Overview of Novel Design Strategies

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Antimicrobial resistance represents one of the most pressing threats to global public health, significantly reducing the effectiveness of current antimicrobial therapies and increasing the incidence of resistant infections [1]. The rapid emergence of multidrug-resistant bacterial strains has highlighted the urgent need for alternative therapeutic approaches capable of overcoming resistance mechanisms. In this context, metal-based compounds have attracted growing interest as promising antimicrobial agents due to their unique chemical and biological properties. Indeed, transition metal complexes offer high structural diversity, tunable reactivity, accessible redox states, and ligand exchange capabilities, enabling interactions with multiple biological targets and mechanisms of action distinct from those of traditional antibiotics [2]. Additionally, the rich photochemistry of certain metal complexes offers opportunities for the development of light-activated antimicrobial strategies, including photodynamic and photorelease therapies [3]. Our research focuses on the exploration of different classes of metal complexes as potential antibacterial agents, with particular attention to Ru(II)-polypyridyl complexes and related metal-based systems. In this contribution, we present an overview of several molecular platforms developed in our group, whose design was rationally tailored to modulate the chemical and biological properties of the compounds, with the aim of finely tuning their reactivity, photochemical behavior, and interactions with bacterial targets. Preliminary biological evaluations further demonstrate the potential of these systems as promising candidates for the development of new antibacterial strategies. Overall, these studies highlight the growing relevance of metal-based complexes as innovative approaches to tackle antimicrobial resistance.

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Synthesis, physico-chemical properties and In Vitro studies of new porphyrazine complexes of the lanthanide series. Exploration of their potential applications in biomedicine

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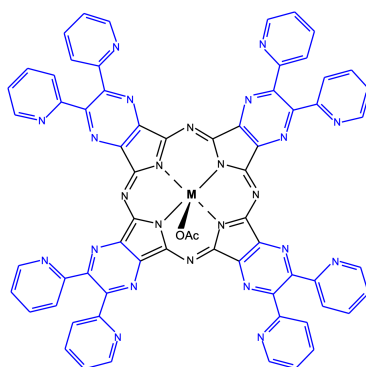
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In our previous extensive studies the synthesis, physico-chemical properties and activity as photosensitizers in photodynamic therapy (PDT) [1] were reported of mononuclear octa(2-pyridyl)tetrapyrzino porphyrazines complexes, having centrally coordinated trivalent diamagnetic metals, formulated as $[\text{Py}_8\text{TPyzPzMX}] \cdot x\text{H}_2\text{O}$ where Py_8TPyzPz = tetrakis-2,3-[5,6-di(2-pyridyl)pyrazino]porphyrazine and $\text{MX} = \text{Al}^{\text{III}}\text{Cl}/\text{OH}$, $\text{Ga}^{\text{III}}\text{Cl}/\text{OH}$, $\text{In}^{\text{III}}\text{OAc}$ (Cl = chloride anion; OH = hydroxide anion; OAc = acetate anion). For the investigated compounds the photoactivity for the generation of singlet oxygen, $^1\text{O}_2$, the main cytotoxic agent in PDT, was explored in DMF and DMF/HCl solutions. These species showed high quantum yield values ($\Phi_\Delta = 0.5\text{--}0.7$) exceeding those obtained for the series $[\text{Py}_8\text{TPyzPzM}]$ ($\text{M} = \text{Zn}^{\text{II}}$, $\text{Mg}^{\text{II}}(\text{H}_2\text{O})$, Pd^{II} , Pt^{II}) [2,3].

In a recent extension of our work on TPyzPzs it was thought interesting to undertake additional studies on new porphyrazine metal derivatives with trivalent metals of lanthanide series, with the aim of examining their potential applications in biomedical field [4]. New mononuclear tetrapyrzino porphyrazine complexes formulated as $[\text{Py}_8\text{TPyzPzM}(\text{OAc})] \cdot x\text{H}_2\text{O}$ ($\text{M} = \text{Nd}^{\text{III}}$, Gd^{III} , Yb^{III} , Lu^{III})



, have been synthesized and characterized. For all complexes the photoactivity for the generation of $^1\text{O}_2$ was explored in DMF and in DMF/HCl. The high Φ_Δ value obtained for the Gd^{III} (0.77) and Lu^{III} (0.86) macrocycles in DMF/HCl solution qualify these complexes as excellent photosensitizers for the generation of $^1\text{O}_2$, with the perspective of being used as potential anticancer agents in PDT [5]. Finally, experimental delivery studies have been carried out with different carrier systems and *In Vitro* tests on HeLa cells cancer line have been performed with promising results.

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Exploring ferroptosis-related metabolomic signature of gold-based anticancer compounds: comparison with Erastin in A2780 ovarian cancer cells

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Gold-based compounds represent a promising class of anticancer agents whose mechanisms of action involve complex metabolic responses that remain only partially understood. Recent evidence suggests that ferroptosis, an iron-dependent regulated cell death characterized by extensive metabolic remodeling, may contribute to the cytotoxic activity of selected gold compounds [1,2]. In this study, Erastin was used as a reference ferroptosis inducer to define the ¹H NMR metabolomic signature of ferroptosis in A2780 ovarian cancer cells and compare it with previously obtained metabolomic profiles for gold-based anticancer compounds (auranofin, monocarbene, biscarbene, and aurothiomalate) in the same cellular model [3], aiming to identify metabolomic biomarkers associated with ferroptosis-related mechanisms.

A2780 cells were treated with Erastin for 24 and 48 h. Cell lysates and culture media were prepared according to standardized operating procedures (SOPs) and analyzed by ¹H NMR spectroscopy [4]. Overall, 45 metabolites were identified in cell lysates and 34 in culture media. Multivariate, univariate, and pathway analyses were performed.

Erastin induced time-dependent metabolic alterations associated with ferroptosis, including decreased glutathione and increased glutamate in cell lysates, along with reduced glutamate and increased cystine in growth media, consistent with inhibition of the cystine/glutamate antiporter. Additional changes involved myo-inositol, choline, glycerophosphocholine, and Krebs cycle intermediates. Glutathione metabolism emerged as the most altered pathway, particularly at 24 h.

Comparative analysis revealed partially overlapping responses with gold compounds, especially biscarbene, highlighting potential metabolomic biomarkers of ferroptosis and supporting the involvement of ferroptosis-related mechanisms in gold compound activity.

