8th International Meeting of the Institute of Metals in Biology of Grenoble

Metal Complexes in Biology: Imaging and Detection

Villard-de-Lans

Conference : September 24th-27th, 2019

Advanced Courses : September 22th-24th, 2019

Welcoming words from the IMBG President

Dear All,

It is with a great pleasure that I welcome you on the behalf of the Institute of the Metals in Biology of Grenoble to the 8th International IMBG conference. I hope that the meeting will be the platform to gather and disseminate the latest knowledge in the field of bioinorganic chemistry and in particular in the field of imaging and sensors. This domain is essential for the research in Health and innovations in this field are of great help for human well being. This activity is also at the crossroad of several scientific specialties, from chemistry to physics and biology, illustrating one again the asset of an interdisciplinary research for a real progress and impact in our society. This represents the major goal of the IMBG Institute.

I would like also to mention the holding of advances courses at the beginning of the meeting, that will help the senior scientists to actively share their knowledge and experience with the younger colleagues and students. This event will allow ample time to engage us in vivid discussions, that should inspire the students to pursue a scientific career themselves. This is another goal of the Institute.

Finally, congratulations to the organizing team for gathering such a high profile mix of international participants, that will help to promote this pressing research area.

My best wishes to you and great success for your presentations and discussions.

Stéphane Ménage

Organization and Partners

Chair

Jennifer Molloy

Scientific and Organizing Committee

Jennifer Molloy
Olivier Sénèque
Fabrice Thomas
Daniel Imbert

Local support

Catherine Belle
Nathalie Chaumery

Sponsors

Advanced Courses Program

Sunday, September 22

16:00 – 19:30 Arrival at Villard de Lans and registration

19:30 – 21:00 Dinner

Monday, September 23

8:00 – 10:00 AC1 – Olivier MAURY
Luminescence properties of d-and f-block metal complexes and their applications in biological imaging

10:00 – 10:30 Coffee break

10:00 – 12:00 AC2 – Eva JAKAB TOTH
MRI contrast agents : towards molecular imaging applications

12:00 – 14:00 Lunch

14:00 – 16:00 AC3 – Sylvain BOHIC
Synchrotron X-ray fluorescence microscopy from basics to sample preparation and experimental applications

16:00 – 16:30 Coffee break

16:30 – 18:30 AC4 – David PARKER
Multinuclear MR Spectral Imaging: A Critical Appraisal

19:30 – 21:00 Dinner

Tuesday, September 24

8:00 – 10:00 AC5 – Peter COMBA
Design, synthesis and evaluation of chelators for tumor imaging and therapy

10:00 – 10:30 Coffee break

10:00 – 12:00 AC6 – Christopher J. CHANG
Bringing Inorganic Chemistry to Life with Fluorescence Imaging

12:00 – 14:00 Lunch

Symposium Program

Tuesday, September 24

15:00 – 18:00 Arrival at Villard de Lans and registration

17:50 – 18:00 Opening

18:00 – 19:00 PL1 – Christopher J. CHANG
Activity-based sensing approaches to decipher metal and redox biology

19:00 – 20:00 Welcome reception sponsored by the town of Villard de Lans

20:00 – 21:30 Dinner

Wednesday, September 25

Session chair: Aline NONAT and Olivier SENEQUE

9:00 – 10:00 PL2 – Olivier MAURY
Lanthanide luminescent bioprobes: from two-photon microscopy imaging to dynamic phototherapy

10:00 – 10:20 OC1 – Elvin SALERNO
Synthesis and luminescence properties of a series of lanthanide(III) metallacrowns with an 8:1 antenna: emitter ratio

10:20 – 10:50 Coffee break

10:50 – 11:20 KL1 – Alexandre SIMIONOVICI
Metals"R"us: Metals for life in earth & planetary sciences

11:20 – 11:40 OC2 – Aurélien DENIAUD
Lessons from the combined use of synchrotron- and electron microscopy-based approaches for the analysis of silver nanoparticle fate in hepatocytes

11:40 – 12:00 OC3 – Vadde RAMU
Ruthenium(II) complex for the cell viability detection in tumour spheroids

12:00 – 13:30 Lunch

13:30 – 15:00 Poster session

Session chair: Christelle HUREAU and Jennifer MOLLOY

15:00 – 16:00 PL3 – Eva JAKAB TOTH
Metal-Based Responsive MR Probes

16:00 – 16:20 OC4 – Kyangwi Patrick MALIKIDOGO
Molecular imaging: New zinc finger peptides MRI probes for in vivo zinc detection

16:20 – 16:40 OC5 – Saida MAJDOUB
Metal-based probes for the visualization of Amylin, an amyloid peptide linked to diabetes

16:40 – 17:10 Coffee break

17:10 – 17:40 KL2 – Carlos GERALDES
Metal-based redox-responsive MRI contrast agents

17:40 – 18:00 OC6 – Xue-Quan ZHOU
Cell imaging of cyclometalated platinum complexes showing aggregation-induced emission based on platinum-platinum interaction

19:30 – 21:00 Dinner

Thursday, September 26

Session chair: Carlos GERALDES and Daniel IMBERT

9:00 – 10:00 PL4 – David PARKER
Very bright lanthanide probes and stains

10:00 – 10:20 OC7 – Emilie MATHIEU
Linking luminescence and redox properties of Yb-complexes

10:20 – 10:50 Coffee break

10:50 – 11:20 KL3 – Aline NONAT
Molecular up-conversion in water using Ln polymetallic assemblies

11:20 – 11:40 OC8 – Matthieu STARCK
Alternative labelling strategy using peptide and protein cysteine side chains and 4-nitropyridyl lanthanide complexes

11:40 – 12:00 OC9 – Ji-Hyung CHOI
Lanthanide-based bioprobes for zinc detection

12:00 – 13:30 Lunch

Session chair: Alexandre SIMIONOVICI and Fabrice THOMAS

13:30 – 14:30 PL5 – Sylvain BOHIC
Nanoscopic X-ray fluorescence imaging of cells with a high energy X-ray cryo nano-probe

14:30 – 14:50 OC10 – Laurence LEMELLE
Quasi-correlative nano-imaging of trace elements down to organelle levels in the brain

14:50 – 15:10 OC11 – Giulia VERONESI
In vivo biotransformation of fluorescent InP-based nanocrystals in a model organism

15:10 – 15:40 Coffee break

15:40 – 16:10 KL4 – Christelle HUREAU
Probes of amyloids' formation and amyloid fibrils

16:10 – 16:30 OC12 – Amandine ROUX
All-in-one lanthanide complexes for protein crystallography

16:30 – 16:50 OC13 – Patrick CIESLIK
Mn^{II} selective bispidine ligands for in-cell experiments

18:50 – 23:30 Banquet at *Auberge des Allières* (bus departure at 18:50)

Friday, September 27

Session chair: Jennifer MOLLOY and Olivier SENEQUE

9:00 – 10:00 PL6 – Peter COMBA
Bispidine coordination chemistry for tumor imaging and therapy

10:00 – 10:20 OC14 – Maryame SY
Bispidine-type ligands for Mn^{2+} complexation and their application to PET/MRI

10:20 – 10:50 Coffee break

10:50 – 11:10 OC15 – Pierre ADUMEAU
Evaluation of novel ^{89}Zr chelators and corresponding ^{89}Zr-labeled immunoconjugates

11:10 – 11:30 OC16 – Gwladys NIZOU
Tuning the design of Pyclen-based lanthanides(III) chelates from β-radiotherapy to theranostic probes

11:30 – 11:50 OC17 – Geneviève BLONDIN
In cellulo ^{57}Fe-Mössbauer spectroscopy

11:50 – 12:00 Conclusions

Activity-based sensing approaches to decipher metal and redox biology

Christopher J. Chang

[1] University of California, Berkeley, USA

Traditional strategies for developing chemoselective imaging reagents rely on molecular recognition and static lock-and-key binding to achieve high specificity. We are advancing an alternative approach to chemical probe design, termed activity-based sensing, in which we exploit inherent differences in chemical reactivity as a foundation for distinguishing between chemical analytes that are similar in shape and size within complex biological systems. This presentation will focus on activity-based sensing to visualize dynamic fluxes of transition metals and reactive oxygen, sulfur, and carbon species and their signal/stress contributions to living systems, along with activity-based proteomics to identify novel targets and pathways that these emerging classes of chemical signals regulate.

Lanthanide luminescent bioprobes: from two-photon microscopy imaging to dynamic phototherapy

Olivier Maury

Université de Lyon, ENS Lyon, CNRS, Université Lyon 1, Laboratoire de Chimie, UMR 5182, 46 allée d'Italie, 69364 Lyon, France

The sensitization of lanthanide luminescence by nonlinear two-photon (2P) absorption process allows a priori to combine the intrinsic advantages of rare earth spectroscopy (line shape emission with large Stokes shift, long lifetime) and those of biphotonic microscopy (NIR excitation, 3D resolution,…) for bio imaging purpose [1]. In this context we reported a family functionalized triazacyclononane ligands leading to the formation of ultra-bright Eu;, Tb, Yb, Dy, Sm and Yb(III) complexes featuring optimized 1P and 2P-brightness [2] We also developed original microscopy set-up enabling two-photon imaging in the NIR-to-NIR configuration, multiplexing experiments, and two-photon time resolved imaging [3]
Recent ongoing works are focused on the design of functional bioprobes enabling direct staining of living cells, bioconjugation, sensing and/or singlet oxygen generation applications [4].

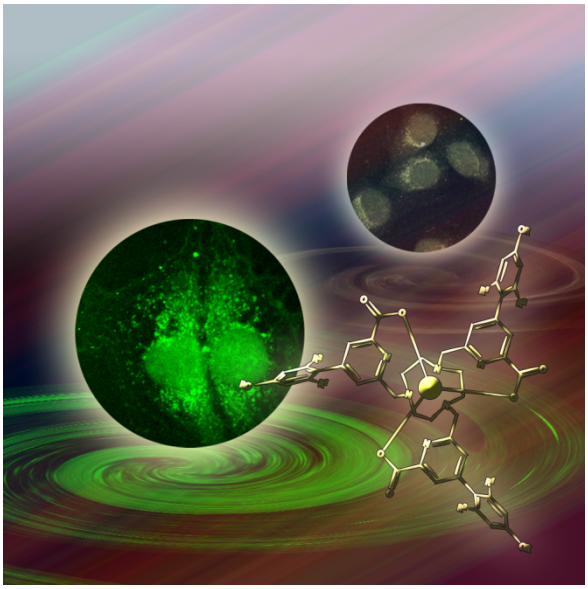

Figure 1 : Terbium complex and two-photon imaging of cells

[1] A. D'Aléo, C. Andraud, O Maury, in "Luminescence of Lanthanide Ions in Coordination Compounds and Nanomaterials" Ed. By A. De Bettencourt-Diaz, Wiley chapt.5 **2014**, 197-226.
[2] A. D'Aléo, A. Bourdolle, S. Brustlein, T. Fauquier, A. Grichine, A. Duperray, P.L. Baldeck, C. Andraud, S. Brasselet, O. Maury *Angew. Chem. Int. Ed.* **2012**, *51*, 6622; J. W. Walton, A. Bourdolle, S.J. Butler, M. Soulier, M. Delbianco, B.K. McMahon, R. Pal, H. Puschmann, J.M. Zwier, L. Lamarque, O. Maury, C. Andraud, D. Parker *Chem. Commun.* **2013**, *49*, 1600; A.-T. Bui, A. Grichine, S. Brasselet, A. Duperray, Chantal Andraud, O. Maury *Chem. Eur. J.* **2015**, *21*, 17757; A.-T. Bui, A. Roux, A. Grichine, A. Duperray, C. Andraud, O. Maury *Chem. Eur. J.* **2018**, *24*, 3408.
[3] V. Placide, A.-T. Bui, A. Grishine, A. Duperray, D. Pitrat, C. Andraud, O. Maury *Dalton Trans.* **2015**, *44*, 4918; A. Grichine, A. Haefele, S. Pascal, A. Duperray, R. Michel, C. Andraud, O. Maury *Chem. Science*, **2014**, *5*, 3475.
[4] A. T. Bui, M. Beyler, A. Grichine, A. Duperray, J.-C. Mulatier, C. Andraud, R. Tripier, S. Brasselet, O. Maury *Chem. Commun.* **2017**, *53*, 6005; M. Galland, T. Le Bahers, A. Banyasz, N. Lascoux, A. Duperray, A. Grichine, R. Tripier, Y. Guyot, M. Maynadier, C. Nguyen, M. Gary-Bobo, C. Andraud, C. Monnereau, O. Maury *Chem. Eur. J.* **2019**, 25, 9026.

