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Innovative vehicles for transdermal drug delivery

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The rational design of nanostructures to be used in drug delivery depends on the organ/tissue target, the route of administration and the type of therapeutic target. In this scenario, the achieved preclinical advances and future prospective on two main platforms intended for therapeutic and prophylactic purposes will be described.

The first platform encompasses the ultradeformable liposomes (UDL) and ultradeformable archaeosomes (UDA). The UDL are unilamellar vesicles of nearly 100 nm hydrodynamic diameters made of raw phospholipids plus a given proportion of surfactants (edge activators) such as sodium cholate, Tween 80, Spans. The UDA are made of phospholipids, edge activators and a given proportion of polar lipids extracted from hyperhalophile archaebacteria. Remarkably, the Young's module of ultradeformable vesicles is nearly 10 folds lower than that of a conventional vesicle, independently of its gel/liquid crystalline phase. Another main feature of UDL/UDA is that when applied in non occlusive conditions on the skin surface, their lipid matrix can penetrate the intact stratum corneum (SC) in the absence of conventional permeation enhancers. The penetration of UDL/UDA would not depend on diffusion (and therefore of a concentration gradient), but on the hydration gradient existing between the surface of the SC and the underlying viable epidermis. This enables the material accumulation in the deep epidermis, applying low material/application area doses and without disrupting the lipids of the intact SC. In our Nanomedicine Research Program (NRP) we have developed nanostructures made of sunlight-excitable hydrophobic Zn phtalocyanin loaded in LUD / AUD. The anti-muco-cutaneous leishmaniasis -an endemic disease from South America- caused by the protozoan Leishmania braziliensis/amazonensis, was tested both in vitro and in vivo on infected Balb-c mice. We also loaded antigen models in AUD and their adjuvant activity was tested after topical non occlusive application on Balb-c mice. In the first case, a significant reduction of the skin ulcer diameters was achieved after a short dose/short treatment. In the second case, a significant humoral and cellular systemic immune reaction was raised in the absence of visible inflammation.

The second platform are the polymeric core-shell tecto-dendrimers (TD), 87-90.000 Daltons, 12 nm hydrodynamic diameter nanoparticles prepared by the introduction of covalent linkages between a generation (G) 5 polyamidoamine (PAMAM) core dendrimer and a shell of G2,5 PAMAM anionic dendrimers. The main advantage of TD is that its chemical synthesis is far simpler that that of a conventional dendrimer of similar molecular weight and size. Ongoing research at the NRP has shown that in spite of the similar rate of uptake, the structural differences between TD and its closest dendrimer counterpart (G6,5 PAMAM) are important

enough to induce their selective uptake and further intracellular processing by target cells. On such bases, we have reported the in vitro anti-melanoma activity of TD G5G2,5. We have also designed protocols in order to load the anti-folate metothrexate (MTX) and the nitrogenated bisphosphonate zoledronic acid (ZOL) to the TG structure. We found not only that void TDG5G2,5 had selective cytotoxicity against SK-Mel 28 cells but also that such toxicity was increased for TDG5G2,5-MTX at non toxic concentrations for HaCat keratinocytes. The resulting TDG5G2,5-ZOL, on the other hand, were cytotoxic both on SK-Mel 28 and on HaCat cells. Deeper collaborative research is required to gain insights on the translational feasibility of these two nanomedical platforms as anti-infective/anti-tumoral agents.

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