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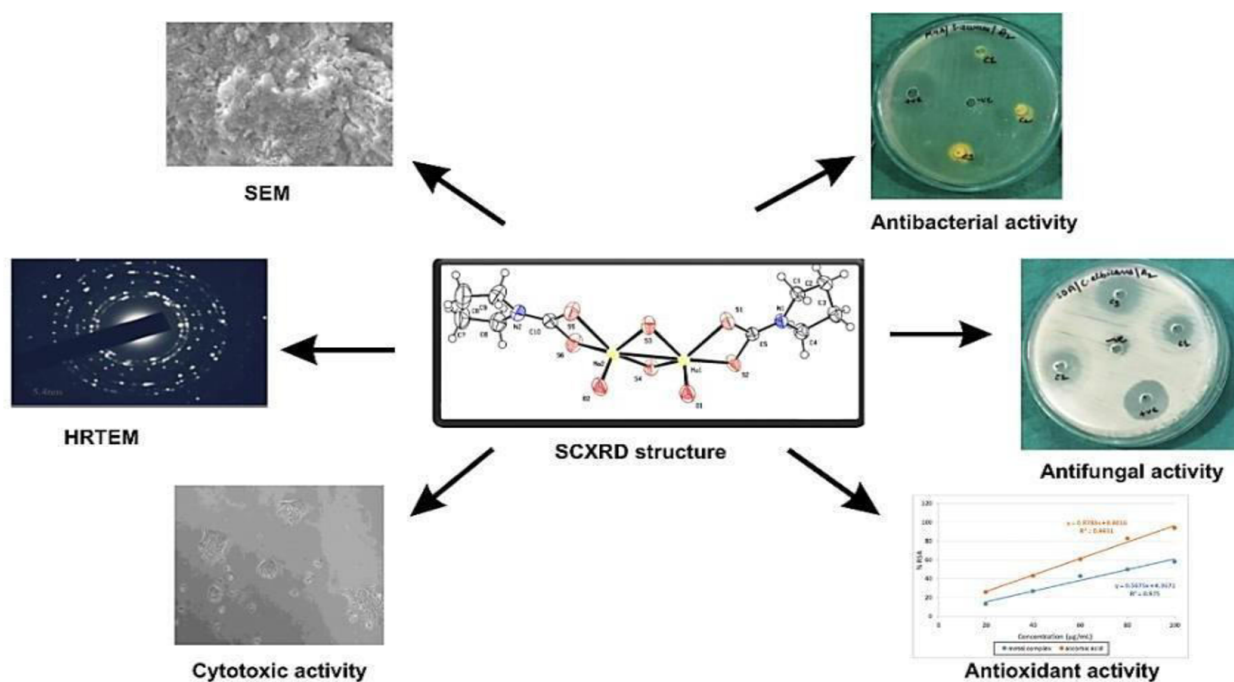
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MoS₂ Nanoparticles Derived from a Bioactive Pyrrolidine Dithiocarbamate Molybdenum(V) Complex

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We present the synthesis of a bioactive pyrrolidine dithiocarbamate complex of molybdenum(V). The complex has been characterized by elemental analysis, FTIR, UV-Vis, and X-ray crystallographic techniques. The complex is fluorescent in nature and shows moderate antioxidant, antimicrobial, and cytotoxic activities. The Mo(V) complex was used as a single-source precursor and thermolysed at 220 °C to prepare HDA-capped MoS₂ nanoparticles, which were characterized by PXRD, SEM-EDS, XPS, and HRTEM-SAED techniques.



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The impact of cavitation treatments on optical properties, aggregation and toxicity of PG7 and PY14

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Phthalocyanines are highly stable macrocyclic coordination compounds valued for their thermal and chemical resistance. However, their persistence complicates removal processes, such as tattoo pigment elimination, where conventional laser treatments often require multiple sessions with risks of generating hazardous byproducts.

This study investigates ultrasonic cavitation as an alternative strategy for degrading persistent pigments. Pigment Green 7 (PG7), a chlorinated copper(II) metallophthalocyanine, was used as a model system and compared against Pigment Yellow 14 (PY14), a stable organic pigment characterized by dense crystalline aggregates.

The effects of varying cavitation frequencies and durations were monitored using UV–Vis spectroscopy. A significant reduction in absorbance intensity was achieved at 0.65 MHz within 10 minutes. Dynamic light scattering (DLS) and scanning electron microscopy (SEM) analyses confirmed that cavitation effectively fragmented the large, bimodal aggregates of PY14 into submicron particles and significantly reduced the aggregate size of PG7.

Given the structural differences between the pigments, their degradation pathways raise distinct bioinorganic and toxicological questions. Unlike the complex, hazardous byproduct profiles typical of laser treatments [1], GC–MS analysis detected no dangerous degradation products, except for naphthalene in PG7, which is likely a synthesis-related impurity. MTT cell viability assays indicated that while cavitation successfully alters the structural identity and aggregation states of both pigments, it introduces non-negligible cytotoxic effects. These findings highlight sonochemistry as an efficient tool for pigment de-aggregation while underscoring the necessity of rigorous toxicological evaluations.

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Antimetastatic Activity of a Novel (Arene)Ruthenium(II) Naphthopyran Complex in Metastatic Cancer Models

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Metastatic dissemination remains the leading cause of cancer-related mortality, underscoring the urgent need for therapeutics that effectively target both tumor growth and metastatic progression. We investigated the antimetastatic potential of a novel (arene)ruthenium(II) naphthopyran complex, dichlorido(p-cymene)[2-amino-4-(pyridin-3-yl)-4H-benzo[h]chromene-3-carbonitrile]ruthenium(II) (complex 1), in clinically relevant metastatic cancer models. Complex 1 displayed potent antiproliferative activity against metastatic LoVo, DU-145, and MDA-MB-231 cell lines, exceeding the efficacy of cisplatin and exhibiting nanomolar potency in LoVo and DU-145 cells. In highly invasive MDA-MB-231 cells, the complex significantly suppressed multiple hallmarks of metastasis, including cell migration, invasion, and re-adhesion. These effects were accompanied by reduced MMP-9 production/activity and pronounced reorganization of the vimentin cytoskeleton, indicating impaired migratory and invasive capacity. Notably, the antimetastatic activity of complex 1 was further validated in a three-dimensional spheroid invasion model, where treatment markedly inhibited tumor cell dissemination into the surrounding extracellular matrix. Collectively, these findings demonstrate that this novel (arene)ruthenium(II) naphthopyran complex effectively targets several key processes involved in metastatic progression and highlight this class of compounds as promising candidates for further preclinical development as antimetastatic anticancer agents.