Synthesis and luminescence properties of a series of lanthanide(III) metallacrowns with an 8:1 antenna: emitter ratio

Elvin Salerno[1], Svetlana Eliseeva[2], Stéphane Petoud[2] and Vincent Pecoraro[1]

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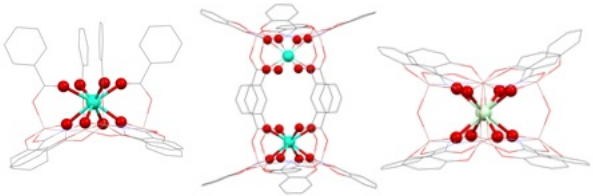
[2] Centre de Biophysique Moléculaire, CNRS UPR 4301, France

Metallacrowns are self-assembled metallamacrocyles containing a ring motif consisting of repeated metal-nitrogen-oxygen sequences, where the metal is an ion such as gallium(III) or zinc(II).(1) One class of metallacrowns (12-MC-4) are notable for their modularity with respect to ring ligand, ring metal and a centrally-bound, emissive lanthanide(III) ion (Ln(III)). Due to this modularity and inherent rigidity of the structure, they represent an attractive system to systematically study effects of the ligand's nature and structure on Ln(III) luminescence properties. The first mixed Ga(III)-Ln(III) metallacrown, LnGa4Shi4(Benzoate)4 [**1**] (Shi2- = salicylhydroximate), was shown to be highly emissive, especially for the near-infrared (NIR) emitting Yb(III) complex.(2) Characteristic emission of different Ln(III) throughout the visible and NIR ranges could be obtained in **1**. Subsequently, dimers of this structure type could be isolated using isophthalate rather than benzoate bridges, Ln2Ga8Shi8(Isophthalate)4 [**2**].(3) In this work, we now provide the simplest metallacrown dimer, LnGa8Shi8(OH)4 [**3**], which uses hydroxide ions as bridges between Ga(III) ions . This modification increases the number of Shi2- sensitizer ligands from four per Ln(III) in **2** to eight per Ln(III) in **3** and provides a much higher symmetry environment for the central Ln(III) atom. In addition, these materials have enhanced water solubility potentially making them more suitable for biological applications. Photophysical properties of a series of LnGa8Shi8(OH)4 with Ln(III) spanning Pr to Yb (excluding Pm) will be presented and discussed.



1 **2** **3**

[1] Mezei, G. *et al. Chem. Rev.* 107, 4933–5003 (2007).
[2] Chow, C. Y. *et al. J. Am. Chem. Soc.* 138, 5100–5109 (2016).
[3] Nguyen, T. N. *et al. Chem. Eur. J.* 24, 1031–1035 (2018).

Metals"R"us: Metals for life in earth & planetary sciences

Alexandre Simionovici[1], Laurence Lemelle[2], Vicente A. Solé[3], Rémi Tucoulou[3], Tom Schoonjans[4], Baptiste Suchéras-Marx[5] and Annachiara Bartolini[6]

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[2] Laboratoire de Géologie de Lyon – Terre, Planètes, Environnement – Ecole Normale Supérieure de Lyon – France
[3] European Synchrotron Radiation Facility, Grenoble – France
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Metals are pre-requisites for life, fingerprints of life and tracers of metabolic processes of biomineralization in living organisms. To study metals at macromolecular interaction scales requires state of the art analytical capabilities down to trace element levels and nanometer spatial resolutions. Fortunately, in the last decade, highly sensitive X-ray probes have been developed at worldwide 3rd generation synchrotron facilities. To date, a limited number of these highly specific nanoimaging probes have been deployed, and the ESRF ID16A/B and ID21 ones are among the leaders.

X-rays are non (*or least*) destructive, noninvasive, penetrative and highly sensitive probes of solid samples and metals are their ideal targets. X-ray fluorescence has reached few tens of nm resolutions and a world record for absolute mass of e.g. 50 zg for Fe, which can be recognized as only about 600 atoms.

Over the past decade, we have developed a multi-analyses methodology of nanoimaging mid-Z elements in low-Z matrices as a direct application to Life and/or Planetary Sciences of trace metals in biological matrices or in C/Si-based ones.

X-ray fluorescence and absorption spectroscopies, deployed at the few nanometer scales, are sensitive probes but they require a re-assessment of the analytical requirements previously established at the few micron levels [1]. We will present some specific analytical developments and methodologies optimized for such applications. They are centered onto absolute quantification of metals using both the Fundamental Parameter Approximation and reference materials, after spectral analysis using the PyMCA package [2] coupled to Monte-Carlo simulations of sample compositions [3] and geometries, pre-requisites for 2D/3D elemental imaging.

Examples based on metal detection were applied to either environmental key organisms such as foraminifers or coccolithofores [4, 5] but also to the oldest living organisms traced back to life's origins on Earth [1].

Finally, our search for life being also aimed at planetary and astronomical scales on exoplanets, we will present our patented methodology and sample holder [6] for Quarantine Extraterrestrial Sample Analyses (QESA) for the upcoming Returned Sample Missions from Mars and asteroids [7].

[1] L. Lemelle, A. Simionovici *et al.*, Trends Anal. Chem. 91, 104–111, 2017.
[2] Solé, V.A., Papillon, *et al.*, Spectrochim. Acta B, 62, 63-68, 2006.
[3] T. Schoonjans, L. Vincze, V.A. Sol_e, *et al.*, Spectrochim. Acta B 70, 10-23, 2012.
[4] L. Lemelle, A. Bartolini, A. Simionovici, *et al.*, Nature Comm., (in review) 2019.
[5] B. Suchéras-Marx, F. Giraud, A. Simionovici *et al.*, Geobiology 14, 390-403, 2016.
[6] A. Simionovici and CNES, European Patent Office # EP2411791A1, 2010.
[7] A. Simionovici, L Lemelle *et al.*, Proc. of the EAS Annual Meeting, EWASS, 2019

Lessons from the combined use of synchrotron- and electron microscopy-based approaches for the analysis of silver nanoparticle fate in hepatocytes

Giulia Veronesi[1], Vanessa Tardillo-Suarez[2], Benoit Gallet[3], Mireille Chevallet[1], Vikas Raj Sharma[1], Elizaveta Karepina[1], Rémi Tucoulou[2], Pierre-Henri Jouneau,[4] Isabelle Michaud-Soret[1] and Aurélien Deniaud[1]

[1] CEA – CNRS – Univ. Grenoble Alpes, Laboratoire de Chimie et Biologie des Métaux (LCBM) UMR 5249, Grenoble, France
[2] European Synchrotron Radiation Facility (ESRF), Grenoble, France
[3] Institut de Biologie Structurale – CEA-Grenoble, CNRS : UMR5075, Univ. Grenoble Alpes, France
[4] CEA – CNRS – Univ. Grenoble Alpes, Modélisation et Exploration des Matériaux (MEM), France

The widespread use of silver nanoparticles (AgNP) in consumer goods raises concerns about their toxicity to humans and their impact on environment[1]. AgNP toxicity in cells and animals has been extensively studied and it has been shown that Ag accumulates in liver following AgNP exposure[2]. At the molecular level it has been shown that the toxicity depends upon the release of Ag(I) ions from the NP[3,4]. However, the molecular processes enabling AgNP dissolution, the subcellular distribution of Ag(I) species, as well as their impact on hepatocyte metal homeostasis and the related functions are still poorly understood.

In this context, we studied AgNP internalization and fate into hepatocytes. We made use of a synchrotron nanoprobe to visualize the subcellular distribution of silver. The combined use of X-ray fluorescence (XRF) microscopy on whole cells and electron microscopy allowed the discrimination between the nanoparticle form located inside endosomes and lysosomes and the ionic species that distribute throughout the cell[5]. Besides, X-ray absorption spectroscopy showed that Ag(I) recombines with sulphur in hepatocytes in the form of AgS2 and AgS3 complexes[5,6].

In the last two years, we developed a correlative electron microscopy – XRF method performed on the same cell section to reveal the sub-cellular distribution of Ag(I) species under long-term AgNP exposure to non-toxic concentrations. We thus observed Ag(I) species in different organelles including in the nucleus[7]. This approach was also used on sections from 3D hepatic cell cultures that mimic liver architecture. XRF allowed following Ag species distribution in this physiologically relevant system. These data were corroborated thanks to 3D electron microscopy using a focused ion beam scanning electron microscope. In this talk, I will show the improvement we have done over the last years that enabled to break new grounds in the study of AgNP fate in eukaryote cells and I will highlight the interest of multimodal imaging.

[1] Chernousova S. and Epple M., *Angewandte Chemie,* 2013*,* **52**, 1636-1653.
[2] Van der Zande M., et al. *ACS Nano,* 2012*,* **6**, 7427-7442.
[3] Herzog F., et al. *Particle and Fibre Toxicology,* 2013*,* **10**, 1-14.
[4] De Matteis V., et al. *Nanomedecine: Nanotechnology, Biol and Med,* 2015*,* ***11***, 731-39.
[5] Veronesi, G. et al.*, Nanoscale,* 2016, **8**, 17012-21.
[6] Veronesi, G. et al.*, Inorg Chem,* 2015, **54**, 11688-96.
[7] Tardillo Suàrez V. et al., *Nanoscale,* in revision.

Ruthenium (II) complex for the cell viability detection in tumour spheroids

Vadde Ramu[1], Nataliia Beztsinna[1], Sylvia Le Dévédec[2], Corjan Van de Griend[1] and Sylvestre Bonnet[1]

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The importance of tumor spheroid imaging cannot be denied. Compared to 2D cell monolayers, 3D spheroids are able to more accurately simulate many features of in vivo human solid tumours, such as their spatial architecture, physiological responses, secretion of soluble mediators, gene expression patterns, and drug resistance mechanisms.1 Hence, it is desirable to use 3D tumour spheroid models for initial drug screening.2–4 However, in fluorescence imaging the problem of probe penetration in the core of a spheroid is significant. This is for example a problem for PI, one of the traditional dye used to image dead cells: it does not penetrate in the necrotic core of 3D spheroids. Here, we demonstrate that $[Ru(bpy)_2(dppz)]^{2+}$($[\mathbf{1}]^{2+}$), the famous "light-switch" metal complex, that can be used as a cell viability imaging agent in HepG2 (liver) and U87 (glioblastoma) 3D tumor spheroids. Imaging in 2D cell monolayers showed that $[\mathbf{1}]^{2+}$ stains nuclear DNA only when the cell membrane is compromised with cytotoxic agents like cisplatin or staurosporine. In 3D tumor spheroids with a diameter of 500 µM, $[\mathbf{1}]^{2+}$ penetrates the deeper layers of the spheroids and stain only the dead cells in the necrotic core. Live cell time lapse confocal imaging also shows that $[\mathbf{1}]^{2+}$ competes out the Hoechst dye used for localizing the nuclei. Overall, $[\mathbf{1}]^{2+}$ appears as an exquisite agent for mapping in real time cell death propagating through a 3D tumor spheroid, and this also in its core. Visualization of deep layers of cryo coupes proves that $[\mathbf{1}]^{2+}$ could stain necrotic cells at spheroid core unlike propidium iodide.

