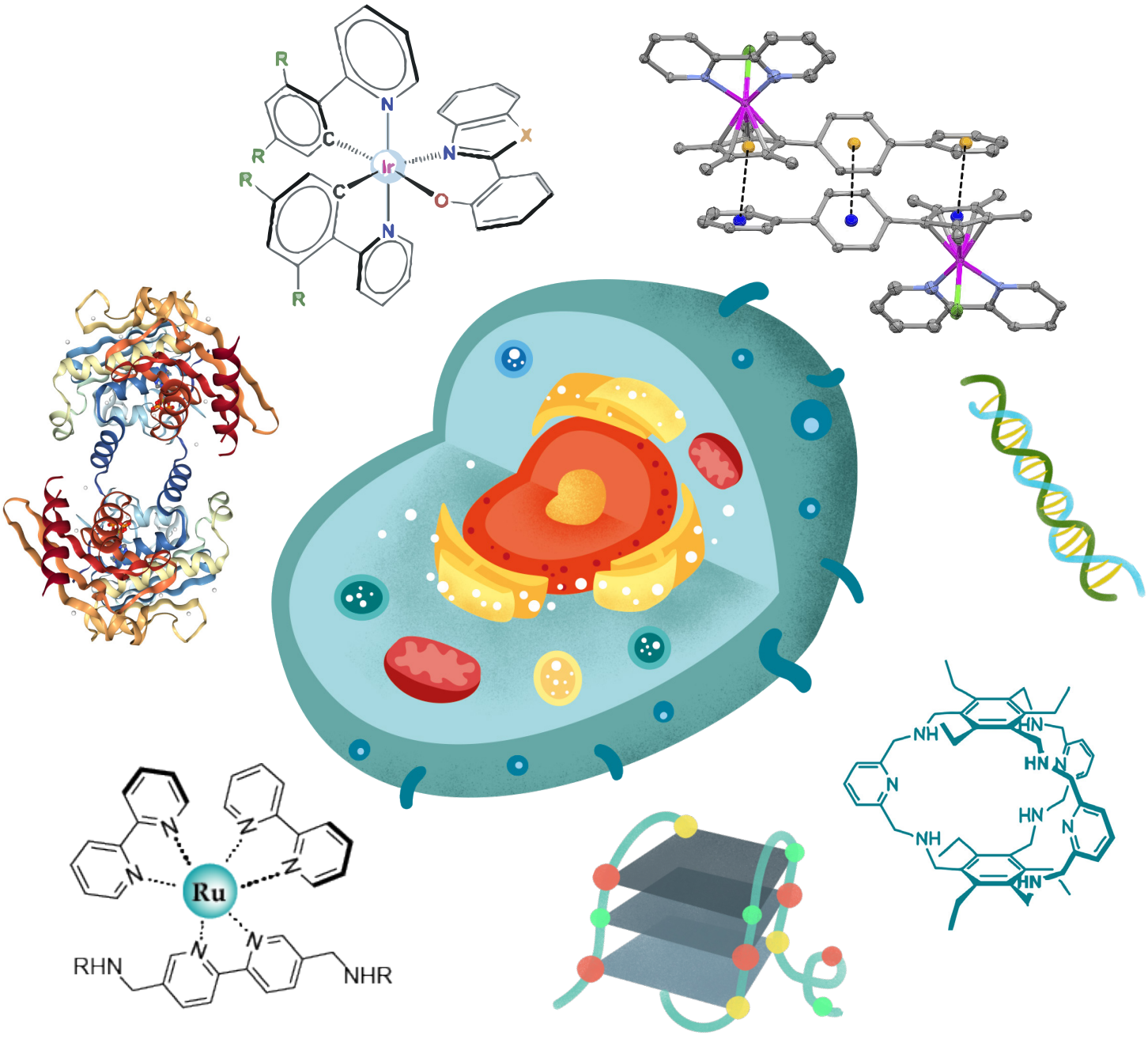
1st Workshop in Inorganic Chemical Biology

November 15th, 2019 Valencia, Spain

Assembly Hall ICMol, University of Valencia.
(Burjassot-Paterna Campus)



Workshop in Inorganic Chemical Biology

Friday, November 15th

9:00 – 9:10 Inauguration of the Workshop

9:10 – 10:00 Prof. José Luis Mascareñas, CIQUS and Departamento de Química Orgánica. Universidade de Santiago de Compostela (Spain). "Metal-based tools in Catalysis and Chemical Biology"

10:00 – 10:30 Dr. Pedro Mateus, LAQV-REQUIMTE, New University of Lisbon (Portugal). "Carbohydrate recognition by aromatic oligoamide capsules"