Acknowledgements:

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Synthesis of Platinum(II) complexes with chelating amines: a greener approach using water/choline chloride-based deep eutectic solvents

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Deep eutectic solvents (DESs) are made up of two or more components, interacting through hydrogen bonds and forming an eutectic mixture with a melting point lower than the individual components. DESs are considered green alternatives to organic solvents [1]. Interestingly, investigations into the chemical reactivity of platinum(II) salts are essentially missing from the literature. Following a previous study of the model reaction of K_2PtCl_4 salt with ethylenediamine (en) [2], the behaviour of other chelating amines, such as 1,2-diaminocyclohexane (1,2-DACH), 4-cyclohexene-1,2-diamine dihydrochloride (1,2-DACHEX), and diethylenetriamine (DIEN), has been evaluated. The reactions were performed at room temperature in a 70% DES (choline chloride/ethylene glycol 1:2) /30% water (1:1 H_2O/D_2O) mixture for NMR lock purposes. Reaction products were characterised by 1H , $^{195}Pt\{^1H\}$, $[^1H, ^{13}C]$ -HSQC and $[^1H, ^{15}N]$ -HSQC NMR experiments. In our previous work, reaction with en led to $[PtCl_2(en)]$, followed by further reaction of an additional en moiety affording $[Pt(en)_2]Cl_2$. Unexpectedly, over a longer time, we observed the precipitation of Magnus-type salt $[Pt(en)_2][PtCl_4]$ [2,3]. Conversely, 1,2-DACH and 1,2-DACHEX coordinated to Pt, leading to the formation of characteristic yellow precipitates, which were isolated from the DES/water mixture and analysed by NMR spectroscopy. The DIEN coordination to the Pt centre led to the cationic $[Pt(DIEN)Cl]^+$, which remains in solution in the mixture. Thus, its formation was evaluated by observing 1H and ^{15}N signals belonging to NH_2 in trans to N (5.51, -29.42 ppm and 5.71, -29.29 ppm) and to NH in trans to Cl (6.78, 8.38 ppm) and further confirmed by the ^{195}Pt signal at -2940 ppm

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Reducing chemoresistance in Triple-Negative Breast Cancer through PON2 silencing: FTIRM insights into response to combined therapy

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Triple-negative breast cancer (TNBC) is an aggressive neoplastic subtype associated with poor prognosis and limited response to conventional chemotherapy [1]. Due to the lack of targetable receptors and the frequent development of chemoresistance, identifying molecular factors involved in drug sensitivity remains clinically relevant. Paraoxonase-2 (PON2), an intracellular enzyme implicated in redox homeostasis, mitochondrial function, and cell survival, may contribute to TNBC chemoresistance by protecting cancer cells from reactive oxygen species, thereby counteracting the effect of cisplatin and other chemotherapeutic agents [2].

In this study, we investigated the biochemical and functional effects of PON2 gene silencing in MDA-MB-231 TNBC cells exposed to combined chemotherapy with doxorubicin, 5-fluorouracil, and cisplatin. Cells were transfected with pLKO.1-puro as the control condition (p0) or with pLKO.1-647 for PON2 silencing (p647), and analyzed after 24, 48, and 72 hours. Cell viability was assessed by MTT assay, while Fourier Transform Infrared Microspectroscopy (FTIRM), a label-free technique applied to tumor cell and tissue characterization [3,4], was used to detect treatment-induced macromolecular alterations and investigate drug response mechanisms [5].

IR spectra were collected in the 4000–900 cm⁻¹ range, using 256 scans and 4 cm⁻¹ resolution. Approximately 80 micro-areas of 30 × 30 μm², containing 2–3 densely packed cells, were analyzed. Raw spectra were pre-processed and subjected to statistical analyses.

Preliminary FTIRM observations revealed time-dependent variations involving lipids, proteins, carbohydrates, and nucleic acids, influenced by PON2 silencing. These changes may reflect altered metabolic adaptation under chemotherapeutic stress and support the use of FTIRM for monitoring pharmacological response in TNBC.

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Electrostatically-driven assembly of cationic lipopeptides with hexacyanoferrate anions: a thermodynamic and in silico study

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Understanding the interplay between electrostatic and hydrophobic interactions during molecular recognition is fundamental to the rational design of functional antimicrobial systems [1,2]. In the present study, the interactions of two KR12-derived lipopeptides differing in hydrophobic chain length (C12-KR12-NH₂ and C14-KR12-NH₂) with hexacyanoferrate(II)/(III) anions, employed as structurally well-defined models of multivalent negatively charged targets, were investigated.

An integrated experimental and computational approach combining isothermal titration calorimetry (ITC), circular dichroism (CD) spectroscopy, and all-atom molecular dynamics (MD) simulations was applied to elucidate the thermodynamic, structural, and molecular determinants of complex formation. ITC measurements demonstrated that the interactions are predominantly enthalpy-driven and strongly influenced by ligand charge, with hexacyanoferrate(II) exhibiting substantially higher binding affinity than hexacyanoferrate(III). CD spectroscopy revealed that electrostatic complexation modulates peptide secondary structure in a hydrophobicity-dependent manner. Whereas complex formation promoted α -helical organization of the C12 lipopeptide, the C14 analogue exhibited a charge-dependent conformational response arising from the competition between intrinsic hydrophobic stabilization and electrostatic constraints. Complementary MD simulations demonstrated that hexacyanoferrate(II) efficiently mediates electrostatic cross-linking between peptide molecules, thereby stabilizing dimeric assemblies, whereas the less negatively charged hexacyanoferrate(III) generated weaker and less persistent complexes [3].

The present findings demonstrate that peptide hydrophobicity and ligand charge cooperatively govern molecular recognition, conformational adaptation, and self-assembly. The molecular-level insights presented herein advance the understanding of electrostatically driven biomolecular interactions and provide a rational basis for the design of antimicrobial lipopeptides with tailored structural and physicochemical properties.

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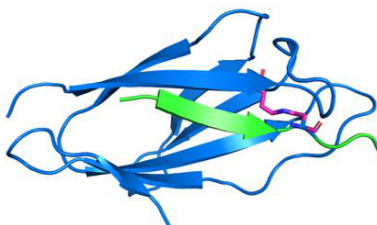
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(The Power of) Vision3D: creating new virtual environments for 3D protein visualization and science dissemination

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The visualization of three-dimensional protein structures through augmented reality (AR) and virtual reality (VR) extends beyond science communication, offering innovative tools for structural analysis and education. The increasing availability of affordable AR/VR technologies enables researchers, students, and the public to explore biomolecular structures in an intuitive and interactive way.



Spy protein

Scan the code, select [AR] in the left side menu, follow the instructions, and enjoy!

