Combating Oxidative Stress : Synthesis and Application of Tri-functional Bioorthogonal Oxylipins

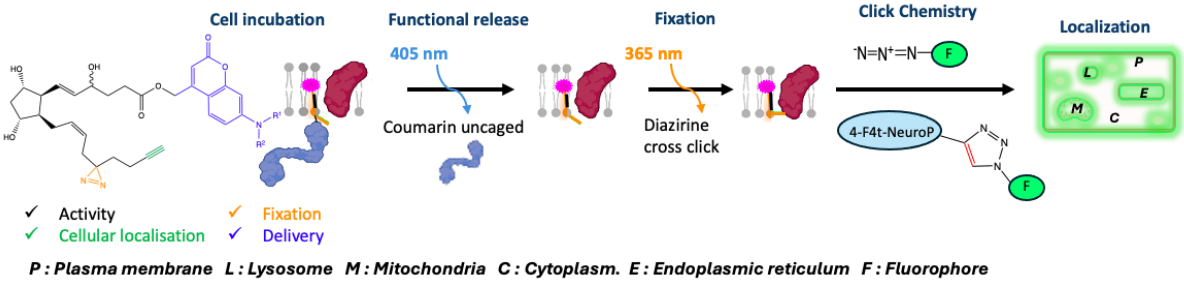
Anna Abramova[1], Jamie Bride[2], Jean-Yves Le Guennec[2], Thierry Durand[1], Valérie Bultel-Poncé[1], Marie Demion[2], Jean-Marie Galano[1]

[1] Department of Bioactive Lipid Synthesis, Chemistry pole Balard, Institute of Biomolecules Max Mousseron (IBMM), UMR5247-CNRS-UM-ENSCM, 1919 rte de Mende, 34000 Montpellier, France ;
[2] Physiologie et médicine expérimentale du cœur et des muscles (PhydMedExp), INSERM, Université de Montpellier, France

Oxidative stress plays a crucial role in various pathological conditions, making lipid oxidation products important mediators of cellular responses. Among them, 4(RS)-4-F_{4t}-NeuroProstane (4-F_{4t}-NeuroP), a major non-enzymatic oxidation product of DHA, displays anti-arrhythmic, anti-apoptotic, and anti-inflammatory properties.[1,2,3] Yet, the molecular mechanisms underlying its activity remain largely unknown. Understanding these mechanisms is crucial as a derivative of this natural oxylipin is currently in phase II clinical development.

Bioorthogonal clickable probes are now widely used in mechanistic studies of active molecules including lipids. In our case, this approach will allow the visualisation of intracellular localisation and profiling of the lipid-protein interactome of 4-F_{4t}-NeuroP. On one hand, advanced probes equipped with photo-crosslinking diazirines will enable proteomic analysis[4], and on the other hand, functionalized coumarins will allow organelle-specific delivery, providing insights into lipid-related signalling pathways at both cellular and subcellular levels.[5]

This presentation will outline the synthetic challenges and strategies behind this unique probe and present our fist results, including its in-cellulo visualisation in macrophages and cardiomyocytes.



References :

[1] Roy, J. et al. Nonenzymatic Lipid Mediators, Neuroprostanes, Exert the Antiarrhythmic Properties of Docosahexaenoic Acid. *Free Radic. Biol. Med.* **2015**, *86*, 269–278.
[2] Roy, J. et al. Non-Enzymatic Oxidized Metabolite of DHA, 4(RS)-4-F4t-Neuroprostane Protects the Heart against Reperfusion Injury. *Free Radic. Biol. Med.* **2017**, *102*, 229–239.
[3] Bosviel, R. et al. DHA-Derived Oxylipins, Neuroprostanes and Protectins, Differentially and Dose-Dependently Modulate the Inflammatory Response in Human Macrophages: Putative Mechanisms through PPAR Activation. *Free Radic. Biol. Med.* **2017**, *103*, 146–154.
[4] Gagestein, B. et al. Comparative Photoaffinity Profiling of Omega-3 Signaling Lipid Probes Reveals Prostaglandin Reductase 1 as a Metabolic Hub in Human Macrophages. *J. Am. Chem. Soc.* **2022**, *144* (41), 18938–18947.
[5] Wagner, N. et al. A Click Cage: Organelle-Specific Uncaging of Lipid Messengers. *Angew. Chem. Int. Ed.* **2018**, *57* (40), 13339–13343.