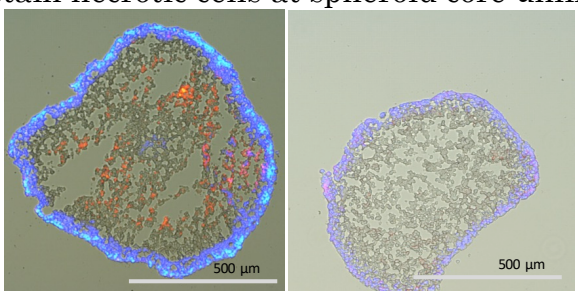

Figure 1 : The dead cells in necrotic core stained by 1 (left) and PI (right) in HepG2, spheroid's cryo coupes.

[1] Mittler, F. et al. High-Content Monitoring of Drug Effects in a 3D Spheroid Model. Front. Oncol. 7, (2017).
[2] Däster, S. et al. Induction of hypoxia and necrosis in multicellular tumor spheroids is associated with resistance to chemotherapy treatment. Oncotarget 8, 1725–1736 (2017).
[3] Riffle, S. & Hegde, R. S. Modeling tumor cell adaptations to hypoxia in multicellular tumor spheroids. J. Exp. Clin. Cancer Res. 36, 1–10 (2017).
[4] Lazzari, G. et al. Multicellular spheroid based on a triple co-culture: A novel 3D model to mimic pancreatic tumor complexity. Acta Biomater. 78, 296–307 (2018).
[5] Lim, W. & Park, S. A Microfluidic Spheroid Culture Device with a Concentration Gradient Generator for High-Throughput Screening of Drug Efficacy. Molecules 23, (2018).

Metal-Based Responsive MR Probes

Eva Jakab Toth

Centre de Biophysique Moléculaire, CNRS, Orléans, France

One important field in molecular imaging is the detection of physico-chemical parameters of tissues, concentration of ions, metabolites, etc. by smart, activatable probes. MRI is well adapted to the design of responsive probes, involving Gd^{3+}-based or PARACEST (Paramagnetic Chemical Exchange Saturation Transfer) agents. The MRI efficacy (relaxivity or CEST properties) of the probe has to be selectively influenced, based on coordination chemistry concepts, by the particular biomarker that we wish to detect. We develop potential smart contrast agents to detect cation or neurotransmitter concentration changes or to monitor enzyme activity.

Molecular imaging: New zinc finger peptides MRI probes for *in vivo* zinc detection

Kyangwi Patrick Malikidogo[1], Kate Lefroy[1], Agnès Pallier[2], William Même[2], Sandra Même[2], Bertrand Kuhnast[3], Célia Bonnet[2] and Olivier Sénèque[1]

[1] Laboratoire de Chimie et Biologie des Métaux (LCBM) – Univ. Grenoble Alpes, CEA, CNRS : UMR5249 – France
[2] Centre de Biophysique Moléculaire (CBM) – CNRS : UPR4301 – France
[3] Service Hospitalier Frédéric Joliot – CEA : DRF/JOLIOT – France

The last few years witnessed a remarkable development of Magnetic Resonance Imaging (MRI). Today, Molecular Imaging (MI) seems to be a revolution in the field of MRI. It is a new application that seeks information at the molecular level by visualizing the expression or function of bioactive molecules. Several physiological parameters can be interesting to detect by MRI, including pH, enzymes or ions. Any Molecular Imaging procedure requires an Imaging Probe (Responsive or Smart agent) that is specific for a given molecular event. The efficacy (relaxivity) of these agents is mainly influenced by the number of water molecules directly coordinated to the Gd^{3+}, q, and the rotational correlation time of the complex, τ_R; these parameters being the easiest to tailor by the chemist [1]. Zn^{2+} *in vivo* detection by non-invasive technique such as MRI remains of prime importance due to its implication in biological processes and diseases [2]. This would help researchers in the biomedical field to understand zinc biological role, and to provide earlier diagnosis for specific pathologies. Zn^{2+} detection by MRI led to the conception of new Gd3+-based contrast agents [3-5]. Here, we report several bioinspered Zinc-responsive contrast agents based on a Zinc Finger peptide $(Zn(His)_4$ site) conjugated to a Gd^{3+} complex (Scheme). They take advantage of a biological ligand already adapted to biological medium and show an increase of relaxivity in the presence of zinc. These Zn^{2+} sensitive MRI agents may prove useful for monitoring zinc in the case of diabetes.

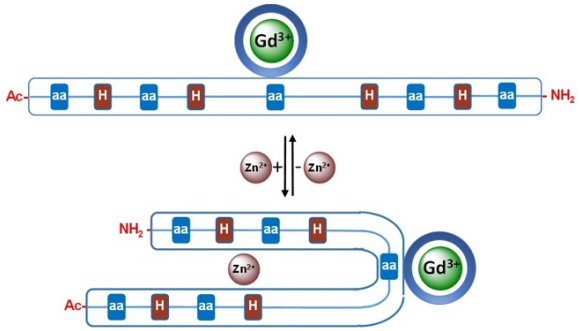

Figure 1 : Zinc responsive MRI probe based on a zinc finger peptide: change of conformation in the presence of zinc.

[1] 1. C. Bonnet et al. « Responsive Probes » In *The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging*, edited by André Merbach, Lothar Helm, and Éva Tóth, 343–85.
[2] G. J. Brewer et al., *Am. J. Alzheimers Dis. Other Demen.* **2010**, 25, 572; S. L. Kelleher et al., A*dv. Nutr.*, **2011**, 2, 101., S. A. Myers, *Int. J. Endocrinol.*, **2015**, 167503; L. De Leon-Rodriguez et at. *Inorg. Chem. Acta,* **2012**, 393, 12.
[3] J. W. Fredy et al. *Chem. Eur. J.*, **2014**, 20, 10959.
[4] A. C. Esqeuda et al. *J. Am. Chem. Soc.*, **2009**, 131, 11387, A. D. Sherry et al. *Proc. Natl. Acad. Sci. USA.,* 2011, 18400. J. Yu et al. *J. Am. Chem. Soc.*, **2015**, 137, 14173.
[5] M. Isaac et al. *Chem. Commun.*, **2018**, 54, 7350.

Metal-based probes for the visualization of Amylin, an amyloid peptide linked to diabetes

Saida Majdoub[1], Jean-François Morfin[1], Célia Bonnet[1] and Eva Jakab Toth[1]

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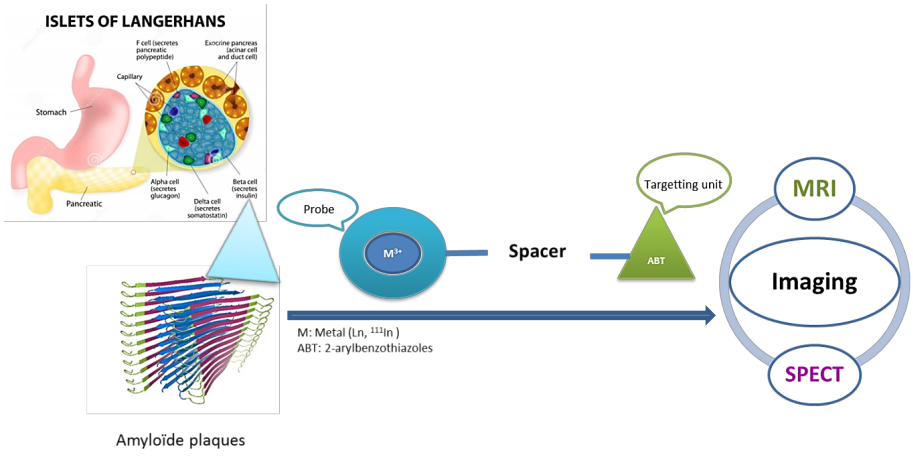
Diabetes is a major cause of death in the world. The number of affected people has reached 422 million worldwide and the insulin-resistant type (Type 2) represents 90% of them.
During the last decade, several positron emission tomography (PET) probes have been developed for the detection of amyloid peptides, mostly Aß aggregates (Aß1-40, Aß1-42), in the context of Alzheimer's disease. Only few probes have been developed for MRI detection of amyloid plaques[1-3], or for the detection of other types of amyloid peptides. In this work, we report new metal-based imaging probes for the visualization of amylin, an amyloid peptide related to diabetes. The probes contain one or two amyloid-targeting units (derivatives of PiB = Pittsburgh compound B[4]), a macrocyclic metal chelate as imaging reporter and a spacer between the two that modulates the lipophilicity of the molecule.
The affinities of our probes to amylin as well as to Aß were characterized by surface plasmon resonance measurements. The influence of the metal complexes on peptide aggregation was studied by circular dichroism and the critical micellar concentrations for these amphiphilic complexes were determined by relaxometry and/or UV-Visible spectrophotometry. We try to gain insight into the relationship between chemical structure and these parameters.



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Keynote Lecture 2

Metal-based redox-responsive MRI contrast agents

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Due to their potential for providing a better characterization and diagnosis of major pathologies like cancer or chronic inflammation, redox-activated Magnetic Resonance Imaging (MRI) probes have attracted much interest from chemists.[1,2] Such redox responsive probes are capable of reporting on specific biomarkers that are related to tissue redox potential disruption or hypoxia. Lately, this research area has experienced important developments, with the design of innovative redox-responsive metal complexes and nanoparticles. We will illustrate these developments with examples demonstrating the different molecular mechanisms that can generate a redox modulated MRI response.[3] These MRI probes are based on the redox activity of the ligand or, alternatively, the metal center, provided that the different oxidation states of the metal ion show different magnetic properties. Intracellular or extracellular redox buffer systems have been assessed by using MRI contrast agents based on lanthanide or transition metal ions using T_1-weighted, T_2-weighted, paraCEST or ^{19}F MRI, and some of those have reached animal model validation.

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Cell imaging of cyclometalated platinum complexes showing aggregation-induced emission based on platinum-platinum interaction

Xue-Quan Zhou

Leiden Institute of Chemistry, The Netherlands

Aggregation-Induced Emission (AIE) recently attracted many attentions for its viscosity-sensing properties and various applications in bioimaging. However, until now compounds showing AIE were found to be essentially based on restricted rotation of organic luminophores; they also always show low solubility in water. Here, we report on a new family of soluble cyclometalated platinum compounds that show AIE in cells via platinum-platinum interaction. Two isomers of these cyclometalated platinum complexes derived from tetrapyridine ligands were synthesized and observed by emission microscopy in cancer cells. These two water-soluble complexes showed strong Aggregation-Induced Emission properties via a combination of π-π* stacking and Pt-Pt interactions. Clearly, serum albumin infetal calf serum led to aggregation into ~200 nm hydrodynamic diameter nanoparticles, which passed through the cell membrane of A549 cancer cells via clathrin-mediated endocytosis. The aggregation of these complexes with intracellular proteins also stimulated Aggregation-Induced Emission inside cells. Confocal imaging demonstrated that these complexes showed emission between 650 nm and 750 nm in the cytoplasm, and outside the nuclei. DFT calculations indicated that the emissive properties of these two complexes were based on excitation of electrons located in a molecular orbital involving the platinum-platinum bond.

Very bright lanthanide probes and stains

Sergey Shuvaev, Laura Jennings, Robert Pal, Edward R. H. Walter and David Parker

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Bright lanthanide (III) complexes have been developed whose emission lifetime, relative intensity and circular polarisation respond to changes in local pH, pM and pX in competitive media, such as serum, as well as *in cellulo* in certain cases [1-3]. In each example, the recognition site is integrated into the structure of highly conjugated chromophores. Examples include systems seeking to signal either magnesium or zinc ions selectively. Circularly polarised luminescence (CPL) spectroscopy has been used to signal the reversible binding to a Eu complex of ADP in the presence of ATP by virtue of the very different CPL profiles (Figure 1) [4]. Binding of the terminal phosphate group to europium occurs in each case and is favoured by bridging to a proximate zinc-binding site. With ADP (and AMP), the helicity of the diastereoisomeric adduct is opposite to that observed with ATP, giving rise to their very different CPL signatures. A similar approach has allowed the monitoring of levels of the broad-spectrum herbicide glyphosate, both in river water and wheat/oat extracts [5].
Moreover, Eu and Tb(III) complexes featuring a bi-aryl chromophore have been shown to bind to the important acute phase protein, α_1-AGP, with an affinity in the micromolar range. A mixture of Eu and Tb complexes allows the ratiometric monitoring of [α_1-AGP] in serum. Intriguingly, the CPL profiles are of opposite sign for human and bovine variants of the protein, reflecting subtle differences in the chiral environment of their binding pockets. Competitive displacement of the lanthanide complex from the binding pocket by selected drugs, such as the anti-cancer agent 'Imatinib' or the common anaesthetics bupivacaine or lidocaine, has permitted the monitoring of drug binding to the protein, by following changes in the induced CPL signal as a function of drug concentration [6].