The VISION3D project aims to establish a multidisciplinary hub for the dissemination of crystallographic and molecular sciences, centered on the Crystallochemistry and Mineralogy Museum Collections of the University of Parma [1,2]. By integrating themes from Earth sciences, chemistry, and structural biology, the project uses 3D visualization, AR, and VR to illustrate the relationships between the structure and properties of natural, synthetic, and biological materials [3]. Structural information from major databases, including the Cambridge Structural Database, the Inorganic Crystal Structure Database, and the Protein Data Bank, is combined with dedicated visualization software and AR/VR devices, such as headsets and smart glasses, to create immersive educational experiences. Virtual exploration paths allow users to investigate materials of environmental, medical, and technological relevance.

VISION3D develops resources tailored to a broad audience, including the general public, schools, and university students. It also provides valuable educational tools for STEM teaching by promoting critical understanding of molecular models through interactive 3D visualization, complementing traditional physical models.

This contribution presents examples of protein structures visualized in augmented reality on smartphones and introduces tutorials for generating AR-ready models using freely available software.

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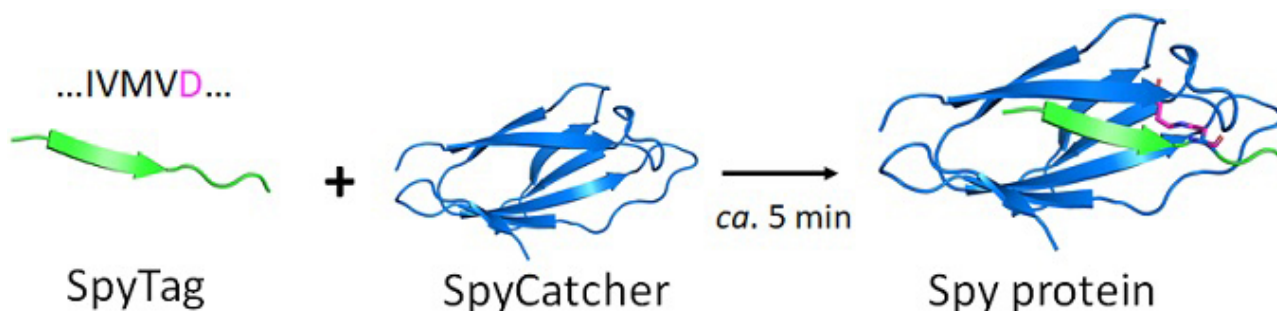
Evolving SpyTag/SpyCatcher system into new artificial proteins

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Metalloproteins play a central role in some of the most complex biomolecular processes found in nature. The SpyTag/SpyCatcher system is an artificial peptide/protein ligation platform derived from the fibronectin-binding protein of *Streptococcus pyogenes* [1]. SpyTag is a short peptide (13 amino acids) that selectively binds the engineered SpyCatcher protein (~150 amino acids), forming a spontaneous, irreversible covalent isopeptide bond without the need for enzymes or cofactors. Owing to its high specificity and efficiency, this reaction enables modular protein assembly, site-specific functionalization, and the stable attachment of a wide range of cargoes, including nanoparticles, enzymes, and therapeutic agents.



In this contribution, we present recent advances in the redesign of the SpyTag/SpyCatcher platform for the development of bioinspired catalysts for hydrogen production, as a biotechnological tool for anchoring artificial catalysts to proteins and living cells, and as a versatile platform for bioimaging applications [2]. This modular strategy bridges rational protein engineering and de novo protein design by transferring much of the molecular complexity from protein engineering to the synthesis of short, functionalized peptides. The ability to incorporate entirely artificial functional groups into SpyTag peptides greatly expands the versatility of the platform, opening new opportunities in catalysis, theranostics, molecular imaging, and precision medicine.

Project "Artificial enzymes for the photocatalytic production of hydrogen in photosynthetic bacteria" National Recovery and Resilience Plan (NRRP), M2 C2 Inv. 3.5 funded by the European Union – NextGenerationEU. Project RSH2A_000009, C.D. 445 29/12/2022 Italian Ministry of Environment and Energy Security.

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Structural characterization of the chimeric enzyme CYP-SOX by pulsed EPR spectroscopy

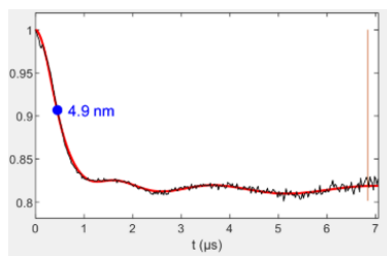
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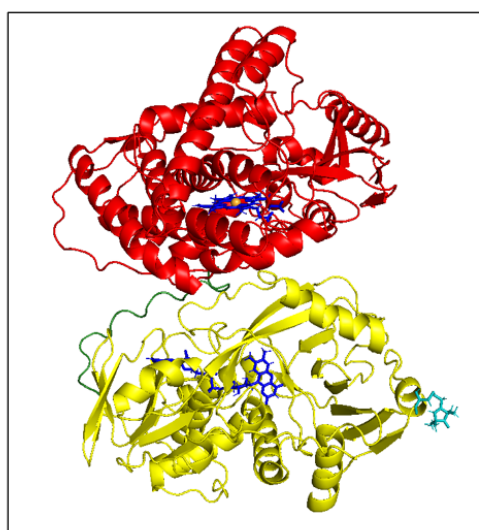
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Fusing enzymes at a genetic level to construct engineered chimeras has enabled inventive biochemists to design and assemble novel nano-tools, like bricks of a “molecular Lego”. Here we discuss the chimeric fusion of two redox enzymes, a H₂O₂ generating flavin oxidase and a P450 peroxygenase into a single polypeptide chain. *Acinetobacter radioresistens* CYP116B5 (CYP) was selected for its peroxygenase activity, and using an engineered poly-proline linker, its native reductase domain was replaced with monomeric sarcosine oxidase (SOX) from *Bacillus subtilis*. The CYP-SOX chimera not only enabled the P450 catalytic cycle by the sole addition of sarcosine but improved its catalytic efficiency (k_{cat}/K_M) towards aromatic compounds both compared to the wild-type enzyme and isolated heme domain.

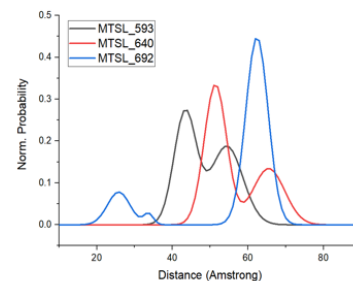
Aiming to structurally characterize the CYP-SOX chimera, we employed site-directed spin labelling (SDSL) to deconvolute the reciprocal position of the chimeric domains. By means of the five pulsed Q-band EPR RIDME sequence, we measured the resonant spin-spin distance between the low-spin heme iron of the CYP domain and the nitroxide labelled SOX. We repeated the measurement four times for the four different labeled mutants, residing at cardinal positions on the SOX domain. Bimodal distributions were measured for each spin-pair suggesting two conformational ensembles of the enzyme. Assembled, the distance distributions were used to guide a modified version of AlphaFold2 algorithm, available as DEERFold [2], and predict the domain arrangement of chimeric enzyme. The outputs of the algorithm were evaluated by earth mover distance (EMD) and clustered by principal component analysis (PCA).



