



Les Séminaires de l'IPBS

*IPBS, salle de conférence n° 1, niveau 2
Campus CNRS, 205 route de Narbonne - TOULOUSE*

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"Nanoemulsions, a potential targeted carrier for the treatment of severe diseases "

The demand for increased specificity of potent active agents to inaccessible pathological tissues has resulted in numerous therapeutic strategies, including the design of targeted delivery systems. Two different pharmaceutical approaches will be presented in this lecture regarding the strategy of enhancing the site-specific delivery of drug loaded nanoemulsions for either metastatic prostate cancer treatment or age-related macular degeneration (AMD) which is the most common cause of vision loss in the elderly in the western world.

Despite the accumulation in the target tumor tissue as a result of enhanced permeability and retention (EPR) effect due to the relatively leaky and immature vasculature of the tumor, nanocarriers cannot provide marked targeting unless specific ligands are attached to them. Thus, trastuzumab, an anti HER2 MAb, was coupled to nanoemulsions previously loaded with paclitaxel palmitate by a thioether bond resulting from the molecular interaction at the o/w interface of maleimide and free thiol groups of the cross-linker and MAb respectively. These immunoemulsions were comprehensively characterized in vitro. In addition, the efficiency of paclitaxel-palmitate loaded anti-HER2 immunoemulsions, was assessed in a well established in-vivo pharmacological model of metastatic prostate cancer which over-expresses the HER2 receptor. Although the tumor growth was not fully inhibited, the results were encouraging and might lead to an improved therapeutic strategy of metastatic prostate cancer treatment.

The second approach for enhancing the site-specific delivery is mediated by the cationic surface charge on the nanonanoemulsions. AMD is characterized by the appearance of drusen in the macula, accompanied by choroidal neovascularization (CNV). Anti-angiogenic antisense oligonucleotides (ODN) are considered important therapeutic macromolecules for treating AMD. However, ODN-based therapy is compromised by rapid degradation of ODN in biological fluids and by their inability to efficiently cross cellular membranes due to their hydrophilic and polyanionic character and large molecular structure. There is a need for ODN efficient delivery to intraocular tissues. For such a purpose, novel cationic nanoemulsions were designed with the ability to penetrate ocular tissues which are normally negatively charged.

Antisense oligonucleotides (ODNs) specific for VEGFR-2-(17 MER) and inhibiting HUVEC proliferation in-vitro were screened. One efficient sequence was selected and incorporated in different types of cationic nanoemulsions the potential toxicity of which was evaluated on HUVEC and ARPE19 cells. Our results showed that the cationic DOTAP nanoemulsion was non toxic on HUVEC and retinal cells. The kinetic results of fluorescent ODN (Hex) distribution in DOTAP nanoemulsion following intravitreal injection in the rat showed that the nanoemulsion penetrates all retinal cells. Pharmacokinetic and ocular tissue distribution of radioactive ODN following intravitreal injection in rabbits showed that the DOTAP nanoemulsion efficiently enhanced the intraretinal penetration of the ODNs up to the inner nuclear layer (INL) and yielded apparently therapeutic levels of ODN in the retina over 72 hours post injection.

The efficiency of the ODN nanoemulsion in a pharmacological corneal neovascularization rat model was assessed. High significant corneal neovascularization inhibition efficiency was elicited. The actual findings can lead to the design of a successful ODN delivery system that will provide, in the future, ophthalmologists with a useful potential therapeutic tool of clinical importance in the treatment of AMD.

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