The power of phospholipids: From drug delivery depots to biogenic vesicles

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By direct deposition of the drug at the site of action, it is possible to limit the immediate exposure of the active principle at a systemic level and to reduce the frequency of administration [1]. As long-term drug delivery systems, depots are in direct prolonged contact with tissues and it is pivotal to choose the formulation's material and design carefully to minimize unwanted local adverse reactions. Phospholipids most certainly represent a material of choice for any administration route thanks to their very low toxicity profile.

Our research group generated long-acting drug delivery systems for parenteral administration via a cation-mediated controlled aggregation of negatively charged liposomes. A series of negatively charged phospholipids were screened for their suitability as scaffolds for depot formulations as a function of their headgroups and acyl chains [2]. The local anesthetic bupivacaine was used as first drug candidate and successfully encapsulated via remote loading into 1,2-distearoyl-*sn*-glycero-3-phospho-(1'-rac-glycerol) (DSPG)-based liposomes. *In vitro* characterizations were correlated to *in vivo* behavior of the depot and to pharmacokinetics profiles in rats [3].

We are currently exploring the potential of this DSPG-based system for intraarticular administration of rapamycin [4]. The liposomal aggregates we developed extended the release of rapamycin beyond the free liposomes. We could show that rapamycin is able to dampen the fibrotic response in human OA synovial fibroblasts and protect the joints' friction. We could also assess the tribological properties of liposomal aggregates on both nano- and macro-tribological scales with silica surfaces and *ex vivo* porcine cartilage.

Phospholipids may also exert a direct bioactive action, and we explored this property to generate new therapeutics for the treatment of liver fibrosis, a condition characterized by the excessive deposition of extracellular matrix via a multifactorial process driven by activated hepatic stellate cells (HSC). If left untreated, this pathological condition may ultimately lead to organ dysfunction, cirrhosis and hepatocarcinoma. To date no anti-fibrotic drug treatment for liver fibrosis is available. In the last years, we investigated the potential of essential phospholipids and polyenephosphatidylcholines as basis of antifibrotic dosage forms and we evaluated their action, also in combination with investigational drugs, on HSCs [5], on extracellular vesicles derived from HSCs [6-7], and, more recently, on biomimetic vesicles produced from HSCs. During the seminar, a high-level overview of our bioderived platforms will be given and future therapeutic perspectives for the treatment of fibrosis will be discussed.

References

[1] L. Rahnfeld, P. Luciani. *Pharmaceutics*, **2020**, 12:567
[2] L. Rahnfeld, J. Thamm, F. Steiniger, P. van Hoogevest, P. Luciani. *Colloids Surf B Biointerfaces*, **2018**, 168:10-17
[3] S. Aleandri, L. Rahnfeld, D. Chatzikleanthous, A. Bergadano, C. Bühr, C. Detotto, S. Fuochi, K. Weber-Wilk, S. Schürch, P. van Hoogevest, P. Luciani. *Eur. J. Pharm. Biopharm.* **2022**, 181:300-309
[4] G. Bordon, S.N. Ramakrishna, S.G. Edalat, R. Eugster, A. Arcifa, S. Aleandri, M. Frank Bertoncelj, L. Isa, R. Crockett, O. Distler, P. Luciani. Manuscript under review, 25 March 2023, Pre-print available at bioRxiv https://doi.org/10.1101/2023.03.23.533793
[5] G. Valentino, C. Zivko, F. Weber, L. Brülisauer, P. Luciani. *Pharmaceutics*, **2019**, 11:676
[6] C. Zivko, K. Fuhrmann, G. Fuhrmann, P. Luciani. *Commun. Biol.* **2022**, 5:1155
[7] C. Zivko, F. Witt, A. Koeberle, G. Fuhrmann, P. Luciani. *Eur. J. Pharm. Biopharm.* **2023**, 182:32-40