10:30 – 11:00 Coffee break

11:00 – 11:45 Prof. Ana M. Pizarro, IMDEA Nanociencia (Spain). "Targeting mitochondria by highly potent iridium metallodrugs"

11:45 – 12:30 Prof. Sarah Martin, Barts Cancer Institute & Queen Mary University of London (United Kingdom). "Targeting the mitochondria for the treatment of DNA Mismatch repair deficient disease"

12:30 – 13:00 Dr. Natalia Busto, Universidad de Burgos (Spain). "New biscyclometallated complexes for photodynamic therapy"

Prof. José Luis Mascareñas

CIQUS and Departamento de Química Orgánica. Universidade de Santiago de Compostela, Santiago de Compostela, Spain

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José Luis Mascareñas obtained his PhD from University of Santiago de Compostela (USC) and completed his postdoctoral stay at Univer sity of Stanford in the Prof. Paul Wender´s group. He became assistant professor in 1993 full professor in 2005 at USC. He is recipient of the Organic Chemistry Award and the Gold Medal of the Spanish Royal Society of Spain (RSEQ). He holds an ERC Advanced Grant for "Development of creative and groundbreaking research at the interface of Chemistry, Biology and Medicine" (METBIOCAT).
Prof. Mascareñas is co-author of more than 170 papers and 120 invited conferences with an extended supervision record (31 PhD with several of them obtaining a Ramon y Cajal fellowship). His research interests cover a synthetic program, focused on the development metal complexes for novel catalytic processes and a bioinorganic program orientated to design and develop new synthetic tools to act at biological level.

Metal-based tools in Catalysis and Chemical Biology

Transition metal complexes have found widespread utility in a variety of scientific fields ranging from catalysis to photophysics and supramolecular chemistry. The different coordination and redox characteristics of metals, together with the possibility of tuning their properties by changing the nature of the ligands, provides innumerable possibilities for generating new reactivities, and for implementing physicochemical responses.
Building upon these characteristics, recent work in our work group aims at unveiling new metal-promoted catalytic reactions, and developing metal-dependent strategies to be used in Biosupramolecular Chemistry and Chemical Biology. Our work in catalysis has been mostly focused on discovering new annulation reactions,[1] while in the chemical biology field we have been mainly centered in the area of DNA recognition and cellular internalization.[2]
Finally, in an effort to combine our knowledge in metal catalysis with our work in Chemical and Cell Biology, we have recently demonstrated the viability of achieving metal-promoted processes in biological media and inside living cells.[3,4]

[1] (a) F. López, J. L. Mascareñas, Chem. Soc. Rev. 2014, 43, 2904. (b) M. Gulías, J. L. Mascareñas, Angew. Chem. Int. Ed., 2016, 55, 11000. [2] (a) J. Rodríguez, S. Learte, J. Mosquera, G. Celaya, D. Rodríguez-Larrea, M. E. Vázquez, J. L. Mascareñas, Chem. Sci., 2018, 9, 4118. (b) J. Rodríguez, J. Mosquera, J. R. Couceiro, M. E. Vázquez, J. L. Mascareñas, Angew. Chem. Int. Ed., 2016, 55, 15615. (c) J. Mosquera, A. Jiménez-Balsa, V. I. Dodero, M. E. Vázquez, J. L. Mascareñas, Nature Commun. 2013, 4, 1874. (d) S. Learte, N. Curado, J. Rodríguez, M. E. Vázquez, J. L. Mascareñas, J. Am. Chem. Soc. 2017, 139, 16188. [3] (a) M. I. Sánchez, C. Penas, M. E. Vázquez, J. L. Mascareñas, Chem. Sci. 2014, 5, 1901 (b) M. Tomás-Gamasa, M. Martínez-Calvo, J. R. Couceiro, J. L. Mascareñas, Nature Commun. 2016, 7, 12538. (c) M. Martinez-Calvo, J. R. Couceiro, J. Rodriguez, J. Mosquera, J. L. Mascareñas ACS Catal. 2018, 8, 6055. (d) Vidal, C.; Tomás-Gamasa, M.; Destito, P.; López, F.; Mascareñas, J. L. Nature Commun. 2018, 9, 1913. [4] Martínez-Calvo, M.; Mascareñas, J. L. Coord. Chem. Rev. 2018, 359, 57.