Dipolar evolution trace from SDSL CYP-SOX and relative fitting.



Spin labeled CYP-SOX, AlphaFold model.



Experimental bimodal distance distributions for each spin pair.

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Single-site hydrogen-bond modulation enhances catalytic ester hydrolysis in a Zn(II)–TPA scaffold

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Zinc-containing metalloenzymes promote hydrolysis reactions through cooperative interactions within well-defined active sites. Inspired by these systems, we designed a Zn(II)-TPA complex incorporating a single-site hydroxymethyl group as a secondary-sphere hydrogen-bond donor to investigate its role in ester hydrolysis. The modified Zn(II)-TPA(CH₂OH) complex was synthesized and structurally characterized, revealing that the hydroxymethyl group does not coordinate to the metal center but remains positioned to enable hydrogen-bonding interactions. Kinetic studies using p-nitrophenyl acetate as a model substrate demonstrated that Zn(II)-TPA(CH₂OH) exhibits an approximately 80-fold increase in catalytic rate constant compared to the parent Zn(II)-TPA complex. Notably, this enhancement occurs despite only a modest decrease in pK_a (8.03 to 7.34), indicating that increased hydroxide concentration alone cannot account for the observed reactivity.

Mechanistic analysis suggests that secondary-sphere hydrogen bonding facilitates substrate activation and stabilizes the transition state, thereby promoting nucleophilic attack by the Zn-bound hydroxide. These findings highlight the critical role of localized hydrogen-bonding interactions and demonstrate that minimal secondary-sphere modification can significantly enhance catalytic efficiency in Zn(II)-based artificial metalloenzymes.

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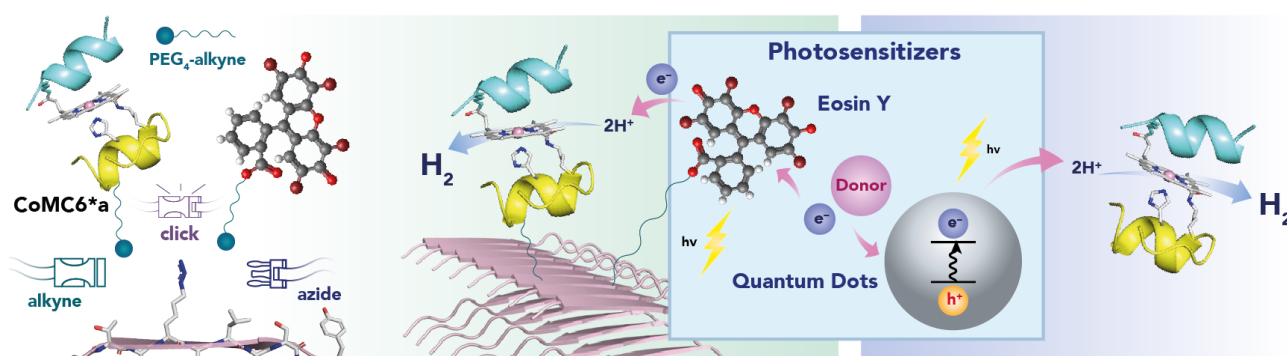
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Coupling Artificial Metalloenzymes with Photosensitizers for H₂ Evolution

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The transition toward sustainable energy technologies requires efficient systems for converting solar energy into chemical fuels. In this framework, photocatalytic H₂ production represents an appealing strategy, relying on the synergy among a photosensitizer, a hydrogen-evolving catalyst (HEC), and an electron donor [1]. Artificial metalloenzymes have emerged as promising HECs by combining the catalytic performance of molecular catalysts with the robustness and tunability of engineered protein scaffolds [2]. Among them, CoMC6*a, a cobalt-porphyrin derivative of the Mimochrome family, has demonstrated remarkable electrocatalytic and photocatalytic H₂ evolution activity when coupled with Ru(bpy)₃²⁺ as photosensitizer and ascorbic acid [3,4]. To develop efficient photocatalytic platforms, we are exploiting alternative photosensitizers as carbon quantum dots (CQDs) and Eosin Y (Figure 1).



First, building on our previous study on the immobilization of FeMC6*a on amyloid fibrils [5], we have extended this approach to CoMC6*a and combined it with Eosin Y to develop a peptide-based light-driven system for hydrogen production. In particular, TTR(105-115) peptide derived from human transthyretin [6], was functionalized with an azido-lysine residue to enable site-selective conjugation of alkyne-modified CoMC6*a through click chemistry. The close proximity between catalyst and photosensitizer is expected to facilitate electron transfer while improving the operational stability of the photocatalyst. In parallel, CQDs are being investigated as metal-free photosensitizers, owing to their low toxicity, tunable optical properties and good photostability, which make them promising candidates for sustainable photocatalytic H₂ production. In summary, our research explores novel paths for the development of multifunctional nanomaterials for catalytic and light-driven energy-related applications.

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From nitrogen to sulfur ligation: reprogramming reactivity in miniaturized heme enzymes

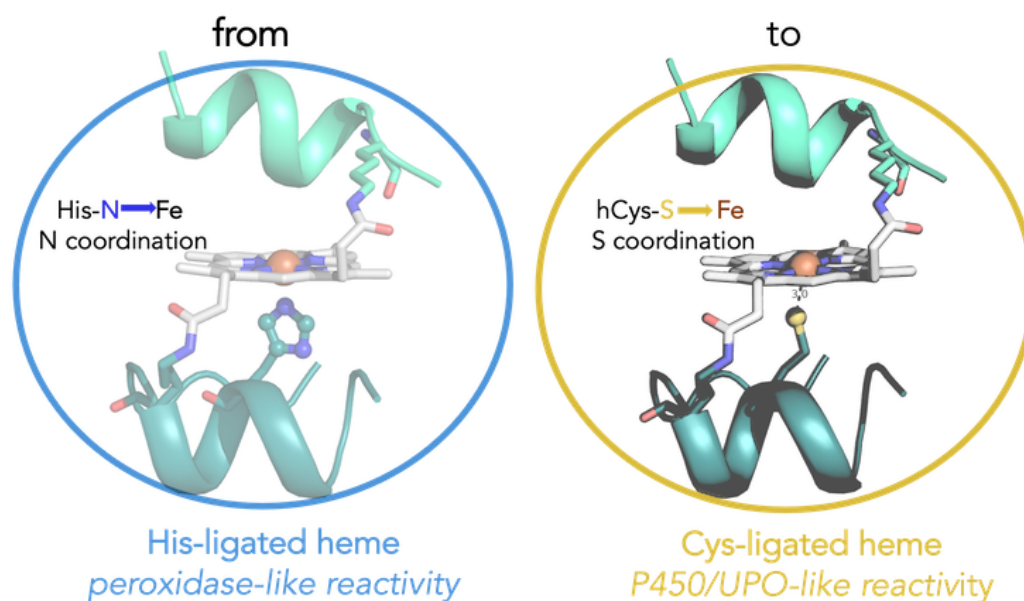
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Reprogramming the reactivity of a heme cofactor within a small and stable scaffold represents a major challenge in artificial metalloenzyme engineering [1]. The reactivity of the heme cofactor is critically governed by its local coordination environment: even subtle changes can markedly alter the electronic structure of the metal centre, thereby redirecting the cofactor toward distinct catalytic pathways [2].

