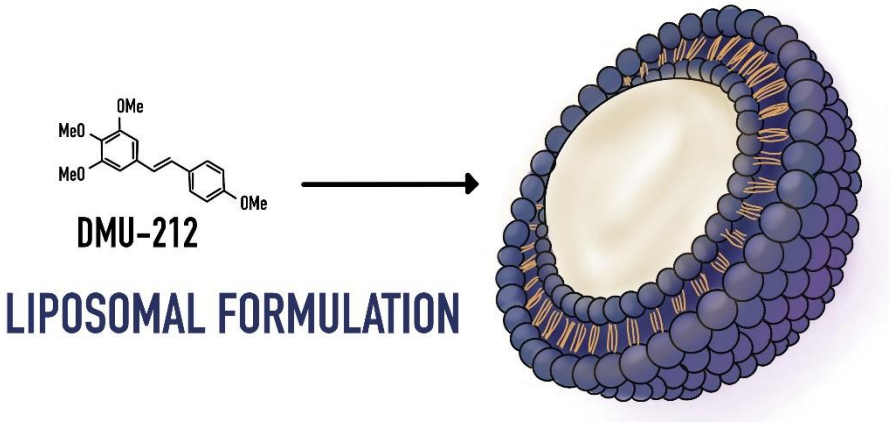
Resveratrol is an antioxidant commonly known from its presence in red wines in substantial concentration. Regular consumption of moderate amounts of wine seems to be an explanation for the "French Paradox", the term describing a relatively low risk of cardiovascular diseases despite of high saturated dietary fat intake.

Although resveratrol exerts a wide spectrum of beneficial activities, its clinical application is strongly limited due to its poor bioavailability and fast elimination from the circulation. **The structural alternations of resveratrol enabled to obtain analogues, such as 3,4,4',5-tetramethoxystilbene (DMU-212), with improved pharmacokinetics and stability.** To obtain an even higher bioavailability and protect DMU-212 from light and other degradative processes, the applicants will use liposomes as the vehicles for the compound tested.



The main goal of the project is to evaluate how the methylated analogue of resveratrol 3,4,4',5-tetramethoxystilbene (DMU-212) affects steroid secretion profile and differentiation ability of human ovarian granulosa cells in primary cell culture assay. Ovarian granulosa cells (GCs) are known to proliferate in the developing follicle and undergo several biochemical processes during folliculogenesis. Together with neighboring theca cells, they play a crucial role in steroidogenesis, particularly the production of estradiol, as well as progesterone following luteinization. Since resveratrol, as a phytoestrogen, binds to the estrogen receptors equally and is structurally similar to estrogens, its steroid activity is now of high interest. **Therefore, the applicants will assess the secretion profile of GCs after DMU-212 treatment. As DMU-212 is also structurally close to estrogen scaffold and is characterized by significantly higher bioavailability, we expect its remarkable effect on steroidogenesis.** Recently, the therapeutic potential of mesenchymal cells has been extensively studied. GCs share many mesenchymal stem cell characteristics since they express the stem cell markers, such as Oct-4, Nanog and Sox-2. This multipotent cell population has been differentiated so far to neuronal cells, chondrocytes, and osteoblasts in *in vitro* model. Resveratrol has been shown to induce differentiation of mesenchymal stem cells (MSCs) **into osteoblasts.** Considering the mesenchymal stem cells properties of GCs and the structural similarity of DMU-212 to the parent compound, **we hypothesize that DMU-212 might also enhance osteogenic differentiation.** Differentiation of GCs into other tissue-specific cells seems to be a useful strategy in regenerative medicine. Considering the increased number of aged people, due to the rise of life expectancy, evaluation of new approaches to limit the bone loss and ameliorate orthopedic degenerative diseases is now of high significance. **Therefore, the applicants aim to investigate differentiation ability of GCs into osteoblasts via several signaling pathways, including SIRT-1 and Wnt- β -catenin ones. To the best of our knowledge, there is no data concerning the biological activity of methylated resveratrol analogues, including DMU-212, in human ovarian granulosa cells.**