Dr. Pedro Mateus

LAQV-REQUIMTE, Faculty of Sciences and Technology, New University of Lisbon, Caparica, Portugal

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Pedro studied Technological Chemistry at the University of Lisbon and obtained his PhD from Instituto de Tecnologia Química e Biológica of New University of Lisbon under the supervision of Prof. Rita Delgado working on supramolecular cavitants and continued as post-doctoral fellow until 2016. He then performed a postdoctoral stay as Marie Skłodowska-Curie Post-doctoral fellow at Institut Européen de Chimie et Biologie (University of Bordeaux, France) working in the team of Prof. Ivan Huc. In 2019, he obtained a postdoctoral position at New University of Lisbon in the group of Dr. Nuno Basílio. His main research interests are the development of artificial receptors to selectively bind substrates with biological and/or environmental interest, to be used as analytical or diagnostic/therapeutic tools.

Carbohydrate recognition by aromatic oligoamide capsules

Carbohydrate recognition is involved in essential biological processes such as cellular differentiation and cell-cell interactions. It plays key roles in various pathologies including tumour growth and metastasis, adhesion of viruses and bacteria to host cells and immune and inflammatory disorders.[1] Consequently, there is much interest in carbohydrate-binding molecules as chemical tools for diagnostics, imaging, or therapeutic purposes.[2]
Aromatic oligoamide helical containers have been designed to possess a reduced diameter at both ends thereby defining cavities that completely surround their guest.[3] Structure elucidation followed by iterative improvements of the designs allowed to obtain receptors that bind monosaccharides with outstanding affinity and selectivity in organic solvents.[4]
Despite this promising outcome, further challenges still lie ahead such as the ability to perform in polar or even protic media and to expand the approach to other large and complex guest molecules.

In this talk, some recent efforts in this regard will be discussed. A new building block has been included in the capsule's sequences such that metal ions contribute both to folding and to guest recognition. In addition, self-assembly of an aromatic oligoamide strand into a double helix has been explored to obtain rapid access to a large supramolecular container capable of binding homo and heteromeric pairs of monosaccharides, in which subtle and novel induced-fit and allosteric effects are at play.

[1] B. Wang, G.-J. Boons, Carbohydrate Recognition: Biological Problems, Methods and Applications (Wiley, 2011). [2] (a) O. Francesconi, S. Roelens, ChemBioChem 2019, 20, 1329. (b) S. Tommasone, F. Allabush, Y. K. Tagger, J. Norman, M. Kopf, J. H. R. Tucker, P. M. Mendes, Chem. Soc. Rev. 2019 DOI: 10.1039/C8CS00768C. [3] Y. Ferrand, I. Huc, Acc. Chem. Res. 2018, 51, 970. [4] N. Chandramouli, Y. Ferrand, G. Lautrette, B. Kauffmann, C. D. Mackereth, M. Laguerre, D. Dubreuil, I. Huc, Nature Chemistry 2015, 7, 334.

Prof. Ana M. Pizarro

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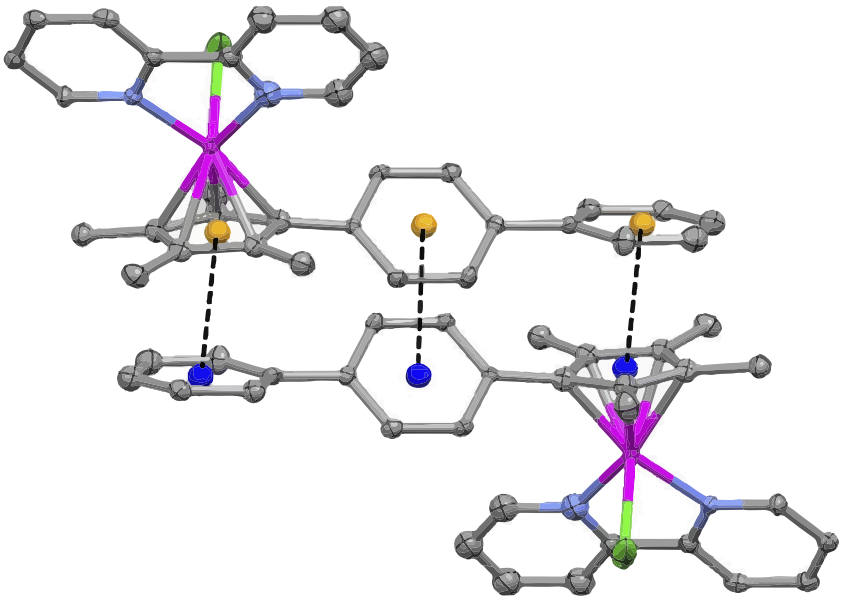
Ana M. Pizarro completed a PhD in Chemistry at the Universidad Autónoma de Madrid under the supervision of Prof. C. Navarro-Ranninger, working on trans-platinum cytotoxic compounds. She was awarded a Marie Curie Fellowship (EIF) to work in the laboratory of Prof. P. J. Sadler FRS at the University of Edinburgh (UK) on new organometallic ruthenium-based organometallics. She then moved to the University of Warwick (UK) where she focused on how selected metallodrugs (based on ruthenium, osmium and iridium) exert their anticancer effects in tumour cells. In January 2014 she was awarded a Ramón y Cajal Fellowship and joined IMDEA Nanociencia as an Assistant Professor. She got tenure in April 2019. Her main interest lies in exploiting the extraordinary features of transition metal complexes inside the human cell to modulate its machinery at the molecular level, and in the context of the intracellular nanospace.