Mimochromes (MCs) are synthetic heme-protein mimics, made up of a deuteroporphyrin covalently linked to two short α -helical peptide chains [3]. Their minimal architecture provides a unique platform for engineering catalytic functions through rational scaffold modification and metal-ion substitution [4]. FeMC6^a features a proximal His ligand and exhibits efficient peroxidase activity. To reprogram the catalytic properties of FeMC6^a, the axial His ligand was replaced with homocysteine, yielding FeMC6^a-S with a sulfur-ligated heme. This substitution replaces the nitrogen coordination of peroxidases with thiolate coordination, as found in cytochromes P450 and unspecific peroxygenases [5]. FeMC6^a-S was synthesized and purified, and its structural and spectroscopic properties were investigated by UV-Vis absorption, CD and Raman spectroscopies to evaluate the influence of the N-to-S donor atom substitution on both the peptide-porphyrin assembly and the electronic environment. Catalytic studies with model substrates are underway to assess whether modifying the first coordination sphere alone can redirect FeMC6^a from peroxidase activity toward P450/peroxygenase-like oxidative transformations.



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Metal Binding Dynamics in Human Ctr1(1–25): A pH-Dependent Coordination Switch

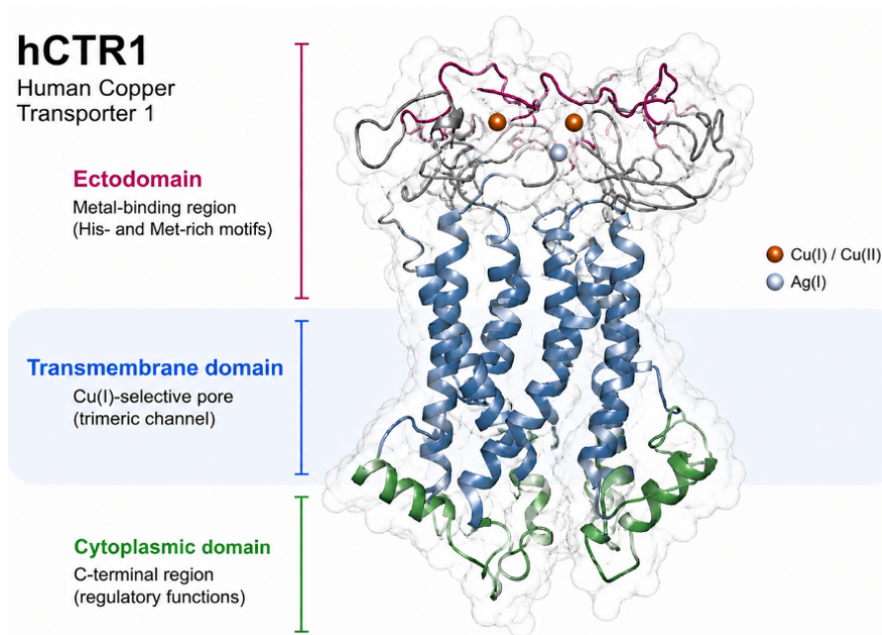
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Human Copper Transporter 1 (Ctr1) mediates cellular copper uptake through its extracellular N-terminal domain, which contains multiple histidine- and methionine-rich motifs involved in metal recognition and transfer. While the metal-binding properties of the shorter Ctr1(1–14) fragment have been previously characterized [1,2], the contribution of the additional donor residues present in the extended Ctr1(1–25) sequence (MDHSHHMGMSYMDS14NSTMQPSHHHP25) remains poorly understood. Here, we investigated the metal-binding behavior of Ctr1(1–25) by combining NMR spectroscopy and electrospray ionization mass spectrometry (ESI-MS), with particular focus on pH-dependent coordination and on the interplay between Cu(II) and Ag(I), the latter used as a redox-stable mimic of Cu(I).

The peptide displays pronounced pH-dependent conformational and coordination plasticity. At neutral and mildly basic pH, metal coordination primarily involves histidine residues, whereas protonation of histidine side chains under acidic conditions induces a reversible switch toward methionine-centered binding, mainly involving the MGMSYM motif. ESI-MS data reveal the progressive formation of polynuclear metal complexes, indicating an enhanced metal-loading capacity compared with Ctr1(1–14). The additional donor residues expand the available coordination network and promote the formation of higher-order species.

Mixed-metal titration experiments further reveal a complex interplay between Cu(II) and Ag(I), suggesting the coexistence of distinct coordination environments and dynamic metal redistribution processes. Overall, these findings support a model in which the N-terminal region of human Ctr1 acts as a dynamic multinuclear metal-binding platform, where coordination flexibility and ligand switching may regulate copper acquisition and trafficking.



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Design, Synthesis and Characterization of a Zn(II)His₃ Site in a Heterodimeric Three-Helix Bundle Scaffold

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Zinc is a versatile and widespread metal ion in biological systems, where it plays key roles in metalloproteins and metalloenzymes. Its redox inertness, flexible coordination geometry, and ability to bind a variety of donor atoms make Zn(II) particularly suited for insertion in protein scaffolds, where it supports functions ranging from structural stabilization to catalysis [1]. Structural Zn(II) sites typically stabilize protein folds through Cys- or His-rich tetrahedral coordination, whereas catalytic Zn(II) centers, commonly coordinated by His and Asp/Glu residues, directly participate in substrate activation, as in carboxypeptidases and carbonic anhydrases [1,2]. This versatility has inspired the design of artificial Zn-based metalloproteins, including α -helical coiled-coil systems that reproduce the tetrahedral Zn(II)His₃ active site of carbonic anhydrase [3-6].

