OP-1

# Photoactivated chemotherapy based on transition metals towards the treatment of hypoxic tumors

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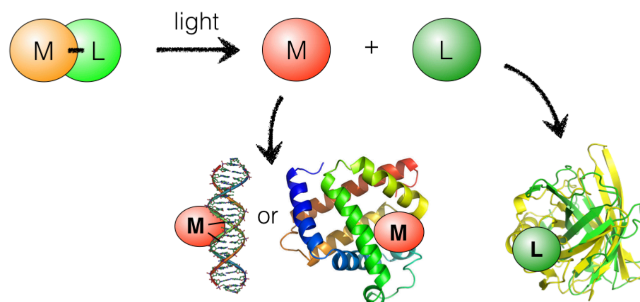
Hypoxic tumors represent a challenge in oncology, as they are more resistant to all known forms of antitumor treatments. Photo-Activated Chemotherapy (PACT), like PhotoDynamic Therapy (PDT), aims at activating anticancer medicines with visible light to circumvent to the tumour site the toxicity of traditional chemotherapy. Unlike PDT however, PACT agents are activated by the photocleavage of a molecule into two fragments that are more toxic than the prodrug in the dark. As this activation mechanism is inherently independent from the presence of dioxygen in the irradiated tissues, it is in principle perfect for the killing of hypoxic tumors, where clinical PDT often fails. In this presentation, I will discuss our group efforts towards the design of new and efficient metal-based PACT agents for the treatment of hypoxic tumors, with a particular focus on hypoxic *in vitro* data and *in vivo* evaluation.




Prodrug activation by bond cleavage in photoactivated chemotherapy.

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OP-2

# Guanidines strike back: Exceptional Substrate Diversity in Oxygenation Reactions Catalyzed by Bis(μ-oxo) Copper Complex

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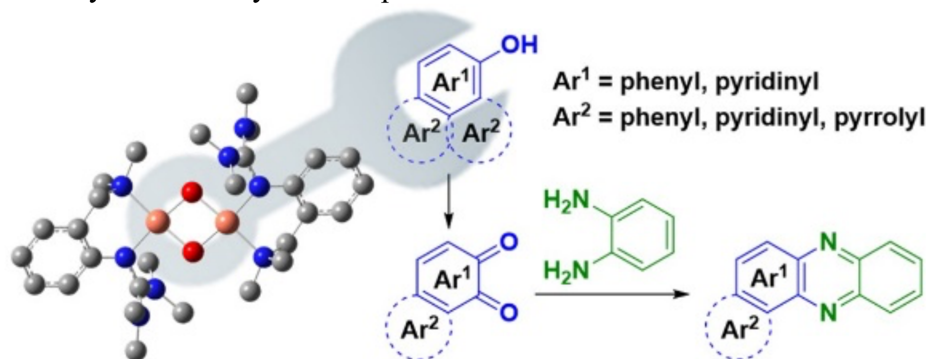
Copper proteins mediate oxygen activation and transfer as well as electron transfer in very efficient ways – optimised by millions of years of evolution.[1] With chemical models, we try to harness their superior reactivity. Oxygen transfer is efficiently mediated by tyrosinases to convert phenols to quinones. Numerous model complexes have been reported but only few with catalytic ability.[2] For several years, we have studied bis(pyrazolyl)methanes[3] and guanidines[4] as ligands for tyrosinase models and found subtle ligand influences to be crucial for the catalytic reactivity.
Recently, we described the synthesis and characterization of bis(μ-oxo) dicopper(III) species $[Cu_2(\mu\text{-}O)_2(\mathbf{L1})_2](X)_2$ ($[\mathbf{O1}](X)_2$, X = $PF_6^-$, $BF_4^-$, $OTf^-$, $ClO_4^-$) via UV/Vis, Raman and XAS spectroscopy as well as cryo-UHR-ESI mass spectrometry, stabilized by the novel hybrid guanidine ligand 2-{2-((dimethylamino)methyl)phenyl}-1,1,3,3-tetramethylguanidine (**L1**).[5] We highlight selective oxygenation of a plethora of phenolic substrates mediated by $[\mathbf{O1}](PF_6)_2$, that results in mono- and bicyclic quinones and provides an attractive strategy on the route to design new phenazines. The selectivity is predictable using the Fukui function which is hereby introduced into tyrosinase model chemistry. Our bioinspired catalysis harnesses molecular dioxygen for organic transformations and achieves a substrate diversity which goes far beyond the enzyme's scope.

