NANOLIPOSOMES AS TOOLS FOR THE TREATMENT OF INFECTIOUS DISEASES

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Infectious diseases (ID) represent an immense global threat, being responsible for 15 million of deaths per year worldwide. The ID caused by intracellular microorganisms, such as *M. tuberculosis, Leishmania, M. avium* and *Plasmodium sp,* are very difficult to eradicate by the conventional therapies due to the low access of drugs to the sites of infection resulting in sub-therapeutic local drug concentration. Besides, severe side effects and poor compliance have been reported, being in the origin of pathogen resistant strains and treatment failure. Therefore non conventional strategies able to modify drugs behaviour and to improve their therapeutic index are needed. One of these strategies is the association of drugs to systems able to direct them to the sites of infection, namely macrophages, instead of using "naked" (free) drugs. Nanoliposomes are the ideal systems for this purpose as they have the tendency to accumulate in macrophages, together with the incorporated drugs. This capability was exploited for the treatment of tuberculosis, *M. avium* infections and leishmaniasis, with liposomes incorporating rifamycins, aminoglycosides and dinitroanilines, respectively.

We have developed different types of liposomes incorporating a rifamycin, Rifabutin (RFB) and tested in murine models of *M. tuberculosis* and *M. avium* infections. RFB incorporated in liposomes showed a superior therapeutic effect than the commercial antibiotic (free RFB) This effect has been observed either through the reduction on the number of viable colony forming units in liver, spleen and lungs as well as through histological and immunological studies [1,2].

Paromomycin (PRM) is an aminoglycoside indicated for treatment of mycobacteriosis and leishmaniasis. Biodistribution studies showed that the liposomal formulations of PRM were able to accumulate in appreciable amounts in liver, spleen and lungs, the infected organs of disseminated *M. tuberculosis* and *M. avium* , even 24 h after administration while the free PRM amounts are negletable The therapeutic effect of PRM liposomal formulations in a model of *M. avium* infections showed the superiority of these formulations over the free drug on reducing the bacterial loads in infected organs (Figure 1).These formulations are currently on test to evaluate the activity in *M. tuberculosis* and *Leishmania* models of infection.

Dinitroanilines are herbicides that showed antiparasitic properties, namely against different strains of *Leishmania in vitro*. Its use *in vivo*, namely by parenteral route, has been limited by inappropriate properties (low water solubility and instability). Liposomal formulations of dinitroanilines were developed with success, acting liposomes as drug solvent, as stabilizing system for their storage and as drugs carriers to the sites of infection (liver and spleen). The therapeutic activity of one dinitroaniline (Trifluralin) in liposomes was assayed in a murine visceral model (*L. donovani*) of infection. As shown in Figure 2 a significant reduction of parasite loads (up to 70%), after treatment with several liposomal formulations, in comparison with the free drug was observed. No signs of toxicity after dinitroaniline liposome treatment were observed [3]. These liposomal formulations also improved the clinical condition of dogs and reduced the density of parasites [4].

References:

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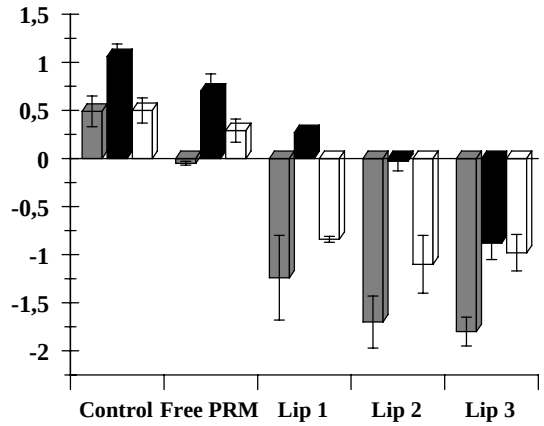

Figure 1 – Therapeutic effect of PRM formulations in a *M. avium* model of infection. Influence of lipid composition on growth index in liver (grey columns), spleen (black columns) and lungs (white columns). Studied formulations: Liposomes: Lip1 - DMPC:DMPG:DSPE-PEG, Lip2-DPPC:DPPG:DSPE-PEG Lip 3 - DPPC:DPPG, Free PRM (Control - infected and non-treated mice).

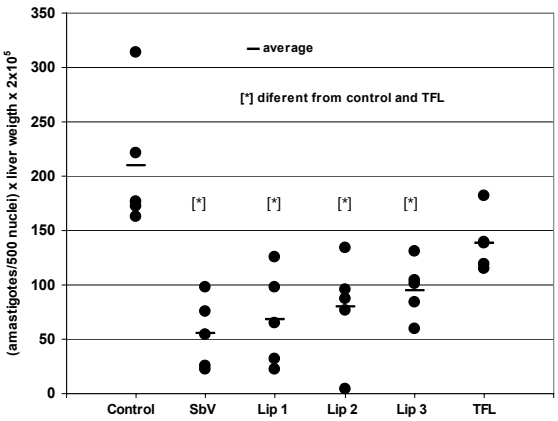

Figure 2 – Therapeutic effect of TFL liposomal formulations in a murine Visceral model of *L. donovani*. Mice received 5 doses of 15mg/kg (in five consecutive days) of three different TFL liposomes (Lip 1 = DOPC:DOPG (7:3); Lip 2 = DSPC:Chol (4:1) and Lip 3 = PC:PG (7:3), free TFL (dissolved in ethanol) and standard drug Glucantime (15 mg Sb^{v} /kg), by i.v. route. Negative control animals were injected with liposomes suspension medium (0.3 M trealose).

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