PROJECT MANDEV: **Man**ganese-based **An**tioxidants **D**elivered by **E**xtracellular **V**esicles (EVs): design of SOD mimics, embedment in mesenchymal stromal cell-derived EVs and cellular studies of anti-inflammatory properties

Partner 1 : Laboratoire chimie physique et chimie du vivant (CPCV), UMR-CNRS 8228n équipe METHROX, , Clotilde Policar and **Partner 2 :** Centre de recherche de l'hôpital Saint-Antoine (CRSA) UMRS_938, Equipe microbiote, intestin et inflammation MI2, Philippe Seksik

Inflammatory Bowel Diseases (IBDs) are non-curable disabling conditions with a high impact on the quality of life. Among the triggers of this inflammation, there is an imbalance in the oxidative stress response in intestinal epithelial cells (IEC), with a deficiency in the antioxidant protective metalloenzyme superoxide dismutase (SOD). The antisuperoxide activity can be reproduced by Mn-complexes. These SOD-mimics are promising catalytic antioxidants and exhibit interesting antioxidant properties, which is not the case for uncoordinated Mn(II). The SOD-mimics that will be studied in this project are bio-inspired from the active site of Mn-SODs, and built on ligands based on a 1,2-diamino-ethane. They are evaluated on cellular models of oxidative stress relevant to IBD (IEC and macrophages) co-developed the *Centre de recherche de l'hôpital Saint-Antoine* and the laboratory *Chimie Physique et Chimie du Vivant*. We have shown recently that, in the intricate cellular environment, the Mn-complexes may exchange Mn(II) for a Zn(II), leading to a redox inactive complex.

We wish to explore the embedment of these complexes within eukaryotic mesenchymal stromal cell (MSC)-derived extracellular vesicles that possess endogenous anti-inflammatory properties. Our hypothesis is that the MSC-EVs may protect the Mn-SOD mimics from the changing bio-environment and favor safe and targeted delivery within the cell cytoplasm. Bioproduction of MSC-EV in the well-controlled environment of bioreactors, pre-, per- or post-production loading of EVs with the Mn-complexes, EV characterization and delivery to targeted IEC and macrophages will be investigated in collaboration with the national IVETh integrator. The bioactivity of the Mn-complexes, loaded or not in EVs, will be evaluated in cells. Overall, this project, owing the advantage of MSC-EVs as biogenic endogenous shuttles, constitutes a unique opportunity to improve the anti-inflammatory cellular effects of the SOD-mimics and bring them from the bench to the bedside.