



## PROJECT

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### 1) Project title

*In vitro* assessment of small molecule lymphatic delivery via novel self-emulsifying lipid systems

### 2) Abstract (max 500 words)

The delivery of low-molecular-weight lipophilic molecules represents a constant challenge for the design of new technologies capable of increasing the bio-accessibility and, hopefully, the bioavailability of these substances, especially if they belong to the Biopharmaceutics Classification System (BCS) class III or IV. The bio-accessibility of lipophilic substances can be improved using technological systems forming micro- or nano-dispersions in contact with gastrointestinal fluids in the form of nanoemulsions, microemulsions or micellar dispersions. These systems, known as self-emulsifying/microemulsifying drug delivery system (SEDDS/SMEDDS), promote aqueous dispersion. However, in the case of substances with low bio-accessibility and high rate of enterohepatic biotransformation (substances extensively biotransformed by intestinal enzymes or in liver microsomes, phase II reactions), increased intestinal bio-accessibility *per se* is not sufficient to improve bioavailability. In this perspective, Lipids-Based Auto-emulsifying Delivery Systems (LiBADS) represent a new technological frontier to improve both the bio-accessibility and bioavailability. In particular, LiBADS containing saturated or unsaturated long-chain fatty acids can potentially promote lymphatic access of active ingredients.

Lymphatic delivery, which starts in enterocytes with chylomicron assembly, implies that the low-molecular-weight lipophilic active ingredient previously dissolved or dispersed in the lipid fraction is encapsulated within chylomicrons and reaches the lymph in the form of long-chain triglycerides. This delivery pathway escapes the portal system and hepatic biotransformation, providing access into the general venous circulation at the thoracic duct outlet into the subclavian vein.

The main objective of this project is to test whether the LiBADS technologies already developed for resveratrol and coenzyme Q10 delivery are effective not only in increasing enteric bio-accessibility, which has already been established, but also in promoting lymphatic access of active ingredients. If for coenzyme Q10 lymphatic access after oral administration, at least in part, is promoted by its physiological incorporation into chylomicrons, for resveratrol this delivery route would be particularly advantageous in order to avoid the extensive presystemic metabolism by phase II enzymes that drastically reduces its bioavailability after oral intake.

The rate of lymphatic access will be initially determined in an established *in vitro* gut model using Caco-2 cells by isolation of chylomicrons (CM) and lipoproteins (LP) through sequential NaCl gradient ultracentrifugation and subsequent active ingredient extraction using appropriate solvents and

HPLC-DAD titration. Subsequently, direct assay of active ingredients within CM and LP will be performed by cannulating the mesenteric lymphatic duct in the mouse.

The project output will reinforce the development of novel nutraceutical formulations with improved pharmacokinetics.