Metals and Peptides: Case Studies

SYLLABUS

1 Lecturer information

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2 Title of the course

Metals and Peptides: Case Studies

3 Course program

Recent advances in peptide chemistry, biophysical characterization, and analytical methodologies have greatly expanded the use of peptides as therapeutic agents and molecular tools. Due to their ability to recognize extended protein surfaces with high affinity and selectivity, peptides represent an important class of compounds for the development of innovative therapeutic strategies and for the investigation of biologically relevant molecular interactions.

This course will present selected topics in contemporary peptide chemistry, integrating rational molecular design, synthetic methodologies, and structural characterization approaches. Particular attention will be devoted to the relationship between peptide structure, chemical reactivity, and biological function, highlighting how peptide-based systems can be exploited to address questions of medicinal, biological, and mechanistic relevance.

A major focus will be placed on the interactions between peptides and metal-containing compounds of pharmacological and toxicological interest. Case studies involving gold-, platinum-, and silver-based metallodrugs, as well as environmentally relevant toxic species such as methylmercury (CH_3Hg^+), will be discussed to illustrate the molecular determinants governing metal binding, selectivity, and biological activity.

The course will further examine the role of key redox-active proteins, including Thioredoxin Reductases and Glutathione Peroxidases, as molecular targets of metal species. These examples will

provide insight into the mechanisms underlying both the therapeutic action of metallodrugs and the toxicity of environmentally relevant metals.

Through the analysis of representative research studies, participants will gain an advanced understanding of peptide-based approaches for investigating metal-protein interactions and their implications for chemical biology, medicinal chemistry, and toxicology.

4 Course content detailed per lesson of two hours (possibly with dates and room real and virtual)

Lesson 1 – Fundamentals of peptide chemistry

- Introduction to peptides
- Peptide design, synthesis and optimization
- Illustrative research case studies based on my work

Lesson 2 – Peptide and metallic compounds interactions

- Coordination chemistry of biologically relevant metal ions.
- Molecular determinants of metal binding in peptides and proteins.
- Experimental approaches to investigate peptide-metal interactions.
- Examples of peptides as models for studying metallodrugs and toxic metals reactivity.

Lesson 3 – Role of selenoenzymes in the therapeutic and toxic activity of metals

- Introduction to selenoenzymes: Thioredoxin Reductases and Glutathione Peroxidases
- Molecular mechanisms of metal-induced enzyme modulation and inhibition.
- Therapeutic and toxicological implications.

5 Suggested reading

General Peptide Chemistry

1. Peptides: Chemistry and Biology
   Sewald, N.; Jakubke, H.-D. *Peptides: Chemistry and Biology*, 2nd ed.; Wiley-VCH, 2009.
2. Fmoc Solid Phase Peptide Synthesis: A Practical Approach
   Chan, W. C.; White, P. D. *Fmoc Solid Phase Peptide Synthesis: A Practical Approach*; Oxford University Press, 2000.

Peptides as Therapeutics

3. Peptide Therapeutics
   Fosgerau, K.; Hoffmann, T. "Peptide therapeutics: current status and future directions." *Drug Discovery Today* **20**(2015), 122–128.
4. Muttenthaler, M.; King, G. F.; Adams, D. J.; Alewood, P. F. "Trends in peptide drug discovery." *Nature Reviews Drug Discovery* **20** (2021), 309–325.

Metallodrugs and Metal–Protein Interactions

5. Bioinorganic Chemistry
   Casini, A.; Sun, R. W.-Y.; Ott, I. (selected reviews on gold-based drugs and metallodrugs).
6. Messori, L.; Merlino, A. "Protein metalation by metal-based drugs: molecular aspects and biological implications." (review articles).

Thioredoxin Reductase and Glutathione Peroxidase Systems

7. Thioredoxin System
   Arnér, E. S. J. "Focus on mammalian thioredoxin reductases." *Biochimica et Biophysica Acta* **1790** (2009), 495–526.
8. Glutathione Peroxidase Family
   Brigelius-Flohé, R.; Maiorino, M. "Glutathione peroxidases." *Biochimica et Biophysica Acta* **1830** (2013), 3289–3303.

Metal Toxicity

9. Methylmercury Toxicology
   Clarkson, T. W.; Magos, L.; Myers, G. J. "The toxicology of mercury—current exposures and clinical manifestations." *New England Journal of Medicine* **349** (2003), 1731–1737.

6 Learning Objectives

The course aims to provide doctoral students with an advanced understanding of contemporary peptide chemistry and its applications in medicinal chemistry, chemical biology, and toxicology. Particular emphasis will be placed on the rational design and synthesis of peptides, the analytical methods used for their characterization, and their use as molecular tools to investigate the interactions of proteins with metal-containing compounds of pharmacological and toxicological relevance. The course will also explore the molecular mechanisms underlying the biological activity of metallodrugs and toxic metals through selected case studies involving redox-active enzymes

7 Knowledge and Skills to be acquired

At the end of the course, students will be able to:

- Understand the principles governing peptide structure, function, and reactivity.
- Understand modern strategies for peptide design and chemical synthesis.
- Critically evaluate analytical techniques used for peptide characterization and metal-binding studies.
- Interpret experimental data related to peptide-metal and protein-metal interactions.
- Explain the molecular basis of the therapeutic activity of selected metallodrugs and the toxicity of environmentally relevant metals.

- Discuss the biological role of redox enzymes such as Thioredoxin Reductases and Glutathione Peroxidases in metal-mediated biological processes.
- Critically analyze and discuss scientific literature in the fields of peptide chemistry, bioinorganic chemistry, and chemical biology.
- Apply interdisciplinary concepts from organic chemistry, biochemistry, and bioinorganic chemistry to current research problems.

8 Prerequisites

Participants are expected to have a background in chemistry, biochemistry, pharmaceutical sciences, biotechnology, or related disciplines. Basic knowledge of:

- organic chemistry,
- biochemistry and protein structure,
- coordination chemistry and metal complexes,
- fundamental analytical techniques (e.g., chromatography, spectroscopy, mass spectrometry),

is recommended.

No prior experience in peptide synthesis is required, although familiarity with protein chemistry and chemical biology will facilitate the understanding of the course material.

9 Teaching Methods

□ MODE 1 - Pre-recorded lessons uploaded on the moodle platform (a meeting must be organized with PhD students in order to clarify eventual doubts)

X MODE 2 (preferred) - Lessons delivered in-person and in remote with simultaneous recording by the WEBEX platform

(The lessons must be recorded and available to all the students that cannot take part to the lessons in streaming. The Webex platform must be used. All course content should be uploaded to the Moodle platform on the Chemical Sciences PhD page "Courses and Seminars of the PhD in Chemical Sciences 2022-2023")

10 Type of Assessment

The final evaluations will have to be validated maximum 1 month after the end of the course.

11 Period

July 6th-10th 2026