Exploring alternative drug delivery strategies for the evolving therapeutic landscape

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The perceived lack of oral bioavailability outside the so-called *Rule of 5* space has often led scientists to abandon challenging targets classifying them as "undruggable". Realizing the full therapeutic potential of small hydrophilic molecules and (bio)macromolecules could be equally challenging because of their short half-life or due to low patient compliance in case a multiple dosage regimen is needed. Besides pushing the boundaries of drug modification strategies, the evolving therapeutic landscape demands also to re-think and adapt quickly drug delivery approaches and technologies.

Controlled-release delivery systems, among which depots, can deliver a plethora of active pharmaceutical ingredients at a tunable, predetermined rate within the therapeutic range for a specified period[1] and may offer alternative avenues to improve medical adherence and broaden the delivery options for the next-generation therapeutics. Our research group generated long-acting drug delivery systems for subcutaneous administration via a cation-mediated controlled aggregation of negatively charged liposomes. A series of negatively charged phospholipids were screened for their suitability as scaffold for depot formulations as a function of their headgroups and acyl chains[2]. The 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* release studies showed differences between the depot formulations and either the plain bupivacaine solution or non-depot liposomes. *In vivo* imaging carried out in rats showed that the depot formulation has a significantly prolonged retention at the injection site compared to the control zwitterionic formulation over two weeks. Pharmacokinetics studies confirmed that inducing a controlled aggregation of DSPG-liposomes with $CaCl_2$ prior to injection is essential to extend the drug release profile[3]. We are currently exploring the potential of this DSPG-based system for intraarticular injection of other drugs with different chemical properties.

DSPG-based liposomal depots could also be used to improve the safety profile of small molecule drugs. We hypothesized that a composite version of our DSPG-based liposomes could modulate the release of pirfenidone (PFD), an antifibrotic drug only available as oral dosage form and often responsible for significant adverse reactions. The liposomal surface was engineered via a layer-by-layer (LbL) self-assembly of bioderived polyelectrolytes and the LbL PFD-loaded liposomes (LbL-LIP) further embedded into a zinc alginate hydrogel. More than 85% PFD could be loaded in LbL-LIP and, by adjusting the LbL thickness, a controlled and tunable release of PFD from hours to several days was obtained. The resultant composite lipid gel is suitable either for injection or for topical application in fibrotic tissues.

We recently demonstrated that charged phospholipids can be used also to fine tune the release properties of lipid mesophase (LMP) gel. Typical LMPs have water channels with a diameter of 3–5 nm and this geometric constraint does not allow the release of large hydrophilic biotherapeutics. Using charged phospholipids to enlarge the water channels of bicontinuous cubic phases, we designed a highly swollen biocompatible gel. Hydrophilic biomacromolecules can be efficiently encapsulated in this easy-to-manufacture drug delivery platform and their release rate tuned. Thanks to its semisolid texture and its release properties, our gel is particularly suited not only for subcutaneous injection but also for direct administration to the mucosal lining of diseased organs, as the rectum or the cervix, minimizing the adverse reactions that may be associated with parenteral administration of biotherapeutics[4].

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