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RNA &GENETHERAPY

National Center for Gene Therapy and Drugs based on RNA Technology

Cationic amphiphilic peptide-based delivery platforms for negatively charged active pharmaceutical ingredients including short interfering RNA

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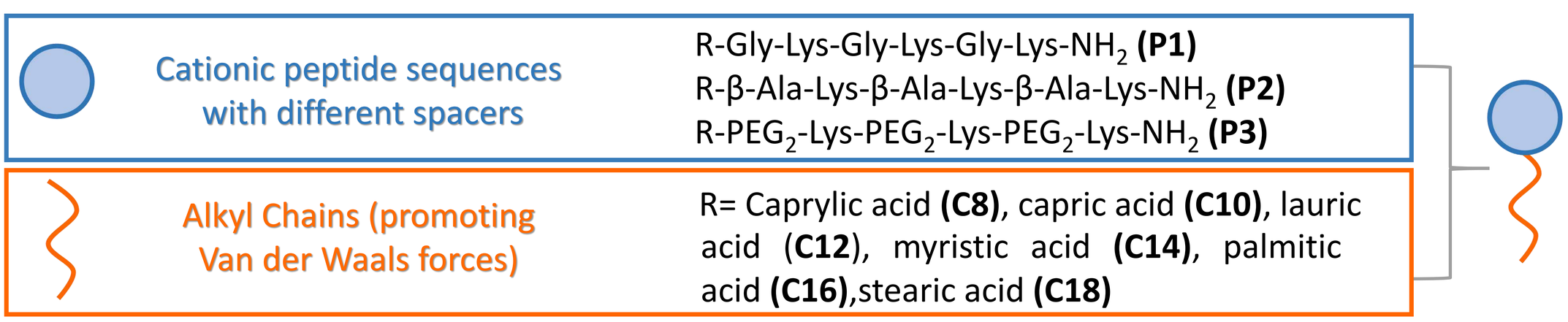
TOPIC: peptide materials

ABSTRACT

Peptide sequences have been recently proposed as suitable building blocks for the formulation of supramolecular aggregates that can be used to deliver diagnostic or therapeutic agents. The encapsulation of these active molecules into nanoparticles allows them to overcome some *in vivo* drawbacks (e.g. degradation, inability to cross barriers).[1] Positively charged nanoparticles, such as micelles or polymeric nanoparticles, have been proposed as suitable delivery carriers for RNA-based therapeutics.[2] Here we report the preparation of novel peptide based nanovectors as promising delivery systems for short interfering RNA (siRNA). We synthesized a **library of eighteen cationic lipopeptides** that were explored as charge modifier of peptide **gels** and **nanogels**.[3] In any case, the presence of a variable number of positive charges were exploited to favor **non-covalent electrostatic interactions** of model siRNA.