In this work, a Zn(II)His₃-binding site was introduced into a *de novo* designed peptide-based scaffold. It consists of a heterodimeric three-helix bundle, made up of a single-helix interacting with a helix-loop-helix peptide. A Zn(II)His₃ coordination center was first modelled *in silico* (Figure 1). Molecular dynamics predicted a stable protein architecture and persistent Zn(II) coordination throughout the simulations. The designed peptides were synthesized by solid-phase peptide synthesis, purified by HPLC, and characterized by LC-MS. Circular dichroism and size-exclusion chromatography were used to investigate helical folding and oligomerization, while UV-vis and fluorescence spectroscopy revealed high-affinity binding of Co(II) and Zn(II) ions.

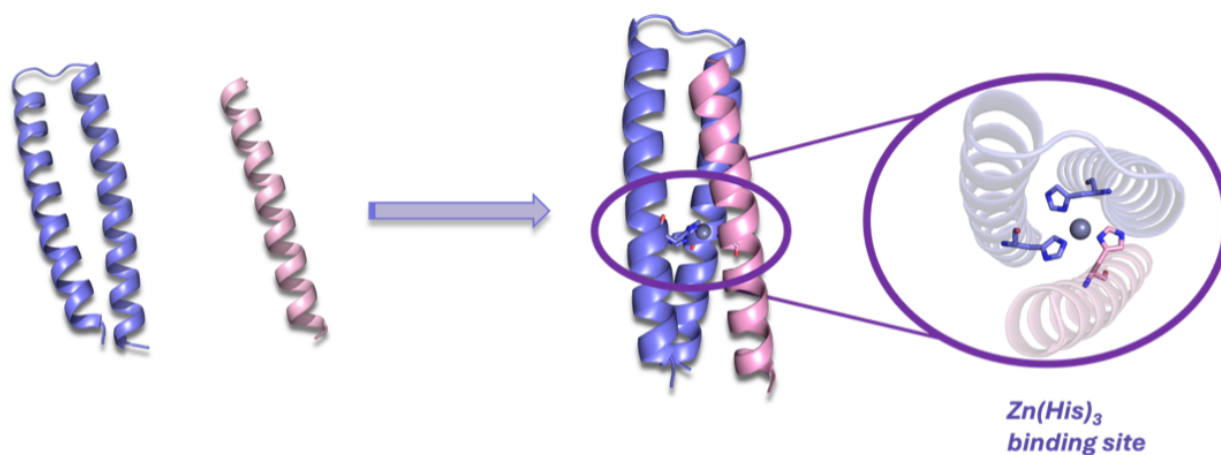


Figure 1: Schematic representation of the designed three helix bundle scaffold with focus on the Zn(II)His₃ binding site.

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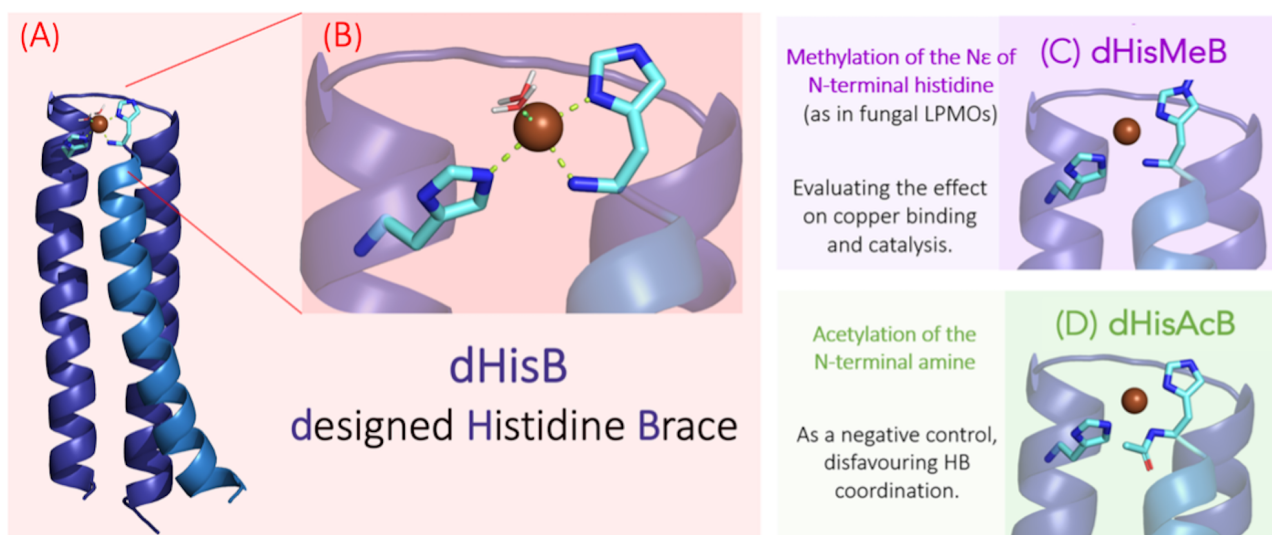
Artificial Type II copper proteins: a spectroscopic characterization

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Lytic polysaccharide monooxygenases (LPMOs) are type II copper enzymes that play a crucial role in the oxidative degradation of lignocellulose and chitin, making them attractive biocatalysts for sustainable biomass valorisation [1]. Their catalytic activity relies on a highly conserved copper-binding site, known as the Histidine Brace (HB), whose structural and mechanistic features are not yet fully understood [2]. Artificial models provide valuable tools to investigate these systems while enabling the rational tuning of structural and functional properties [3,4]. This work focuses on the spectroscopic characterization of three de novo designed peptide-based LPMO mimics: the heterodimeric *designed Histidine Brace* (dHisB) and two analogues, dHisMeB and dHisAcB. dHisB is composed of two peptide chains: a 62-residue peptide featuring a helix-loop-helix (HLH) motif containing an internal histidine residue (H26), and a 28-residue peptide consisting of a single α -helix and bearing an N-terminal histidine (H1) (Figure 1). The two analogues feature modifications at the N-terminal histidine of the H peptide: in dHisMeB, the imidazole N ϵ atom is methylated, whereas in dHisAcB the N-terminal amino group is acetylated to assess its role in copper coordination. The peptide complexes were chemically synthesized and characterized by spectroscopic methods. The results confirmed the formation of the designed peptide assemblies, preservation of the secondary structure, and successful copper coordination. Fluorescence studies provided insights into copper binding and quenching mechanisms.