Targeting mitochondria by highly potent iridium metallodrugs

The versatility of the metal coordination bond and its low energy dynamics make it quite attractive in the design of metal-based drugs. I will be presenting a family of some of the most potent iridium-based compounds reported to date (nanomolar cytotoxicty in a number of cancer cell lines). In our design the metal centre is highly protected against nucleophilic attack, so that its reactivity is deterred and its detoxification prior reaching the target hampered. We have unequivocally located a member of this family, an untagged and non-fluorescent Ir(III) complex, in the mitochondria of cancer cells by means of cryo X-ray tomography (cryo-SXT) and X-ray fluorescence tomography (cryo-XRF) correlatively on the same cryopreserved cell. We will discuss the SAR analysis in relation to the compound's effect on the mitochondria.



Prof. Sarah Martin

Barts Cancer Institute & Queen Mary University of London. Charterhouse Square, EC1M 6BQ, London, United Kingdom

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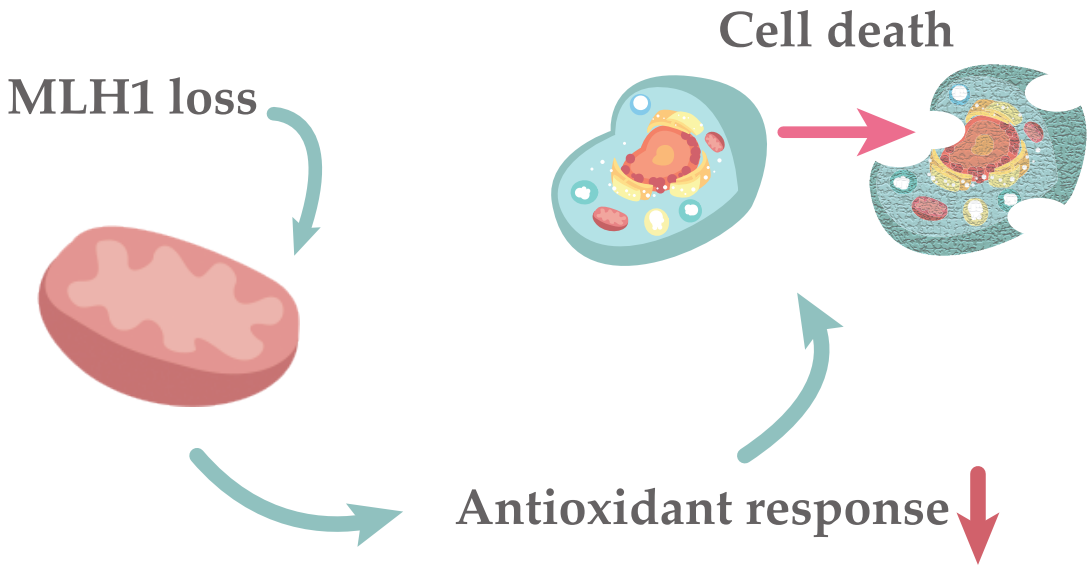
Sarah Martin studied a BSc in Microbiology at the National University of Ireland (Galway) and completed her PhD in molecular biology from the same University with Dr Richard Powell. She then moved to Mount Sinai School of Medicine (USA) to join Dr. Toru Ouchi's group, where she investigated the role of BRCA1 and its functional binding partners. In 2006, she joined Prof Alan Ashworth's group in the Breakthrough Breast Cancer Research Centre in the Institute of Cancer Research (UK) and joined Barts Cancer Institute as a principal investigator in September 2010. Her research group is focused on DNA mismatch repair deficiency and identifying new ways of treating cancer by targeting defects in nuclear and mitochondrial DNA repair.

