Together with Professors Markus Meuwly in Lausanne, Qiang Cui in Boston, and a Dutch coordinator, Professor Celia Fonseca-Guerra in Leiden, we propose to co-organize a Lorentz meeting which would focus on the modelling of Zn(II) and Ru(II) complexes.

Zn(II) is an essential co-factor of numerous Zn-metallo-enzymes, which play a prominent role in a diversity of cell growth and morphogenesis processes, but are responsible, when deregulated, for major diseases [L. Riccardi, V. Genna, M. De Vivo. 'Metal-Ligand Interactions in Drug Design'. Nature Rev. Chem., 2018, 2, 100]. Although there are many high-resolution structures available, there is nowadays a limited number of effective drugs [A. Y. Chen, R. N. Adamek, B. L. Dick, C. V. Credille, C. N. Morrison, S. M. Cohen. 'Targeting Metalloenzymes for Therapeutic Intervention'. Chem. Rev. 2019, 119, 1323].

We wish to bring together theoretical chemists, synthetic organic and inorganic chemists, biochemists and structural biologists. This could foster multi-disciplinary collaborations aiming at targeting some Zn-metallo-enzymes such as bacterial metallo-β-lactamases involved in the resistance of bacteria to antibiotics, histone deacetylase, histone decarboxylases, and matrix metalloproteinases. This would occur by a combination of diverse disciplines, including emerging accurate polarizable molecular dynamics potentials and semi-empirical DFT methods, structural biology, synthetic organic chemistry, and biochemistry.

There are emerging complexes of Ru(II) which could act as anti-cancer 'metallo-drugs' [Ang and Dyson, Eur. J. Inorg. Chem. 2006, 4003] and in photo-dynamics therapy [Mari et al., Chem. Sci. 2015, 6, 2660]. It would be very rewarding to bring together, in the context of a Lorentz meeting, quantum and computational chemists in the domains of time-dependent DFT and polarizable molecular dynamics, as well as photophysicists and organic chemists. This could enable to identify some privileged leads for the photosensitization of targets such as DNA and proteins such as kinases or superoxide dismutase.

This presentation is done in three parts. The first focuses on Zn(II) metalloproteins as targets for new drugs designed by joint experimental and computational approaches. The second focuses on Ru(II)-complexes as new-generation 'metallo-drugs' targeting DNA or proteins, and of potential chemotherapeutic interest. The third mentions the theoretical and experimental procedures resorted to. An organization schedule for the presentations is proposed at the end. The references given are from some of the contributors we intend to invite.

### 1. Zn(II) metalloproteins.

There are two essential Zn(II) metalloprotein targets: Zn-dependent metalloenzymes having a mono- or a binuclear Zn-catalytic site, and non-enzymatic Zn-proteins, such as retroviral Zn-fingers or steroid receptors.

**Zn-metalloenzymes.** The following list is not limitative. We would like to mention:

a) Zn-metallo-β-lactamases (MBL), responsible for the acquired resistance of bacteria to antibiotics which they cleave and inactivate. There are two strains responsible for nosocomial diseases in hospitals: New Delhi MBL and VIM-2 (Verona Integrated MBL), against which there are no inhibitors of sufficient affinity and selectivity to be used as drugs. High-resolution X-ray structures are available [1, 2]. Therefore this would be an ideal topic for a collaboration associating: a) synthetic organic chemists, b) structural biologists, and theoretical chemists from both c) quantum chemistry and d) force-field development. A paper reporting on the results of a novel Zn-binding motive, triazole thione (TZT), and its complexes with the binuclear Zn-binding sites of L1 and Vim2 strains was recently published by one of us, jointly with experimentalists [3], and efforts are underway on a series of TZT-containing VIM2 inhibitors. Promising new leads, which
could also lend themselves to joint experimental and computational studies, are in the class of boron-based compounds [4].
b) histone deacetylase (HDAC), a class of enzymes removing acetyl groups from an N-acetyl lysine amino acid on a histone, allowing the histones to wrap the DNA more tightly. Upregulated HDAC activity is observed in cancer and neurodegenerative disease. HDACs are among the most promising therapeutic targets for anti-cancer inhibitor design [5, 6].
c) histone demethylases, which remove a terminal methyl group from Lys or Arg residues in histones. As for HDAC, their overexpression is linked to cancer [7].
d) Zn-dependent metalloproteinas, which belong to several classes, denoted as MMP-1 to MMP-12. They are responsible for metastases, tumor cell invasion, auto-immune diseases, neuro-inflammation, arthritis. There are several high-resolution X-ray structures, but few, if at all, efficient inhibitors [8, 9].
e) Phosphomannose isomerase (PMI), responsible for microbial and parasitic diseases [10].

Non-enzymatic Zn-fingers.

