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COMMUNICATION

Glycosylated nucleoside lipid promotes the liposome internalization in stem cells†

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We report new glycosyl-nucleoside-lipid based liposomes decorated with sugar moieties. The GNL-liposomes feature a suitable glycosylated surface for their internalization into ADSC stem cells.

Owing to their intrinsic amphiphilic structures, lipids have long been of interest to the scientific community. Their multiple uses in pure and applied sciences range from the formulation of cosmetics for example, to more sophisticated biomedical applications. The latter includes drug delivery systems,[1] human gene therapy,[2] scaffolds for tissue engineering[3] as well as applications in cancer therapy.[4] A major trend in biomedical research with high potential is the development of drug delivery systems (DDS) allowing the internalization of bioactive principles into stem cells.[5] Such systems are of critical importance for cell culture engineering or regenerative medicine. As our understanding of the interactions occurring between cells and DDS advances, the use of synthetic sugar-containing systems to address cells is becoming an area of great interest.[6] Herein we describe an approach towards coating liposomes surface with a sugar moiety to allow their internalization into ADSC stem cells (Fig. 1). The cornerstone of our approach relies on the "triumvirate" associating sugar, nucleic acid and lipid moieties.

Interestingly, nucleoside-lipids exhibit both the aggregation properties of lipids and the molecular recognition features present in DNA and RNA, giving rise to self-organized structures like vesicles, fibers, hydro- and organogels.[7] We previously reported different nucleolipid structures, including zwitterionic uridine phosphocholine amphiphiles,[8] nucleolipids conjugates[9] and oligonucleotide-based amphiphiles.[10] The supramolecular systems obtained have been used for the delivery of bio-macromolecules such as DNA,[11,12] and siRNA.[13]

Neutral nucleolipids featuring sugar moieties, namely Glycosyl-NucleoLipids (GNLs) feature a supplementary molecular recognition capabilities gained by the added carbohydrate moiety.[14] Indeed, a lot of carbohydrate-binding proteins (*e.g.* lectins) are expressed on the stem cell surface.[15] Hence, the key to our approach is the preparation of synthetic GNLs capable of assembling into liposome-like aggregates with sugar functionality presented at the surface into solution. The aim is to develop suitable GNLs based liposomes, which might be recognized by carbohydrate–lectin that bind to glycosylated residues on the cell. Glucose was selected as it exhibits weak individual interactions with receptors, but a strong binding can occur when multiple sugar moieties are present on a polyvalent structure.[16] Thus, we hypothesize that the multiple glucosyl moieties present at the liposome surface would allow the interactions with the cells. A glucosyl-lipid, *N*-octanoyl-glucosylceramide, was previously reported to enhance the doxorubicin accumulation in epidermoid carcinoma cells.[17]

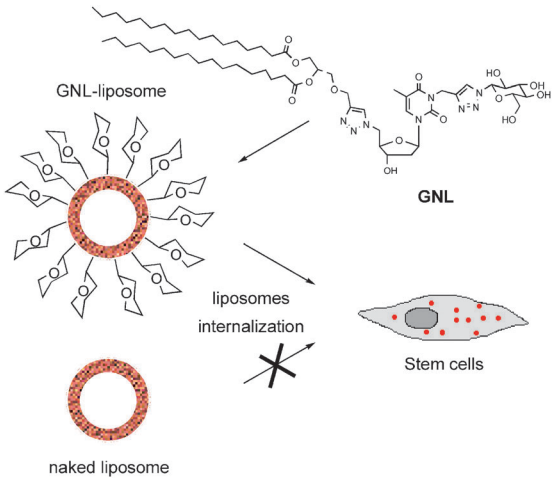

Fig. 1 Schematic representation of GNL, the sugar based liposomes formed by the GNL and the lecithin based liposomes. These GNL based liposomes are able to enter into human cells.

In the present study, we investigate the ability of a new double chain GNL to allow the internalization of liposomes into stem cells. The cellular uptake of GNL based liposomes was compared with both non-nucleoside glycosylated lipid (GL) and naked liposomes.

Connecting the three natural building blocks (lipid, nucleoside and sugar moieties) was performed using a double-click chemistry approach.[14] The preparation of **9** is illustrated in Scheme 1.

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