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OP-4

## The intersection of nutrition and infection at the host-pathogen interface

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All cells require nutrient metal to carry out essential biochemical processes. This requirement is something that the vertebrate immune system has exploited as a strategy to defend against infection by restricting microbial access to nutrient metal. This process of nutrient restriction during infection is called "nutritional immunity". Bacterial pathogens have evolved elaborate mechanisms to circumvent nutritional immunity and acquire metal during infection. This struggle for nutrient metal impacts both microbial virulence as well as the immune response of the host, profoundly impacting the outcome of host-pathogen interactions.

To study these interactions in more detail, we have developed a powerful imaging workflow that can be applied to murine models of infectious disease. All diseases, including infections, are characterized by distinct changes in tissue molecular distribution. Molecular analysis of intact tissues traditionally requires knowledge and reagents relevant to the targets of interest as well as destructive processing for downstream identification platforms. Tissue-based analyses therefore sacrifice discovery to gain spatial distribution of known targets, or sacrifice tissue architecture for discovery of unknown targets.

To overcome these obstacles, we developed a multi-modality, three-dimensional imaging platform for discovery-based molecular histology. We have applied this platform to the study of multiple murine models of infection, leading to the discovery of infection-associated alterations in the distribution and abundance of macromolecules and elements in tissue. These data provide a three-dimensional analysis of how disease impacts the molecular architecture of complex tissues in infected animals, enable diagnosis of infection through imaging-based detection of bacterial and host analytes, and reveal molecular heterogeneity at the host-pathogen interface.

OP-5

# Metal Sequestration by Calprotectin and Consequences on Microbial Physiology

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Most microbial pathogens have a metabolic iron requirement, necessitating the acquisition of this nutrient in the host. In response to pathogen invasion, the human host limits iron availability to starve pathogens of this nutrient. Canonical examples of nutritional immunity are host strategies that limit pathogen access to Fe(III). In contrast, little is known about how the host restricts access to another biologically relevant oxidation state of this metal, Fe(II). This redox species is prevalent at certain infection sites and is utilized by bacteria during chronic infection.

Human calprotectin (CP, S100A8/S100A9 or MRP8/MRP14 heterooligomer) is an abundant metal-sequestering innate immune protein that utilizes an unusual hexahistidine (His6) site to coordinate multiple nutrient metal ions in the divalent oxidation state. We describe the Fe(II)- binding properties of CP, and report that CP inhibits iron uptake and induces an iron starvation response in Pseudomonas aeruginosa by sequestering Fe(II) at the His6 site.

We show that, under aerobic conditions in which the Fe(III) oxidation state is favored, Fe(II)-withholding by CP was enabled by (i) its ability to stabilize this redox state in solution and (ii) the production and secretion of redox-active phenazines by P. aeruginosa which reduce Fe(III) to Fe(II). Analyses of the interplay between P. aeruginosa secondary metabolites and CP indicated that Fe(II) withholding alters P. aeruginosa physiology and expression of virulence traits. This work implicates CP-mediated Fe(II) sequestration as a component of nutritional immunity in both aerobic and anaerobic milieus during P. aeruginosa infection.

OP-6

# Molecular imaging tools to understand the inorganic chemistry of cells

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The inorganic chemistry of the cell is key to the processes essential from life: for example, almost half of all enzymes require a metal to function, while redox-active metals are key to the maintenance of redox homeostasis in cells. Medicinal inorganic chemistry, whether involving metal-containing pharmaceuticals or agents that perturb metal homeostasis, plays an important role in the treatment of disease, particularly cancer, but much remains to be learnt about how these agents interact with cells and alter the cellular environment.

We are interested in developing molecular imaging tools to understand these interactions, with a focus on fluorescent and magnetic resonance (MR) sensors. This talk will present progress we have made in visualising redox changes in the cell, whether oxidative stress and hypoxia, and how these are perturbed by changes in metal homeostasis.