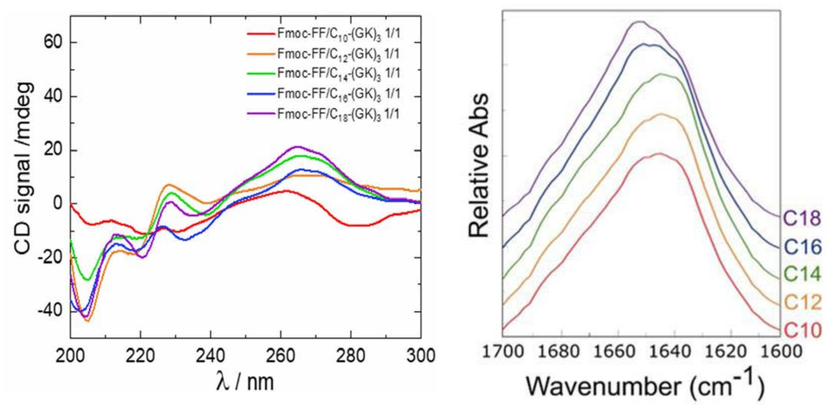


HYDROGELS

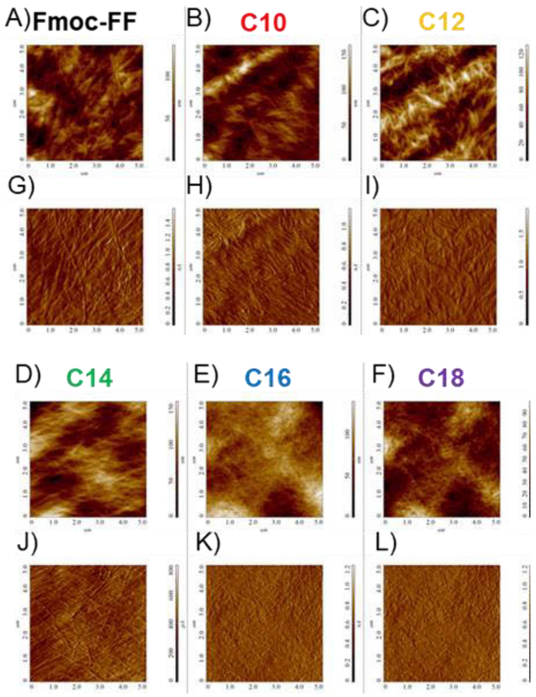
Mixed hydrogels were prepared using **DMSO/H_2O solvent-switch method**: a Fmoc-FF stock DMSO (100 mg mL^{-1}) solution was used to dissolve the cationic peptides. The mixed stock was then rehydrated with water and vortexed to ensure homogeneity of the sample. Secondary structural and topography characterization were performed via CD, FTIR and AFM. Gels were tested as reservoirs for 5-carboxyfluorescein (5-FAM).

Inverted test tube for Fmoc-FF/Cn-P1

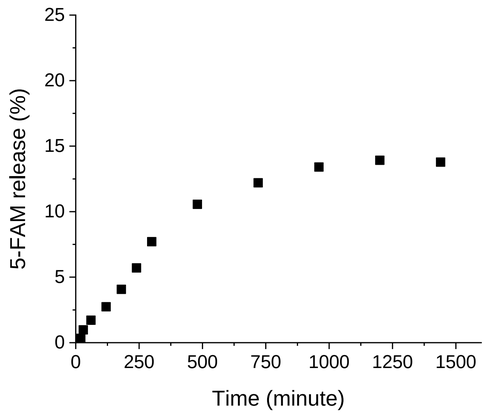
CD and FTIR of mixed HGs



AFM characterization

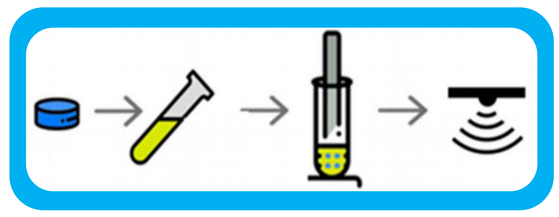


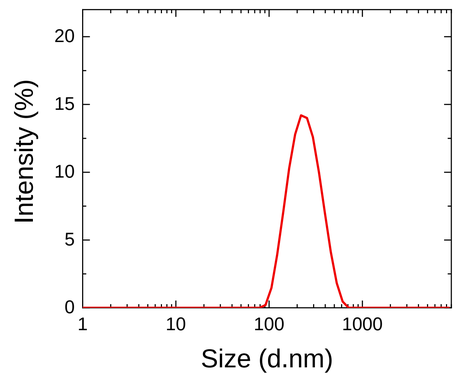
Encapsulation and release of 5-FAM overtime



NANOGELS

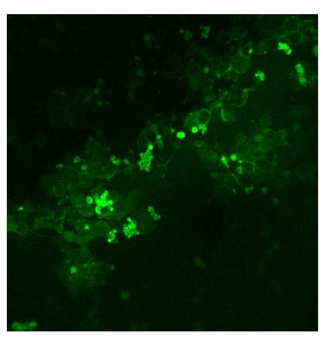
Nanogels were prepared using the **top-down** method: an aqueous filtered solution of TWEEN® 80/SPAN® 80 at a w/w ratio of 53/47 was added to the preformed hydrogels. The resulting suspensions were homogenized and tip sonicated.





Main diameter: 190 nm
ζ potential: +33 mV

Next step was the **encapsulation** of **siRNA** into NGs



The internalization of the obtained formulations into cells was estimated through **confocal microscopy**.

(1) R. Zhong et al, Nature Materials, 2023, 811-831. **(2)** J.A. Kulkarni et al, ACS Nano, 2018, 12, 4787-4795. **(3)** E.Rosa et al, Soft Matter, 2023, 19, 4686-4696.