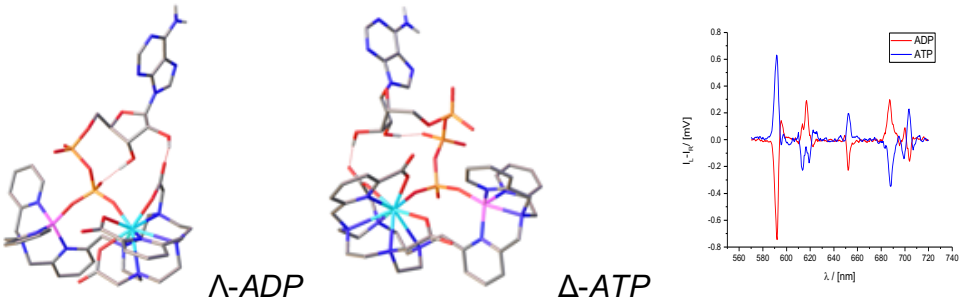

Figure 1 : Favoured structures of diastereoisomeric adducts of ADP and ATP with Eu CPL signatures.

We thank EPSRC, the Royal Society and Durham University for support.

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Linking luminescence and redox properties of Yb-complexes

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Among the lanthanides, Yb show the particularity to display luminescence emission even when there is a poor spectral overlap between the light-harvesting antenna and the low lying Yb(III) excited state. The sensitization occurs through electron transfer from the excited antenna to the Yb(III) leading temporarily to the formation of $Ant^{+\cdot}$-Ln(II) species. It is followed by a back electron transfer that can yield an excited state Yb(III) species, and thus sensitize luminescence emission. This process is dependent on the reductive power of the antenna in its excited state, and on the reduction potential of the Yb(III) ion.
In this work, a series of Yb(III)-complexes based on a cyclen scaffold were designed and synthesized. The pendant arms were substituted with either carboxylate or amide groups in order to modulate the reduction potential of the metal centre. The redox properties of the complexes, as well as their luminescent properties were investigated. Changes of the ligand-based and metal-based emissions were observed, that correlated with the tuned reduction potential of Yb(II)/Yb(III). Control of the reduction potential of the metal centre could thus modulate Yb emission. This strategy represents an alternative to altering the light-harvesting antenna.

Keynote Lecture 3

Molecular up-conversion in water using Ln polymetallic assemblies

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Based on the conversion of low energy photons in the near-infrared to visible photons, upconversion (UC) is very appealing for molecular imaging and theranostic applications. In particular, Yb-based probes absorbing in the biological transparency window at 980 nm offer an excellent signal-to-noise ratio. Although this phenomenon is usually observed in solid state materials and nanomaterials, UC is also possible with molecular systems by using lanthanide coordination complexes (*Nature Commun*. **2016**, *7* :11978; *J. Am. Chem. Soc*. **2017**, *139*, 4, 1456). A third series of polynuclear assemblies based on TACN-based ligands with pyridinephosphonate units will be presented. The directed synthesis of heteronuclear $[(YbL)_2Tb_x]$ (x=1,2) assemblies resulted in the first observation of upconversion at the molecular level in water and at room temperature (*J. Am. Chem. Soc*., **2019**, *141*, 4, 1568).

Alternative labelling strategy using peptide and protein cysteine side chains and 4-nitropyridyl lanthanide complexes

Matthieu Starck[1], Jack D. Fradgley[1], Stefania Di Vita[1], Robert Pal[1], Amandine Roux[1], Jackie Mosely[1], Anokhi Shah[2], Janet Lovett[2] and David Parker[1]

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[2] University of St. Andrews – United Kingdom

Lanthanides complexes have been widely used for various applications in biological science owing to their unique properties. In certain cases, labelling of a particular biomolecule is necessary and remains an issue when conjugation should not involve amide bond formation either with the amine or carboxylic acid groups of the biomolecules or at the C-Ter or N-Ter positions.

Here, we propose an alternative labelling strategy, orthogonal with amine and carboxylic acid labelling, and selective to the cysteine side chain, using a 4-nitro pyridine moiety under mild conditions. Two examples of complex conjugation designed for specific applications are presented, including a gadolinium(III) EPR label for selective bioconjugation and a europium(III) complex for targeted live cell imaging.

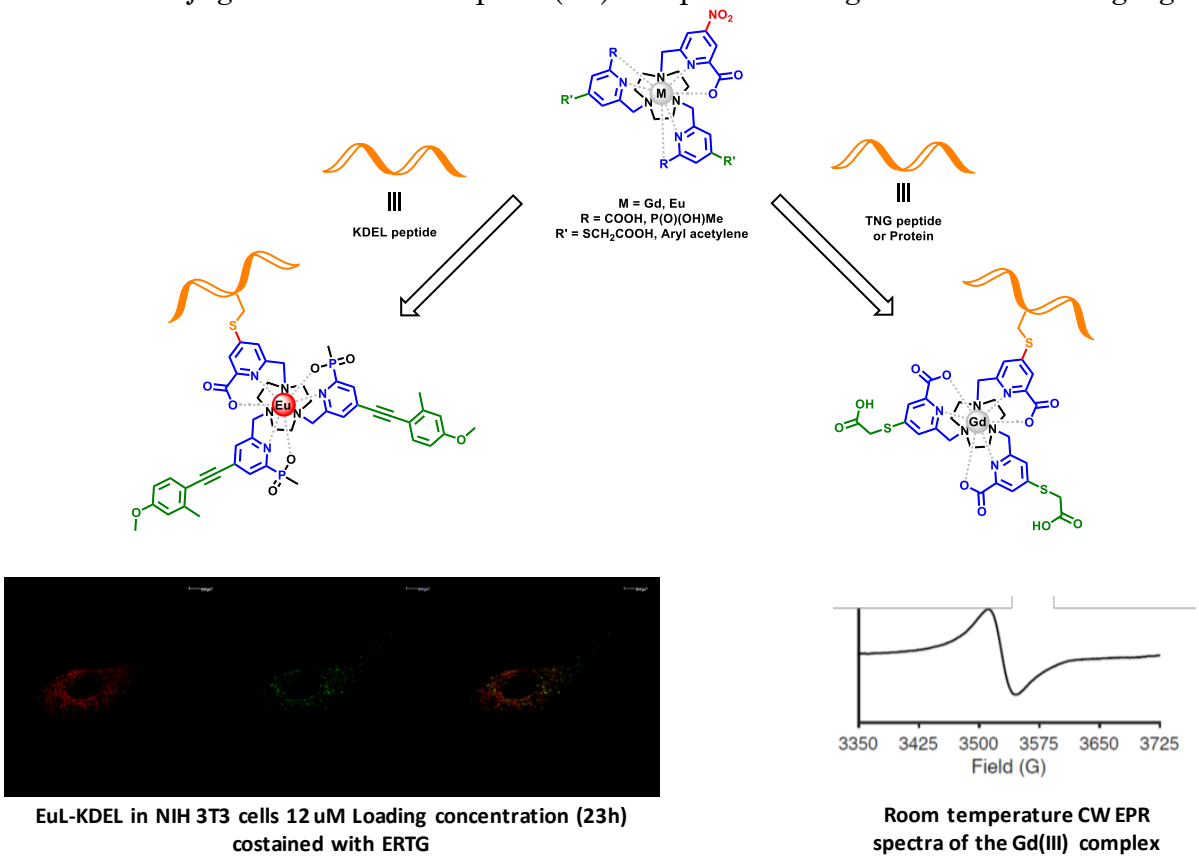

Figure 1 : Two examples of complex conjugation, a gadolinium(III) EPR label for selective bioconjugation and a europium(III) complex for targeted live cell imaging

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Lanthanide-based bioprobes for zinc detection

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Better understanding of cellular processes requires probes targeting specific molecules and specific organelles. For living cells application, they must be conscientiously designed: they should cross the lipid membrane, avoid degradation, not interfere with cellular homeostasis and also be robust to concentration variation, pH, photobleaching, etc. As for lanthanide-based bioprobes, they offer several advantageous properties for imaging in biological media as opposed to low molecular-weight organic dyes. Indeed, lanthanide's long luminescence lifetime allows time-resolved detection to reduce background noise. Emission wavelengths bands are sharp and specific to each lanthanide allowing multiplexed detection or ratiometric probe design, for instance. However, they still need to cope with cellular application constraints mentioned above.

We aim to use luminescent lanthanide complexes conjugated to a peptidic recognition unit with a cell penetrating peptide domain in order to detect biomolecules by fluorescence microscopy in living cells. Here we will present different probes that are responsive to zinc. Zinc is a good target for cellular imaging, as zinc is known to be essential and ubiquitous in our body but there is still a lot to understand about zinc regulation and zinc-related diseases.

We will describe our strategies for the synthesis of conjugatable lanthanide complexes and the spectroscopic properties of several probes synthesized in our laboratory.

Nanoscopic X-ray fluorescence imaging of cells with a high energy X-ray cryo nano-probe

Sylvain Bohic[1,2], Alexandra Pacureanu[1], Yang Yang[1], Murielle Salomé[1], Julio Cesar da Silva[1], François Villar[1], Lionel André[1], Peter Van Der Linden[1], Peter Cloetens[1]

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Several essential metal ions participate in the control of numerous metabolic and signaling pathways, but their rich coordination chemistry and redox properties confer them a propensity to randomly coordinate and catalytically react inside the cell with protein sites other than those tailored for that purpose. Investigating metal homeostasis and its dysfunctions is crucial to better understand the cell functions and the influence on cellular pathology [1]. The associated challenge to analytical chemistry techniques, consists in locating and quantifying these elements, mostly present at trace level, within the highly complex intracellular landscape. As such, cutting-edge technique providing quantitative imaging for detailed study of elemental homeostasis or the intracellular distribution of metal-based drugs at biologically relevant concentration in a label-free fashion is highly desirable. The synchrotron X-ray fluorescence (XRF) nanoprobe as developed today provide the required sensitivity and spatial resolution to elucidating the 2D and 3D distribution, concentration of elements particularly metals inside entire cells at the organelle level. The new state-of-the-art Nano-Imaging beamline ID16A-NI at ESRF offers unique capabilities for X-ray imaging at nanometer scale delivering an extremely bright, nanofocused beam ($> 5\times10^{11}$ph/s at $\Delta\lambda/\lambda\sim10^{-2}$) at high energies (~30nm at 17kev [2]. X-ray tomography techniques offer the potential to image and quantify 'thick' cells and tissues in 3D without excessive sample preparation [3,4]. Recently, we reported the use of correlative synchrotron X-ray holographic and X-ray fluorescence nanotomography to quantify elemental 3D distribution within fixed or freeze-dried single cells [5] but also on frozen-hydrated cells. We will illustrate the capabilities of this techniques to provide quantitative nanoscopic cryo-XRF of cell as diverse as cancer cells exposed to organometallic drugs, neurons or human cells exposed to metal-based nanowires.

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Quasi-correlative nano-imaging of trace elements down to organelle levels in the brain

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[d] Brain Mind Institute – EPFL – Switzerland
[e] ID16A – ESRF – France

Parkinson's disease (PD) is an age-dependent neurodegenerative disorder mainly characterized by the loss of dopaminergic neurons in the *substantia nigra*, a brain structure involved in the control of voluntary movements. Accumulation and misfolding of the α-synuclein protein is considered a key step in the disease process. Furthermore, perturbations of the mitochondrial and lysosomal functions [1] and increased levels of iron [2] are critically implicated in the accelerated demise of nigral dopaminergic neurons in PD.