OP-7

## Artificial Metalloenzymes
## From enzyme models to model enzymes?

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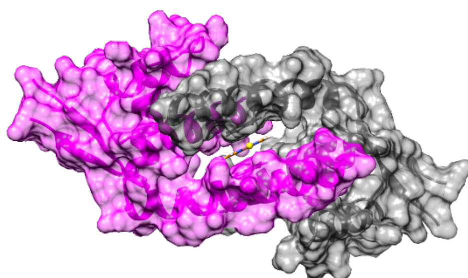
The catalytic efficiency and high selectivities achieved by natural metalloenzymes are a source of inspiration for the design of novel bio inspired catalysts. A powerful approach for creating artificial metalloenzymes involves incorporating an biological metal cofactor into a protein. We have developed a new concept for the design of artificial metalloenzymes that involves creation of a novel active site at the dimer interface of the transcription factor LmrR (Lactococcal multidrug resistance Regulator).[1] LmrR was selected as the protein scaffold because it contains an unusual large hydrophobic pocket on the dimer interface.

Here, two novel classes of LmrR-based artificial metalloenzymes will be presented, involving either supramolecular anchoring of the metal complex[2,3] or biosynthetic incorporation of an unnatural metal binding amino acid using expanded genetic code methodology.[4] These artificial metalloenzymes have been applied successfully in catalytic



asymmetric C-C bond forming and hydration reactions. Our recent progress in the evolution and in vivo application of these artificial metalloenzymes will be discussed.

Structure of an LmrR based artificial metalloenzyme

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OP-8

# Small Molecule Activation at Transition Metal Centers: Structure-Function Correlations

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Small molecule activation constitutes one of the main frontiers of inorganic and organometallic chemistry, with much effort directed towards the development of new processes for the selective and sustainable transformation of abundant small molecules such as dioxygen ($O_2$), water ($H_2O$), hydrogen peroxide ($H_2O_2$) or protons ($H^+$) into high-value chemical feedstocks and energy resources. Because nature mostly uses metal ions to activate these relatively inert molecules and modulate their reactivity, much inspiration for the field has come from bioinorganic chemistry.

This talk will focus on some of the recent highlights from our group on homogenously catalyzed bioinspired activation of small molecules, as well as stoichiometric reactions that further our understanding towards such ends. It will cover many aspects of small molecule activation including: organometallic chemistry, spectroscopy, synthesis, and detailed mechanistic studies involving trapping of reactive intermediates. The demonstrated examples will help to emphasize the continuous effort of our group in uncovering the structure reactivity relationships of biomimetic model complexes, which may allow vital insights into the prerequisites necessary for the design of efficient catalysts for the selective functionalization of unactivated C–H bonds, $O_2$/$H_2O$/$H_2O_2$ activations, or $H^+$ reductions by using cheap and readily available first-row transition metals under ambient conditions.

OP-9

# Deciphering the mechanism of Artificial Enzymes: A rationale for the Unexpected Selectivity of an Artificial Ru-dependent Oxidase for alkene conversion.

**Sarah Lopez,[1,2] David Michael Mayes,[1] Serge Crouzy,[1†]Christine Cavazza,[1] Chloé Leprêtre,[1] Yohann Moreau,[1] Nicolai Burzlaff,[3] Caroline Marchi-Delapierre[1] and Stéphane Ménage[1]**

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Artificial enzymes represent an attractive alternative to design abiotic biocatalysis. [1] *Ec*NikA-**Ru1,** an artificial metalloenzyme developed by embedding a ruthenium-based catalyst into the cavity of the periplasmic nickel-binding protein NikA, was found to efficiently and selectively transform certain alkenes. The protein scaffold activates the bound Ru complex to produce a catalyst with high regio- and stereo-selectivity. The hybrid efficiently and stably produced α-hydroxy-β-chloro chlorohydrins from alkenes (up to 180 TON with a TOF of 1050 $hr^{-1}$). Unexpected substrate-dependent chemoselectivity of *Ec*NikA-**Ru1** was observed. [1] We will describe a mechanistic rationale based a dual experimental/computational study. We will show that the *de novo* active site allows the formation of the terminal oxidant *via* the formation of a ruthenium aquo species that subsequently reacts with the hypervalent iodine of phenyl iodide diacetic acid. The oxidation process relies on a $Ru^{IV}$=O pathway *via* a two-step reaction with a radical intermediate, resulting in the formation of either a chlorohydrin or an epoxide.

The results discussed here emphasize the impact of the protein scaffold on the kinetics of the reaction, through i) the promotion of the starting oxidizing species *via* the exchange of a CO ligand with a water molecule; and ii) the control of the substrate orientation on the intermediate structures, formed after the $Ru^{IV}$=O attack, controlling the attack on the carbons of the double bonds. [2]

This work provides another example that artificial enzymes mimic the functional behavior of their natural counterparts.

*This lecture is dedicated to Dr. Serge Crouzy who left us last April.*

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