Retroviral proteins. A prominent example is the the nucleocapsid of HIV-1 retrovirus, denoted as NCp7, which has two invariant Zn-fingers. These play an essential role in the chaperone activity of NCp7 on DNA [11]. Contrary to the HIV-1 protease, reverse transcriptase and integrase, NCp7 cannot evade treatment by mutations as these inactivate the virus. NCp7 is thus a target for anti-retroviral therapies [12, 13]. The Laboratoire de Chimie Theorique has an earlier contribution with the National Institute of Health in Bethesda [14], which we plan to reactivate, and an ongoing one with the Laboratoire de Pharmacologie Structurale in Paris [15] aiming at the design of novel inhibitors targeting a complex between NCp7 and DNA [11].

Steroid receptors. Steroid or nuclear hormone receptors constitute an important superfamily of transcription regulators [16]. Their DNA-binding domains consist of two zinc-nucleated modules and a C-terminal extension. Residues in the first zinc module determine the specificity of the DNA recognition and residues in the second zinc module are involved in dimerisation. They are involved in diverse functions, including control of embryonic development, cell differentiation and homeostasis.

When overexpressed, they lead to disease, and are thus also a target for drug design.

References.


### 2. Ru(II)-based metallodrugs.

Ru(II)-coordination complexes are an emerging class of 'metallo-drugs' [1] which can bind to protein targets such as kinases [2], as well as to DNA [3]. A notable difference with respect to the other major class of metallodrugs, namely Pt(II) complexes, is their photoactivable character under infra-red radiation. They could be used in non-invasive photodynamic therapy against cancer, owing to the longer penetration of IR radiation in the body. Several potential Ru(II) metallodrugs have been put forth, such as ruthenium arene, Ru(II)-polypyrrolid complexes, and some complexes with DNA or a kinase protein have been characterized [4-7]. Complexes of Ru(II) with nucleobases have lent themselves to QC studies [8]. It could be very rewarding to design derivatives with enhanced affinities and selectivity for their DNA or protein targets. This could be enabled by a synergistic use of polarizable molecular dynamics and the so-called 'QM/PMM' approach [9]. In this context, a core surrounding Ru(II) could be treated quantum mechanically, and the rest of the protein or DNA target, by classical polarizable molecular mechanics. The latter approach could be essential to study the photoactivation process under the effect of IR radiation, resorting to time-dependent DFT. The structures then used would be the lowest-energy poses resulting from polarizable molecular dynamics. The design of Ru(II)-based supramolecular complexes with photoactivable properties constitutes another important topic for joint experimental and theoretical approaches [10].

### References.


### 3. Computational procedures.

The main two procedures will be quantum chemistry: ab initio (QC), DFT and tight-binding DFT (DFT-TB), and polarizable molecular mechanics/dynamics (PMM/PMD). All four coorganizers have contributions in either field with applications to biological molecules [1-4].

QC is used to calibrate and validate PMM/PMD and to enable QM/MM studies. Regarding Zn-metalloenzymes, the latter approach could be used to simulate the mechanism of enzymatic cleavage. Regarding Ru(II) metallodrugs, they could be used to simulate the mechanism of light activation on radical-induced cleavage of the DNA or protein targets. PMD is benefiting from dramatic enhancements of the computational speed. These have resulted from massive parallelism, considerable speed-ups in the computation of the iterative polarization, and more efficient integrators. It should now be possible to use PMD in long-duration MD, enabling a more detailed exploration of the potential energy hypersurface of the ligand-macromolecule complexes.

### References.


**Organization.**

The five-day conference could be organized as follows.

**First day.** Morning session. Presentation by experimentalists of Zn-metalloenzymes (I). Afternoon session. Presentation by experimentalists of Ru(II) metallodrugs (I).

**Second day.** Morning session. Presentations of advances in PMM/PMD (I). Afternoon session. Presentation by experimentalists of Zn-metalloenzymes (II). Some 'flash' presentations.


**Fourth day.** Morning. Presentation by experimentalists of non-enzymatic Zn-metalloproteins. Afternoon. Presentation of advances in QC, DFT, DFT-TB, and PMM/PMD (I). Discussion in one or two groups.

**Fifth day.** Morning. Presentation of advances in PMM/PMD, and QC, DFT, and DFT-TB (II). Afternoon. Discussion in one or two groups.

**Requested fundings from CECAM-FR-MOSER: 3000 euros**
List of proposed participants.

1. Zn-metalloproteins.
Zn-metalloenzymes.

1. Christopher Schofield. Oxford University
http://schofield.chem.ox.ac.uk/antibiotics.aspx
MBL targeting

2. David W. Christianson. University of Pennsylvania
Histone Deacetylase Structure and Function

3. Seth Cohen. University of California at San Diego
http://cohenlab.ucsd.edu
Design, synthesis, and evaluation of inhibitors of metalloproteins.

4. Marco De Vivo. Laboratory of Molecular Modeling and Drug Discovery, Istituto
Italiano di Tecnologia, Genoa, Italy.
Ligand-metal interactions in biomolecules.