Synchrotron Radiation X-ray Fluorescence (SR-XRF) imaging techniques are currently being developed to estimate the metal levels and/or their intracellular distribution at the nanometer scale in individual cultured neurons [3,4]. Up to now, such quantification inside brain tissues down to organelle levels seemed elusive. Here we overcome this challenge by a correlative microscopy approach exploiting the unique elemental sensitivity of the synchrotron X-ray fluorescence nanoprobe and the ultrastructural strengths of transmission electron microscopy.

Dopaminergic neurons in the *substantia nigra* were explored in a rat model of Parkinson's disease based on the over-expression of the alpha-synuclein pathogenic protein. We used SR-XRF excited by the hard X-ray nanobeams of the ID16A beamline (ESRF) to quantify the content and distribution of native trace elements in thin sections. Trace element contents were quantified in sub-cellular compartments (nucleus, nucleoli, specific organelles in the cytoplasm) and revealed local pathological shifts in the levels of iron and sulphur.

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In vivo biotransformation of fluorescent InP-based nanocrystals in a model organism

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Due to their size-tunable and bright photoluminescence in the UV/VIS range, semiconductor nanocrystals, i.e. Quantum Dots (QDs), are promising fluorescent probes for bioimaging and FRET-based biosensing *in vivo* [1]. InP QDs recently emerged as the best candidates for biomedical applications, being less toxic and more stable than Cd-based QDs, considered in a first time [2]. Therefore, prior to any medical application, the biocompatibility and the stability of InP QDs *in vivo* must be thoroughly assessed.
We investigated the biodistribution and transformations of two different InP QDs formulations, InPZnS core and InPZnS/ZnSe/ZnS core-shell QD, in a model animal system, the invertebrate *Hydra vulgaris*. The polyps were exposed to sub-toxic doses of QDs that do not alter morphology nor reproduction [3]. Although the QDs show no measurable optical activity after 3 h in the animal, synchrotron micro-beam X-Ray Fluorescence (μXRF) imaging detected the presence of Indium in several compartments of Hydra transversal sections. Micro-beam X-ray Absorption Spectroscopy (μXAS) revealed the absence of InP species after 3 h *in vivo*, but rather the presence of In-O bonds, indicating a degradation of the QD material. This shows that the unexpectedly quick loss of optical properties is not due to clearance but to the transformation into optically-inactive indium species in the animal. Surprisingly, *in vitro* assays showed no degradation of the QDs, even after 24 h at pH 4.5. This highlights the importance of *in vivo* models to assess the biotransformation of metal-based probes for biomedical applications.
All synchrotron analysis were carried out on the beamline ID21 of the ESRF [4], on sections of the animals in the frozen hydrated state, in order to preserve the ionic content and elemental speciation. Our work demonstrates that *Hydra vulgaris* is an ideal model to assess the stability of nanomaterials *in vivo*, yet reducing vertebrate experimentation. Synchrotron μXRF imaging and μXAS proved to provide unique information about the fate of photoluminescent metallic nanocrystals *in vivo*, especially in case of loss of the optical properties, and can help design biocompatible fluorescent probes.

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Keynote Lecture 4

Probes of amyloids' formation and amyloid fibrils

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Developing molecular probes of amyloids formation and amyloid-containing species is important for the better understanding and diagnosis of amyloid-related pathologies, such as Alzheimer's Disease (AD) where the amyloid-ß peptide (Aß) is involved. During the presentation, several strategies and tools currently developed in the group will be shown to illustrate this research field. This includes (i) $Re(CO)_3$-like and Gd(dota)-like complexes where a recognition unit based on a 2-aryl-benzothiazole (ABT) derivative has been appended to the metallic centre for an enhanced interaction with amyloid fibrils ; (ii) Ln-based complexes and all-inorganic polyoxometallates complexes that interfere with the native aggregation process leading to amyloid fibrils.

Acknowledgements: ERC StG-638712 and ANR-DIVA are acknowledged for financial support. All our external collaborators (Amandine Roux-Gossart, François Riobé, Olivier Maury (LYON), Eva Töth, Saida Madjoub, Jean-François Morfin, Célia Bonnet (ORLEANS), Sébastien Blanchard (PARIS), Eric Benoist (TOULOUSE)) who provide us with some of the studies compounds are warmly acknowledged.

All-in-one lanthanide complexes for protein crystallography

Amandine Roux[1], Zaynab Alsalman[2], François Riobe[1], Sylvain Engilberge[2], Elise Dumont[1], Eric Girard[2] and Olivier Maury[1]

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Proteins are essential components of biological processes and so are involved in the development of diseases. Nowadays, solving the structure of these biomolecules is a crucial point because their 3D structure is tightly linked to their biological functions and consequently to their role in the disease. Protein structures are in majority obtained by biocrystallography, a field in rapid expansion, and thousands of structures have been determined thanks to this method.
We are currently developing new lanthanide complexes as useful auxiliary for protein structure determination, possessing a triple function. It works as a nucleant agent, as a phasing tool and as a detector of protein crystals. The first complex, Tb-Xo4, based on a triazacyclononane macrocycle substituted with two picolinate antennae, has shown excellent results with soluble proteins and a dozens of protein structures have already been solved in presence of this complex (Figure 1) [1,2,3].
Here, we will present recent development of the Xo4 family in order to enlarge the conditions of protein crystallizations. For that purpose, the structure of the complex is modified in order to tune the charge, the polarity and the stability of the molecule (insertion of new functions or change on the nature of the metal ion). Physico-chemical and theoretical studies have been carried out in order to understand the protein-TbXo4 interactions and consequently the crystallization process.

Figure 1: Structure of Tb-Xo4 (left), crystals of Pb6 protein with Tb-Xo4 (middle) and interaction in the solid state (left)

Figure 1 : Structure of Tb-Xo4 (left), crystals of Pb6 protein with Tb-Xo4 (middle) and interaction in the solid state (right)

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Mn^{II} selective bispidine ligands for in-cell experiments

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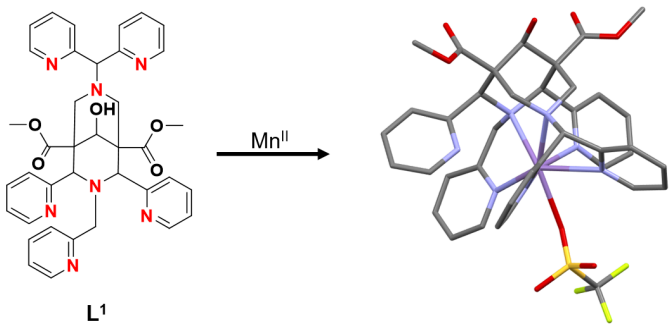
Manganese is an essential metal in all forms of life, e.g., in the oxygen evolving complex in photosynthesis and as a superoxide dismutase enzyme. Manganese is also a versatile tool for biological studies, e.g., for in-cell structure determination using paramagnetic NMR [1-3], and optical probes have been used for the localization of Mn^{II} in cells [4,5]. However, in-cell experiments with Mn^{II} are difficult because Mn^{II} selective ligands – especially in presence of Zn^{II} – are extremely challenging since, according to the Irving-Williams series, Mn^{II} always has a lower stability than all other divalent first transition metal row ions.

We present a new pyridine-based heptadentate bispidin ligand (**L**[1]) with high Mn^{II} complex stability and relatively slow ligand exchange rates. The Mn^{II} and Zn^{II} stability constants of **L**[1] ($\log K_{Mn(II)} = 25.13$; $\log K_{Zn(II)} = 9.15$), determined by potentiometric titration, show a high selectivity towards Mn^{II} over Zn^{II}, and the approx. decomplexation rate of $k = 10^{-25}$ indicates that the complex is relatively inert under physiological conditions. Also discussed are the design principles of this ligand and derivatives as well as possible applications.



L[1]

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Bispidine coordination chemistry for tumor imaging and therapy

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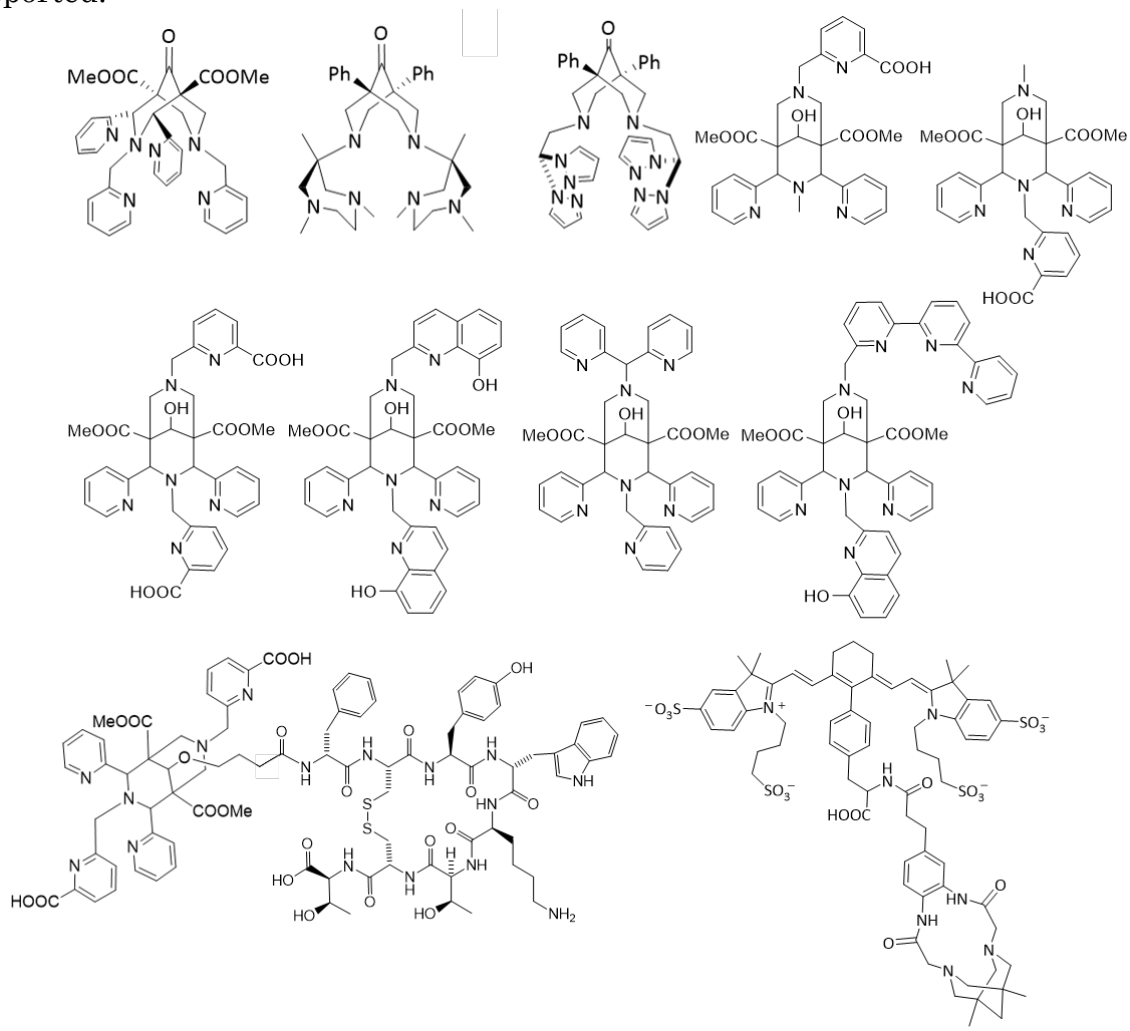
The development of multi-functional ligands for imaging (SPECT, PET, MRI, OI) is a fast developing field. Important requirements for promising ligands are relatively fast and efficient complexation, high complex stability and slow transmetallation with specific metal ions as well as molecules that are easy to couple to biological vectors or nanoparticles. The very rigid 3,7-diazabicyclo[3.3.1]-nonane (bispidine) scaffold leads to ligands with relatively fast formation kinetics and metal ion selectivities that are tunable via the wide variability in terms of donor groups and denticity as well as straightforward backbone functionalization, and makes these ligands an ideal platform for multimodal imaging. General aspects as well as bispidine derivatives for radiopharmaceutical applications with Cu^{II} and various lanthanides, actinides and main group metal ions, their functionalization as well as the related coordination chemistry, biodistribution studies and applications in tumor imaging and therapy will be reported.



