Targeted Release of Drugs using Photolabile Groups and Photoactivatable Nanoparticles : Application to Neovascular Diseases of the Retina

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Résumé

Neovascular diseases of the retina represent a leading cause of blindness. They are characterized by an extensive proliferation of new permeable blood vessels, also called angiogenesis. The leakage of the permeable blood vessels can cause inflammation and at term affects the vision. Angiogenesis is the final common pathway of many retinal diseases such as age-related macular degeneration (AMD) and diabetic retinopathy (1),(2). Current therapies for the treatment of retinal pathologies are mainly based on strategies able to block the progress of neovascularization by inhibiting VEGF (vascular endothelial growth factor), a key player in pathological neovascularization (2). However, VEGF also has neuroprotective and neurotrophic effects on the retina (3). Consequently, the VEGF inhibition needs to be carefully balanced and targeted to the pathological regions.
Therefore, we want to introduce a new strategy based on a light activated version of VEGF inhibitor. The main advantage of light triggered therapy should be to precisely control a drug's activity, to minimize side effects and to increase the therapeutic efficiency. Unfortunately, light-based therapies for eye treatment are already described (2),(4) but are often invasive or not specific to the targeted cells, inducing undesirable side effects.

We propose the development of a novel therapeutic strategy for pathological neovascularization, characterized by superior spatial resolution. The idea is to administer an inactive, but light-activatable NPs into the bloodstream and subsequent photoactivation using light will liberate the VEGF inhibitor and potentially restrict anti-angiogenesis treatment to pathological regions.

In this project, we aim to develop light-activatable liposomes based on the concept of light induced permeabilization (5). The idea is to work with coumarin photolabile protecting group (PPG) to cage different lipid analogs. Two distinct strategies will be developed in parallel. In the first one, a blue sensitive coumarin derivative is going to be coupled with dioleoylphosphatidylethanolamine (DOPE), a phospholipid known to induce liposome destabilization (6). After liposomal formulation of the caged phospholipid analog and irradiation, it should lead to a liposomal permeation. The second strategy is a new concept, where a blue sensitive coumarin will be coupled to different fatty acids. Upon light irradiation, the

*Intervenant

resulting amphiphilic byproduct is expected to destabilize the liposomal membrane, leading to a permeation. To enhance the versatility of our lipid mimics, we propose to use a copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction to couple diverse hydrophilic moieties.

At term, the most promising candidate of this project should lead to a general application of light induced VEGFR inhibitor, allowing the incorporation of various drug types during liposome formulation.

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