5. Jean-Francois Hernandez. Laboratoire des Biomolecules Max Mousseron,
Universite de Montpellier.
Ibmmpeptide.com/jean-francois-hernandez
Design and synthesis of MBL inhibitors

6. Vincent Dive, Centre d'Etudes Atomiques, Saclay
http://joliot.cea.fr/df/doc/joliot/Pages/Entites_de_recherche/medicaments_technologies
_sante/SIMOPRO/lcv.aspx
Zn-metalloprotease inhibition.

7-8. Maria Ramos, Sergio Sousa, University of Porto
https://www.fc.up.pt/pessoas/mjramos/index.html
https://biosim.pt/sergio-f-sousa/
Zn metallo-proteinase inhibition.

9. Laurent Salmon, University of Paris-Saclay
https://www.icmмо.u-psud.fr/fr/perso/laurent-salmon
Design, synthesis and tests of Zn-dependent metalloenzymes

10. Bogdan Iorga, Institut de Chimie des Substances Naturelles, Gif-sur-Yvette,
Design of inhibitors of Zn-MBL.
11. Lars Hemmingsen. University of Copenhagen
https://chem.ku.dk/ansatte/alle/?pure=en/persons/124560
Design of MBL inhibitors
12. Lars Olsen. Department of Drug Design and Pharmacology, University of
Copenhagen
Histone demethylase targeting.
http://strynadkalab.biochem.ubc.ca/research/antibiotic-resistance.php
X-ray structure of New-Delhi MBL.
14. Jean-Denis Docquier University of Sienna, Italy.
https://www.researchgate.net/profile/Jean_Denis_Docquier
X-ray structure of VIM-2 MBL.

Non-enzymatic Zn-metalloproteins.

15, 16. Ettore Appella, Lisa Miller Jenkins
National Institute of Health, Bethesda, Maryland.
https://irp.nih.gov/pi/ettore-appella

17. Yves Mely
Laboratoire de Bioimagerie et Pathologies, UMR CNRS 7213.

18. Serge Bouaziz
Cibles Thérapeutiques et Conception de Médicaments -CiTCoM UMR 8038 - CNRS
Université Paris Descartes

2. Ru(II)-based compounds.

Ru(II)-based photoactivating compounds.

https://lpc.univ-lorraine.fr/
Complexes of Ru(II) metallodrugs with DNA.

https://www.universiteitleiden.nl > staffmembers > sylvestre-bonnet
Light activation of Ru(II) metallodrug complexes with oligonucleotides.

Design of metallo-drugs.

24. Nils Metzler Nolte, University of Bochum.
https://www.ruhr-uni-bochum.de/zemos/nolte
Design of metallo-drugs.

Design of anti-cancer Ru(II) metallodrugs.

Ru(II)-based metallo-drugs.

http://Cce.caltech.edu/people/Jacqueline-k-barton.
Synthesis and characterization of DNA-binding probes.

28. Eli Zysman-Colman, University of St Andrews
Design of supra-molecular materials

3. Theoretical and computational chemistry.

29. Dennis R. Salahub, University of Calgary

30. Ursula Rothlisberger, Ecole Polytechnique Federale de Lausanne
https://www.epfl.ch/labs/lcb/c-roethlisberger/

31. Kenneth K. Merz, Michigan State University
http://www.merzgroup.org/

32. Jean-Philip Piquemal, Laboratoire de Chimie Theorique, Paris
http://piquemalresearch.com/

33. Sergei Noskov, University of Calgary.
http://contacts.ucalgary.ca/info/bio/profiles/124-2251

34. Jaroslav V. Burda, Charles University, Prague.
https://physics.mff.cuni.cz/kchfo/burda/

35. Todor Dudev, University of Sofia.
http://www.chem.uni-sofia.bg/otchem/LabCCS/group-members-tdudev.html

36. Pengyu Ren, University of Texas at Austin
https://cns.utexas.edu/directory/item/1577-ren-pengyu?Itemid=349

37. Michael Schnieders, University of Iowa
https://www.engineering.uiowa.edu/faculty-staff/michael-j-schnieders


39. Celia Fonseca-Guerra University of Leiden
http://www.few.vu.nl/~guerra/

40. Qiang Cui, University of Boston.
https://www.bu.edu/chemistry/faculty/cui/

41. Markus Meuwly, University of Basel
https://www.chemie1.unibas.ch/~meuwly/index.html

42. Nohad Gresh, Laboratoire de Chimie Theorique, Paris.
https://scholar.google.fr/citations?user=V4pAy7YAAAAJ&hl=fr
Bruno Chaudret.

Design of Ru(II)-based nanoparticles.

Organometallic Ruthenium Nanoparticles : Synthesis, Surface Chemistry, and Insights into Ligand Coordination
L. M. Martínez-Prieto, B. Chaudret
Theoretical characterization of the surface composition of ruthenium nanoparticles in equilibrium with syngas
Cusinato, Lucy ; Martinez-Prieto, Luis M. ; Chaudret, Bruno ; del Rosal, Iker ; Poteau, Romuald
Tuning the catalytic activity and selectivity of water-soluble bimetallic RuPt nanoparticles by modifying their surface metal distribution