Bispidine-type ligands for Mn^{2+} complexation and their application to PET/MRI

Maryame Sy[1], Aline Nonat[1], Daouda Ndiaye[2], Sara Lacerda[2], Eva Jakab Toth[2] and Loïc Charbonnière[1]

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Bispidine-type ligands are preoganized for metal complexation. They form highly stable complexes with radiometals of interest like $^{64}Cu(II)$ [1], $^{111}In(III)$ [2,3], $^{225}Ac(III)$ [2] and $^{177}Lu(III)$ [3], which allows to consider the development of bispidine-based radiopharmaceuticals. Our study will focus on bispidine-Mn complexes. Indeed, Mn^{2+} with its isotope ^{52}Mn (t1/2 = 5.5 d), a positron emitting nuclide, is the unique metal ion able to offer detection capability in both MRI and PET modalities and as consequence, bimodal PET/MRI imaging with a single complex. However, the development of stable and kinetically inert Mn-complexes remains a challenge. Here we show the synthesis of bispidine-Mn complexes which showed relaxivity close to Gd-based contrasting agent (> 4 $mM^{-1}. s^{-1}$ at 60 MHz, 25 °C) due to one inner sphere H_2O. These bispidine complexes were also bioconjugated with an RGD-peptide and the radiolabelling with ^{52}Mn is in progress.

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Evaluation of novel ^{89}Zr chelators and corresponding ^{89}Zr-labeled immunoconjugates

Pierre Adumeau[1], René Raavé[2], Chrstian Borch Jacobsen[3], Gerwin Sandker[2], Sandra Heskamp[2], Otto Boerman[2], Mark Rijpkema[2], Floriane Mangin[1], Michel Meyer[1], Jean-Claude Chambron[1], Mathieu Moreau[1], Claire Bernhard[1], Adrien Dubois[1], Laurène Da Costa[1], Victor Goncalves[1] and Franck Denat[1]

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For immunoPET imaging with ^{89}Zr, the current gold standard to label antibodies is desferrioxamine (DFO). However, preclinical studies have shown that the ^{89}Zr-DFO complex is partly unstable in vivo, leading to ^{89}Zr release and subsequent accumulation in mineral bone. This bone uptake may impede the detection of bone metastases, and hampers accurate estimation of the radiation dose to the bone marrow in dose planning for radioimmunotherapy. Therefore, there is a need for more stable ^{89}Zr chelators.

We have synthesized new octacoordinating ^{89}Zr-bifunctional chelating agents derivated from the DFO* chelator. The model antibody trastuzumab was conjugated to the NCS-derivated chelators and DFO-pPhe-NCS as a reference, and radiolabeled with ^{89}Zr. The stability of the radiolabeled chelators and radiolabeled conjugates were evaluated in human plasma, and in PBS in presence of EDTA or DFO. The *in vitro* behavior of the most promising compounds was investigated more thoroughly using HER2-experessing SK-OV3 cells, and *in vivo* distribution was studied in mice with subcutaneous SK-OV3 xenografts by PET imaging and *ex vivo* tissue analysis.

The bifunctional chelators were conjugated efficiently to trastuzumab. Radiolabeling of the conjugates with ^{89}Zr yielded the radioconjugates with high yield, purity and specific activity. When challenged with EDTA or DFO, the ^{89}Zr-chelates and the corresponding radioconjugates displayed an improved stability compared to ^{89}Zr-DFO and ^{89}Zr-DFO-trastuzumab, with the best results obtained for the chelator dubbed DFOcyclo*. The immunoreactive fraction and IC50 were similar for ^{89}Zr-DFO-trastuzumab and ^{89}Zr-cycloDFO*-trastuzumab. Internalisation after 2h was significantly higher for ^{89}Zr-cycloDFO*-trastuzumab compared to 8^{9}Zr-DFO-trastuzumab. Accumulation of ^{89}Zr in bone was significantly lower for ^{89}Zr-DFOcyclo*-trastuzumab compared to ^{89}Zr-DFO-trastuzumab in knee (3.6 ± 0.4% vs 5.9 ±0.6%), femur (2.2 ± 0.2% vs 3.4 ± 0.3%), and sternum (3.5± 0.4% vs 4.5 ±0.4%) at 72 h after injection. Uptake in the SK-OV3 tumor was similar for both antibody conjugates. The new 89Zr-chelators and the associated radioconjugates show improved in vitro stability compared to DFO and ^{89}Zr-DFO-trastuzumab. The radioconjugate derivated from the more promising chelator, ^{89}Zr-DFOcyclo*-trastuzumab, demonstrated a better in vivo stability compared to ^{89}Zr-DFO-trastuzumab. Therefore, less radiation exposure to bone marrow and improved bone metastasis detection could be achieved using DFOcyclo*.

Tuning the design of Pyclen-based lanthanides(III) chelates from β-radiotherapy to theranostic probes

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[2] Laboratory of Radiochemistry and Environmental Chemistry, Paul Scherrer Institute, Switzerland
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Lanthanides ions (Ln^{3+}) are interesting elements as they give access to many diverse imaging and therapy modalities. The most known Ln^{3+} are employed for MRI (Gd^{3+}) and optical imaging (Eu^{3+}, Tb^{3+}) applications. Our aim is to explore the radio-emissive isotopes $^{161}Tb^{3+}$ and $^{177}Lu^{3+}$ for radiotherapy. However, due to their toxicity, they have to be injected as thermodynamically and kinetically stable metal complexes. Among various chelating agents, polyazamacrocycles judiciously functionalized are known to strongly bind a large variety of metals. For example, pyclen has been regiospecifically functionalized with picolinate and acetate pendant arms[1] leading to a complete family of ligands. These compounds have been deeply investigated for the $^{90}Y^{3+}$ radiolabelling[2] and the complexation of paramagnetic Gd^{3+} (Figure 1).[3] The incredible properties of these ligands[4,5] lead us to take benefit of this new family of chelators for the complexation of $^{161}Tb^{3+}$ and $^{177}Lu^{3+}$ ß-emitters. In this purpose, physico-chemical and coordination properties of these lanthanide complexes as well as the $^{161}Tb^{3+}$ and $^{177}Lu^{3+}$ radiolabelling will be presented. Also, the potential of a new generation of these ligands for a theranostic application combining luminescence and radiotherapy will be demonstrated.

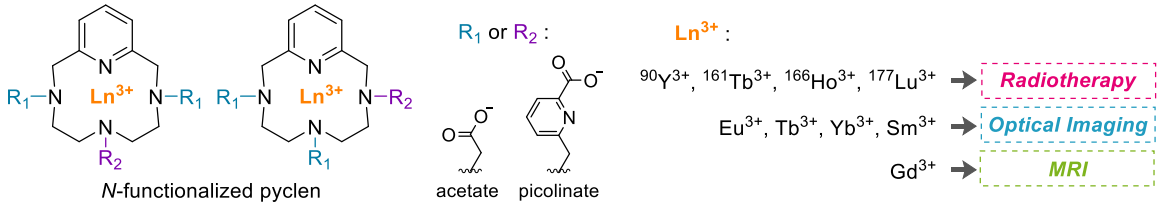

Figure 1 : Lanthanide complexes of N-functionalized pyclen and their applications.

[1] M. Le Fur, R. Tripier, O. Rousseaux, M. Beyler, 2017, WO/2017/109217.
[2] M. Le Fur, M. Beyler, E. Molnár, O. Fougère, D. Esteban-Gómez, G. Tircsó, C. Platas-Iglesias, N. Lepareur, O. Rousseaux, R. Tripier. Inorg. Chem. 2018, 57, 2051– 2063.
[3] M. Le Fur, E. Molnár, M. Beyler, F. K. Kálmán, O. Fougère, D. Esteban-Gómez, O. Rousseaux, R. Tripier, G. Tircsó, C. Platas-Iglesias. Chem. Eur. J. 2018, 24, 3127– 3131.
[4] M. Le Fur, M. Beyler, E. Molnár, O. Fougère, D. Esteban-Gómez, G. Tircsó, C. Platas-Iglesias, N. Lepareur, O. Rousseaux, R. Tripier. Chem. Commun. 2017, 53, 9534–9537.
[5] M. Le Fur, E. Molnár, M. Beyler, O. Fougère, D. Esteban-Gómez, O. Rousseaux, R. Tripier, G. Tircsó, C. Platas-Iglesias. Inorg. Chem. 2018, 57, 6932–6945.

In cellulo ^{57}Fe-Mössbauer spectroscopy

Geneviève Blondin[1], M. Clémancey[1], M.-A. Hograindleur[1,2], J.-M. Latour[1] and S. Ollagnier de Choudens[2]

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Mössbauer spectroscopy is an appropriate tool to probe iron. This technic is specific to the ^{57}Fe isotope and detects all ^{57}Fe nuclei that are present in the sample. The Mössbauer signatures depend on the oxidation and spin states, and on the chemical environment of the Fe ions, allowing the identification and the quantitation of the different forms of Fe.

This presentation will focus on Mössbauer spectroscopy performed on bacterial cells overexpressing or not murine ISCA1 and/or ISCA2 proteins that are involved in the Iron-Sulfur Cluster assembly. The abundance and the nuclearity of the Fe/S clusters that are detected will be discussed as the change in the iron distribution within the cell induced by the overexpression of these ISCA proteins.

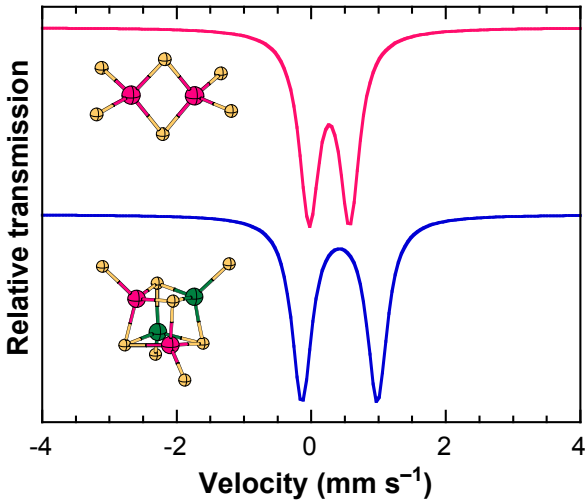

Figure 1 : Typical Mössbauer spectra detected at 4 K for diamagnetic 2Fe2S and 4Fe4S clusters

Poster 1

Highly Emissive Lanthanide Probes with CPL Properties

Junhui Zhang, Dai Lixiong, Lo Wai-Sum and Law Ga-Lai

The Hong Kong Polytechnic University – Hong Kong SAR China

Highly luminescent macrocyclic lanthanide complexes were optimised based on two aspects to obtain reasonable luminescent quantum yields and exhibit circularly polarized luminescence (CPL) properties. Firstly, the complex was optimised for one-step coupling reactions as a fast-screening tool for evaluating the sensitization suitability of various chromophores. Secondly, the intrinsic quantum yield was optimised by introducing chiral substituents symmetrically onto the macrocyclic chelator. Chiral substituents could also selectively control the range of stereoisomers of the lanthanide complexes formed to get very high CPL signals. These water-soluble lanthanide complexes have improved rigidity, stability as well as outstanding photophysical properties. The biocompatible linker on the chromophore also provides probabilities for conjugation with peptide, antibody and other small molecules. All these favourable properties make these lanthanide complexes ideal biological probes and tags.