Targeting the mitochondria for the treatment of DNA Mismatch repair deficient disease

The DNA Mismatch repair (MMR) pathway is responsible for the repair of base-base mismatches and insertion/deletion loops that arise during DNA replication. MMR deficiency is currently estimated to be present in 15-17% of colorectal cancer cases and 30% of endometrial cancers. MLH1 is one of the key proteins involved in the MMR pathway. Inhibition of a number of mitochondrial genes, including POLG and PINK1 can induce synthetic lethality in MLH1 deficient cells. We have recently demonstrated for the first time that loss of MLH1 is associated with a deregulated mitochondrial metabolism, with reduced basal oxygen consumption rate and reduced spare respiratory capacity. Furthermore, MLH1 deficient cells display a significant reduction in activity of the respiratory chain Complex I. As a functional consequence of this perturbed mitochondrial metabolism, MLH1-deficient cells have a reduced anti-oxidant response and show increased sensitivity to reactive oxidative species (ROS)-inducing drugs. Taken together, our results provide evidence for an intrinsic mitochondrial dysfunction in MLH1-deficient cells and a requirement for MLH1 in the regulation of mitochondrial function.



Dr. Natalia Busto

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Graduated in Fundamental Biology and Biotechnology at Salamanca University (Spain) in 2006, she obtained her PhD in Chemistry at University of Burgos (Spain) with highest honors in 2011. In the course of her predoctoral research, she stayed at the Genetic Department of the Medical School, New University of Lisbon (Portugal), carrying out cytoxicity and genotoxicity studies of new potential anticancer drugs and at the Chemistry Department of Pisa University (Italy) performing kinetic studies on DNA-drug interactions. Since 2012, she works as a postdoc in the group of Prof. Begoña García at University of Burgos studying newly synthesized drugs with potential antitumor activity from different perspectives. During this postdoctoral stage, she has performed several short research stays at the CiMUS (University of Santiago de Compostela, Spain) evaluating the ability of small molecules to inhibit transcription and at the IECB (INSERM U1212, CNRS UMR 5320), University of Bordeaux,(France) studying perylene diimide derivatives as G-quadruplexes binders. She has been awarded with the Excellent Young Researcher Award of "Obra Social Caja de Burgos" in 2011 and 2012, with the Extraordinary PhD Award by the University of Burgos, and with the Fernando Pulidori Prize 9th edition by the International Group of Metal Complexes in 2016. Currently, her research broadens towards the development of new drugs against multidrug resistant bacteria.

New biscyclometallated complexes for photodynamic therapy

Photodynamic therapy (PDT) is based on the combination of three non-toxic elements: visible light, oxygen and a photosensitizer (PS) which can produce highly reactive oxygen species (ROS) upon irradiation causing cell death by necrotic or apoptotic pathways.[1] This strategy has emerged as a promising anticancer treatment since it enables local and transitory activation to achieve spatio-temporal control over drug biological action. Indeed, it is successfully applied for the clinical treatment of localized cancers such as skin, esophagus, lung, bladder…[2] On the other hand, PDT is also an interesting strategy increasingly applied in both therapeutic and prophylactic modalities for the eradication of multidrug resistant bacteria strains. Its main advantage is the possibility of killing microorganisms without developing resistance, extremely important in the era of ever-increasing resistance. In this case, the localization of the PS does not need to be specific since there are no defined targets; the oxidative burst-mediated death is pretended.[3]

Despite the existence of several approved PDT agents, there is still a need of new PSs since conventional agents have poor solubility in aqueous media at physiological pH and their synthesis used to be very challenging hindering the modification of their chemical structures.[4] In this context, biscyclometallated complexes are being extensively studied as potential PDT agents, specially Ir(III) complexes due to their photophysical properties.[5] The role played by some biscyclometallated complexes as PSs in cancer and in microorganism inhibition will be evaluated.

[1] D. Dolmans, D. Fukumura, D,. Jain, Nat. Rev. Cancer 2003, 3, 380. [2] D. Van Straten, V. Mashayekhi, S. H. De Bruijn, S. Oliveira, J. D. Robinson, Cancers. 2017, 9, 2072. [3] F. Cieplik, D. Deng, W. Crielaard, W. Buchalla, et al. Crit. Rev. Microbiol. 2018, 44, 571. [4] W. Fan, P. Huang, X. Chen, Chem. Soc. Rev. 2016, 45, 6488. [5] (a) A. Zamora, G. Vigueras, V. Rodriguez, M. D. Santana, J. Ruiz, Coord. Chem. Rev. 2018, 360, 34. (b) H. Huang, S. Banerjee, P. J. Sadler, ChemBioChem 2018, 19, 1574.

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