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Oxidative biotransformation of lignin by a miniaturized heme-enzyme

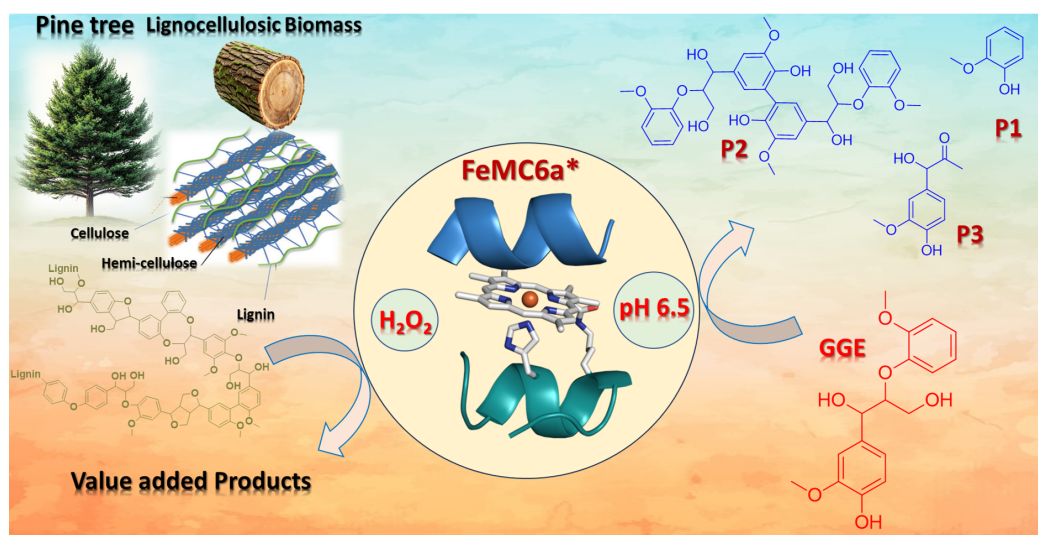
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Lignin is one of the most abundant renewable sources of aromatic carbon and a major by-product of the pulp and paper industry. However, its structural complexity and heterogeneity hinder its efficient conversion into value-added chemicals, making the development of mild and selective lignin depolymerization strategies a major challenge for sustainable biomass valorization [1]. Enzymatic approaches have emerged as attractive alternatives to conventional chemical methods owing to their selectivity and operation under mild conditions. Laccases and peroxidases are the most extensively investigated enzymes for the oxidative transformation of lignin and lignin-derived compounds [2]. Inspired by these enzymes, considerable efforts are being devoted to developing artificial enzymes capable of reproducing their reactivity within simpler molecular scaffolds [3].

Fe-MC6*a is a miniaturized artificial heme-enzyme, consisting of two short helices covalently linked to the deuteroporphyrin cofactor and folded into a helix-heme-helix architecture [4]. Despite its small size (~3 kDa), Fe-MC6*a exhibits remarkable peroxidase activity, providing a robust and tunable platform for oxidative catalysis [5]. Here, we investigated the Fe-MC6*a-catalyzed oxidation of guaiacylglycerol- β -guaiacyl ether (GGE), a model compound containing the β -O-4' linkage, the most abundant interunit bond in lignin. Kinetic experiments demonstrated the H₂O₂-dependent oxidation of GGE, MS analyses of the reaction mixture enabled the identification of products, and provided insights into the oxidative mechanism. Based on these results, the activity of Fe-MC6*a was further explored toward Kraft lignin as a substrate. Two-dimensional NMR analyses revealed significant structural modifications, demonstrating the ability of this artificial enzyme to promote oxidative lignin transformation under mild conditions.



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Ruthenium Hexamine-Mediated Paper-Based PNA Biosensor for Pancreatic Ductal Adenocarcinoma Diagnosis

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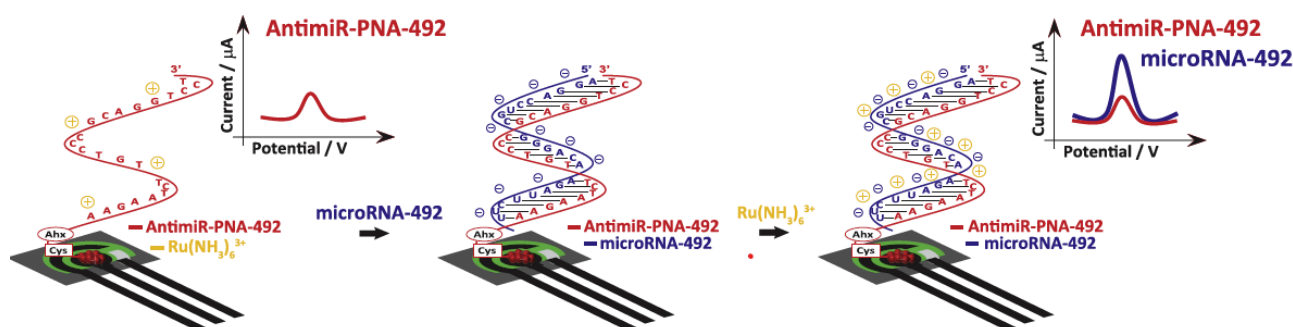
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Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies, characterized by poor prognosis and limited opportunities for early diagnosis [1]. Circulating microRNAs have emerged as promising non-invasive biomarkers for cancer detection [2], among which miRNA-492 has been associated with PDAC progression. In this work, we developed a paper-based electrochemical biosensor employing a peptide nucleic acid (PNA) probe for the selective detection of miRNA-492 [3]



The sensing platform was fabricated on wax-patterned office paper incorporating screen-printed electrodes modified with gold nanoparticles. A thiolated PNA probe complementary to miRNA-492 was immobilized onto the electrode surface. Detection was achieved through a signal-on strategy based on hexaammineruthenium(III) chloride (ruthenium hexamine), which acts as an electrochemical mediator. Following hybridization, the negatively charged PNA/miRNA duplex promotes the electrostatic accumulation of the positively charged ruthenium complex, generating an enhanced differential pulse voltammetric signal. The biosensor exhibited high affinity and specificity toward miRNA-492, as confirmed by PNA/RNA duplex characterization. Under optimized conditions, the platform showed a linear response in the nanomolar range and demonstrated excellent discrimination against mismatched and scrambled sequences. The analytical performance was successfully validated in undiluted serum samples, highlighting the robustness of the sensing strategy in complex biological matrices. The combination of a low-cost paper-based format, highly selective PNA recognition, and ruthenium hexamine-mediated signal amplification provides a promising approach for rapid and decentralized detection of PDAC-associated biomarkers, supporting future applications in liquid biopsy and point-of-care cancer diagnostics.

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