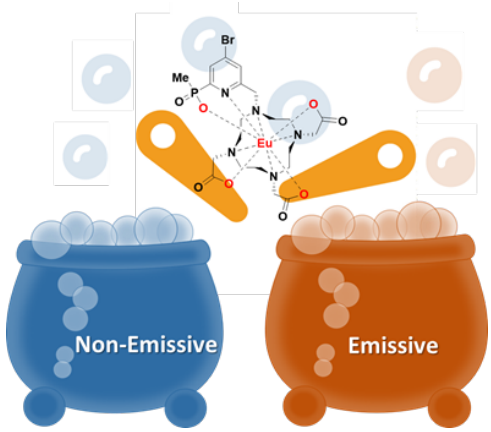

Figure 1 : EuBR as an intermediate for screening of chromophores.

This work was supported by The Hong Kong Polytechnic University (4BCC8), the Hong Kong RGC (PolyU253002/14P), China NSFC (NSFC, 21401158) and the University Life Sciences Facilities (ULS).

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Poster 2

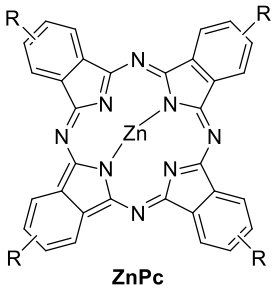
Tumor-homing phthalocyanine derivatives with improved bioavailability for both chemo- and photodynamic therapy

Weiyuan Xu and Ga-Lai Law

The Hong Kong Polytechnic University – Hong Kong SAR China

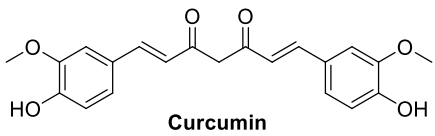
Phthalocyanine (Pc) is an ideal dye adopted as a photosensitizer for photodynamic therapy (PDT) due to long absorption wavelengths (λmax > 660 nm), high extinction coefficients and feasible chemical modifications [1]. Introducing hydrophilic groups to the periphery of Pc ring enhances both bioavailability and production of reactive oxygen species (ROS). In this study, we have linked several molecules with intrinsic anticancer properties to water-soluble zinc Pc (ZnPc), generating imaging agents with different subcellular localizations and high PDT efficiencies.

Hydrophilically modified ZnPc shows tumor preference together with other ZnPc derivatives, while its dark toxicity in HeLa cells is limited, with 1 day IC50 of 1342 μM. Curcumin was found to interact with nucleophosmin in nucleolus, initiating an apoptotic program [2]. Water-soluble ZnPc-curcumin conjugate is prepared to target cell nucleus, with IC50 decreasing from 30 to 18 μM for 1 and 3 days of incubation in HeLa cells. As a retinoid X receptor agonist [3], bexarotene is conjugated to ZnPc to exhibit lysosome localization in HeLa cells. The 1 day IC50 of this combination is 28 μM, and its phototoxicity is found at 0.21 μM of IC50 after only 2 hours cell uptake, compared to that of 0.14 and 0.42 μM for ZnPc and ZnPc-curcumin respectively.

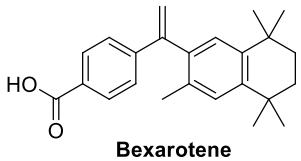


ZnPc

R= hydrophilic groups



Curcumin



Bexarotene

This work was supported by the Hong Kong RGC (PolyU 153013/17P) and the Hong Kong Polytechnic University ((a) University Research Facility in Chemical and Environmental Analysis (UCEA); (b) University Research Facility in Life Sciences (ULS)).

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Bioconjugatable macrocyclic complexes of Eu(III) and Tb(III) bearing azide, alkyne and ester reactive groups

Salauat Kiraev[1], Eszter Borbas[1], Daniel Kovacs[1], Dulcie Phipps[1] and Andreas Orthaber[2]

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[2] Department of Chemistry -Ångström Laboratory – Sweden

Lanthanide(III) ions such as Eu^{3+} and Tb^{3+} are known for their unique spectroscopic properties that are useful for cellular imaging and biolabeling[1]. Ligands incorporating light-harvesting antennae can overcome the drawbacks that these metals have (i.e. low extinction coefficients, UV excitation), and capitalize on their characteristic line-like emissions and long emission lifetimes. As their lifetimes are longer than that of fluorescent biomolecules, they are amenable to time-resolved detection, which can eliminate autofluorescence, and thus increase the signal-to-noise ratio.

Here, we report a series of Ln(III) complexes of ligands comprising a 1,4,7,10-tetraazacyclododecane-1,4,7-triacetate (DO3A) metal binding site and azide- and alkyne-functionalised carbostyril antennae (Figure 1). The connection between the antennae and DO3A is provided by secondary or tertiary amide linkers. The latter affords more efficient sensitization of the Ln(III) ion compared to the secondary amide linkage, as recently demonstrated[2].

The bioconjugatable azide or alkyne groups were installed into the antennae by the late-stage modifications of the ethyl ester-protected precursors. The functionalisation of the ester group to azide or alkyne reactive handles in carbostyril antennae had only a small effect on the luminescence properties of the Eu(III) and Tb(III) complexes. Moreover, the azide group underwent strain-promoted azide-alkyne cycloaddition with dibenzocyclooctyne-amine yielding triazole complexes.

To eliminate the quenching of the lanthanide luminescence from the metal—bound water molecule, the Ln(III) inner coordination sphere was saturated by replacement of a carboxylate pendant arm with a bidentate pyridylcarboxylate arm. This modification enhanced Tb(III) green emission by 5%, while the Eu(III) quantum yield was unaffected. Such behaviour could be due to the appearance of a new quenching pathway that offsets the effects of the O-H oscillator removal.

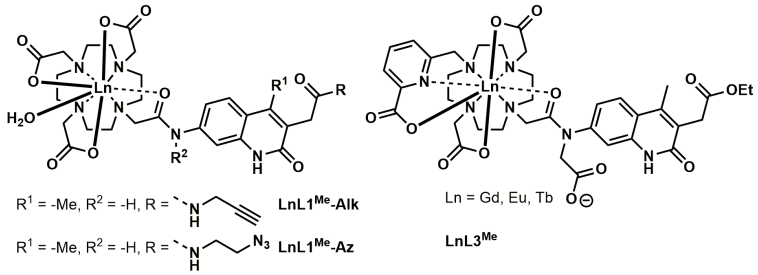

Figure 1 : Structure of the reported octa- (left) and nonadentate (right) complexes.

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[2] Kovacs, D.; Phipps, D.; Orthaber, A.; Borbas, K. E., Highly luminescent lanthanide complexes sensitized by tertiary amide-linked carbostyril antennae. Dalton Trans. 2018, 47, 10702-10714.

Poster 4

Development of Lanthanide(III)-Based Dendrimeric Metallacrowns for Biological Imaging

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[2] Centre de Biophysique Moléculaire – CNRS : UPR4301 – France

Lanthanide(III)-based dendrimeric metallacrowns (MCs) are designed and synthesized as probes for luminescent biological imaging. MCs have been shown to be suitable at exploiting the luminescent properties of lanthanide(III) ions (LnIII) [1,2]. However, their limited biocompatibility has restricted their application as bioimaging agents. To overcome this limitation, dendrimers are built from luminescent metallacrowns. The MC cores are constituted by dimeric $(LnIII)_2(Mip)_4([12\text{-}MC_{Ga(III)Shi\text{-}4}])_2$ MCs (Ln: Sm^{III}-Yb^{III}) linked together by four isophthalate ligands functionalized with maleimide appendages (Mip). The self-assembled monomers are synthesized in a one-pot reaction using salicylhydroxamic acid (H_2Shi) with Ga^{III} and Ln^{III} nitrates. Thiol focal-point poly(amidoamine) (PAMAM) dendrons of the desired generation are prepared by convergent synthesis and then reacted with the MC core via thiol-maleimide Michael addition, resulting in a strap-like dendrimer (Figure 1). Compared to standard PAMAM dendrimers of the same generation, dendrimeric MCs have twice as many surface groups, and reach larger diameters at smaller generations – e.g. a G:0.5 dendrimeric MC has roughly the same diameter as a G:3.5 PAMAM dendrimer. Photophysical characterization of a G:0 dendrimeric MCs made with Yb^{III} demonstrates that not only the luminescent properties of the core are still preserved, but the brightness of the complex in solution is an order of magnitude larger than the brightest ytterbium MC previously reported2. Furthermore, preliminary epifluorescence microscopy images of HeLa cells incubated with G:0 Yb^{III}-based dendrimeric MCs demonstrate the following: the complex is stable in cell culture medium; it is probably uptaken by cells; and although some degree of aggregation is observed, intracellular vesicles appear to be labeled. Altogether, these preliminary results indicate that dendrimeric metallacrowns are promising lanthanide-based luminescent probes.

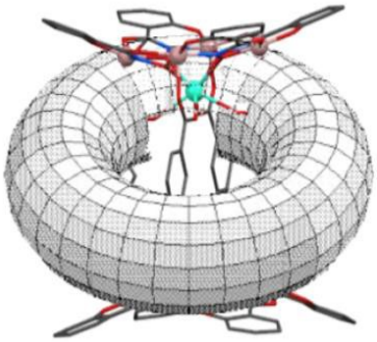

Figure 1 : Representation of strap-like dendrimeric metallacrown.

[1] Chow, C. Y., Eliseeva, S. V., Trivedi, E. R., Nguyen, T. N., Kampf, J. W., Petoud, S., and Pecoraro, V. L. J. Am. Chem. Soc. 138, 5100–5109 (2016).
[2] Martinić, I., Eliseeva, S. V., Nguyen, T. N., Pecoraro, V. L., and Petoud, S. J. Am. Chem. Soc. 139, 8388–8391 (2017).

Poster 5

New π-conjugated lanthanide complexes as useful tool for solving protein structures

Margaux Roux[1], Amandine Roux[1], François Riobe[1], Eric Girard[2] and Olivier Maury[1]

[1] 1Laboratoire de Chimie (ENS Lyon) – CNRS : UMR5182, Ecole Normale Supérieure - Lyon, Université Claude Bernard - Lyon I – France
[2] Institut de biologie structurale (IBS) – Université Grenoble Alpes, Commissariat à l'énergie atomique et aux énergies alternatives : DRF/IBS, Centre National de la Recherche Scientifique : UMR 5075, Grenoble, France

Protein structure determination is mainly based on X-ray diffraction and meets with the problem that number of proteins are difficult to crystallize. In order to improve the crystallization process, nucleant agents are added to the crystallization media.

In this context, lanthanide complexes, based on a triazacyclononane (TACN) platform, called *crystallophore* (TbXo4), have been developed and proved to co-crystallize with number of proteins (nucleant effect) but also to assist the structure resolution due to their strong anomalous scattering (phasant effect, figure 1) [1-3]. However, role of the crystallophore in crystallization process remains to be elucidated, in particular, the comprehension of the nature of the involved supramolecular interactions.

To that end, a new generation of complexes, based on π-conjugated antennae, is developed allowing us to carry out advanced spectroscopic and biological imaging studies.

Synthesis, crystallization trials and first spectroscopic results for these new complexes will be described and compared with the first generation of TbXo4.

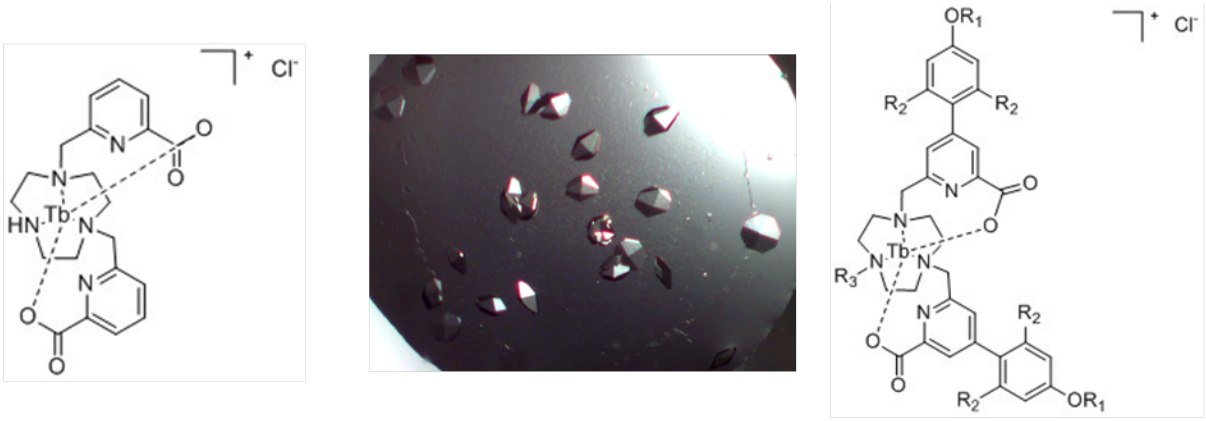

Figure 1 : Structure of TbXo4 (left), crystals of HEWL with TbXo4 (middle), structure of new crystallophores (right).

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[3] Engilberge S., Riobé F., Wagner T., Di Pietro S. and al., *Chem. Eur. J.*, **2018**, *24*, 9739-9746

Poster 6

A non-invasive method to quantify zinc sparks after fertilization to score embryos for implantation

Manon Isaac[1], Seth. A. Garwin[1], Jessica E. Hornick[2], Nan Zhang[2], Francesca E. Duncan[2], Teresa K. Woodruff[2], Thomas V. O'Halloran[1]

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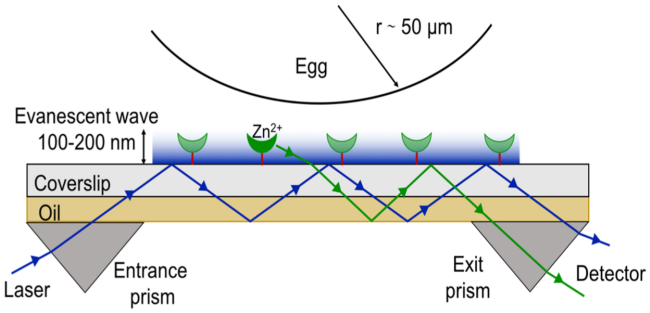
[2] Department of Obstetrics and Gynecology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois 60611, USA

Zinc dynamic fluxes are essential for the regulation of oocyte maturation and fertilization. The mouse oocyte accumulates ~20 billion zinc ions, (a 50% increase) during maturation. After fertilization, ~15% of total zinc content is expelled from the egg through exocytotic bursts, called zinc sparks[1]. The more zinc released from the egg, the more successful embryos are to reach the blastocyst phase of development[2]. The magnitude of zinc sparks is thus a hallmark of egg quality. However, zinc sparks detected by confocal microscopy with a soluble fluorescent probe damages the egg due to intense illumination. So, this protocol cannot be performed on eggs that will be implanted.

To quantify zinc sparks, an in vitro fertilization (IVF) dish with a glass coverslip bottom is derivatized with a zinc-specific fluorescent probe, and imaged with Total Internal Reflection Fluorescence (TIRF) Microscopy where only the probe layer is excited, significantly lowering both background and photodamage to the egg. The coating is composed of silane, a linker to minimize steric hindrance, and a zinc-specific fluorescent probe to detect zinc. The synthesis and characterization of this dish will be presented.



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Poster 7

Nonadentate bispidine ligands for the potential application in nuclear medicine

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Early stage diagnosis of cancer is of utmost importance to ensure adequate treatment. To this end, a variety of diagnostic imaging techniques, such as positron emission tomography (PET), are used in nuclear medicine. These non-invasive techniques allow examination of pathological tissue and functional disorders at an early stage. Therefore, the use of radiometal-based pharmaceuticals has become increasingly popular [1].
Important conditions for ligands used in radiometal-based imaging are relatively fast complexation under physiological conditions, as well as high kinetic and thermodynamic stability (inertness and stability). In recent years, the highly preorganized bispidine (3,7-diazabicyclo[3.3.1.]nonane) ligands established themselves as promising bifunctional chelators (BFCs) in this field[2-5]. To widen the range of nuclear-medicine-relevant metal centers coordinated by these ligands, we have extended the denticity of the bispidines to nine donor atoms. Here we report the synthesis of new picolinic acid, chinolinol and bipyridine based bispidine ligands and their metal complexes. Regarding the potential radiopharmaceutical applications, the coordination chemistry of the ligands with various metal ions (In(III), Bi(III), Ln(III), An(III)) was investigated, using a range of different techniques, including nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS), potentiometric titrations and single-crystal X-ray structure analysis.

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Poster 8

Redox active lanthanide complexes for medical imaging

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The development of luminescent redox active probes is an exciting field of research due to their potential as useful tools in medical imaging for in vivo detection [1]. Lanthanide complexes possess fascinating luminescent and magnetic properties due to their unique configuration [2]. However, the lack of controllable changeable oxidation states hinders their use as redox active probes. Our approach focuses on the incorporation of redox active ligands which, when oxidized independently of the metal ion, produce an easily detectable change in the complex properties. This could lead the way in the development of new families of redox probes capable of detection in biological media [3,4]. We report a family of macrocyclic lanthanide complexes whereby selective oxidation of the redox active unit induces a switching in relaxivity of the water molecule coordinated by the lanthanide ion. The properties of these redox active complexes have been studied by electrochemistry, UV-vis absorption, relaxivity and EPR. An additional peptide grafting site is introduced to increase relaxivity and biocompatibility in the same time.

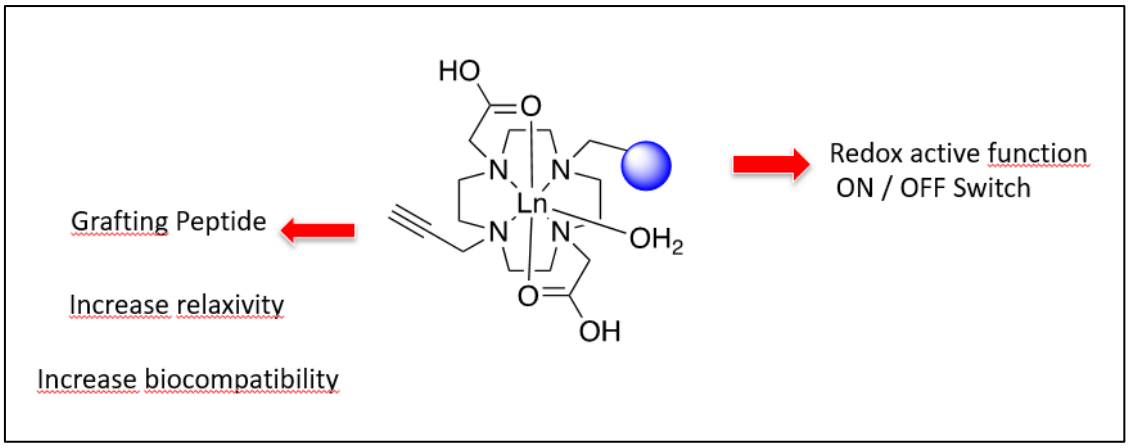

Figure 1 : Lanthanides complexes model as targeted radical redox active probes

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Poster 9

Lanthanide complexes with ligand centered redox-activity: A redox active luminescent and magnetic switch

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The development of novel redox active probes is a fascinating topic of research due to their potential to facilitate in vivo detection of oxidative stress [1,2]. Lanthanide ions in medical imaging are well known due to their fascinating magnetic and photophysical properties [3,4], which however, have been unexploited as redox probes due to their propensity to remain in the +III state. We report a series of cyclen based redox active derivatives which show specific responses in the luminescence and magnetic properties of the Ln^{III} upon changes in oxidation status [5]. These complexes have been studied by electrochemistry, EPR, UV Vis absorption, fluorescence spectroscopy and relaxivity.

[1] M. Masarik, J. Gumulec, M Halvna, M. Sztalmoachova, P. Babula, M. Raudenska, M. Pavkova-Goldbergova, N. Cernei, J Sochor, O Zitka, B. Ruttkay-Nedecky, S. Krizkova, V. Adam, R. Kizek, *Integr.Biol*, **2012**, *4*, 672.
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Quinoline-ligated dinuclear zinc complex for phosphatidylserine detection

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Biological membranes consist of a phospholipid bilayer with embedded proteins used in communication and transportation of chemicals and ions. Phosphatidylserine (PS) is an anionic phospholipid commonly located in the inner leaflet of the phospholipid bilayer. In response to different stimuli, like apoptosis, PS is exposed on the outer leaflet and leads to the release of membrane microvesicles (MVs) [1]. Blood MVs concentrations are indicative of different illness like thrombosis. MVs contain information about their parent cell so there is an interest in diagnostic and therapeutic potential of detecting MVs [2].
In a first approach, a set of bimetallic Zn(II) and Cu(II) complexes based on DPA ligand with a phenoxo spacer has been synthesized. Those complexes have been grafted on solid surface to test and validate their interaction with PS presented in model vesicles. To reproduce MVs, small unilamellar vesicles (SUVs) of defined size and composition were formed. The interaction between both complexes and SUVs were studied using surface-sensitive analysis technics: surface plasmon resonance (SPR) and biolayer interferometry (BLI).
Then, a new generation of complexes based on quinoline unit, chosen for its fluorescent properties, has been synthesized (Figure 1a) [3]. Interactions of the new Zinc(II) complex with PS polar head alone and with microvesicles have been monitored by fluorescence (Figure 1b). Recognition studies with model vesicles were also conducted by BLI.

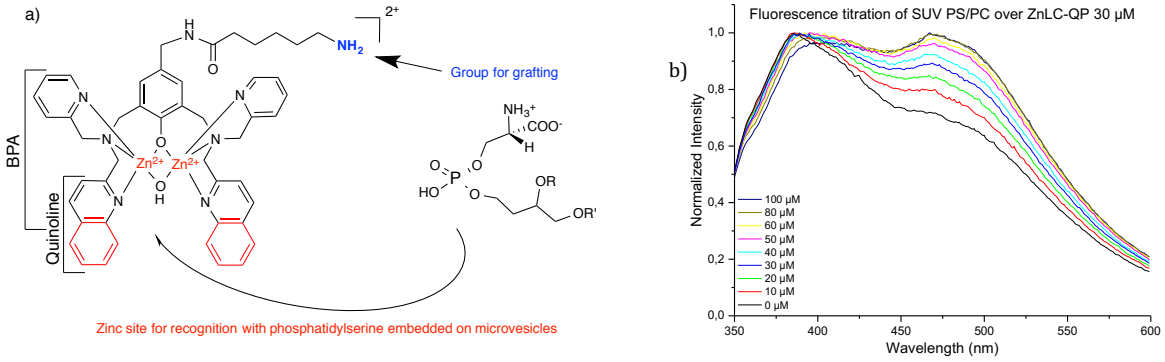

Figure 1 : a) Binuclear Zinc complex for PS recognition b) Fluorescence spectra for ZnQP-LC complex in the presence of increasing amount of SUVs PS/PC

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Poster 11

Dual MRI/luminescence Zn^{2+} detection with a lanthanide complex–zinc finger peptide conjugate

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Magnetic Resonance Imaging (MRI) is a powerful technique to obtain anatomical images with high resolution. Recently, the field of molecular imaging has emerged, seeking information at the molecular level by visualizing the expression or function of bioactive molecules. Zinc is of particular interest as it is an essential micronutriment required for over 300 different biological processes, including metalloenzyme function, signaling, or DNA and protein synthesis. Misregulation of zinc homeostasis has been clearly associated with several diseases such as pancreatic, prostatic and breast cancers, diabetes and neurodegenerative diseases.

We have designed a Zn^{2+}-responsive probe that allows both MRI and luminescence detection. The probe comprises a zinc finger peptide as a recognition unit and a DOTAmonoamide-lanthanide complex as a signaling unit. We will present the zinc-binding properties of the probe loaded with Tb^{3+} or Gd^{3+} as well as related luminescence and MRI properties. We will show that the lanthanide complex–zinc finger peptide conjugate offers interesting perspectives for dual MRI/luminescence detection of Zn^{2+} within the same probe architecture.

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