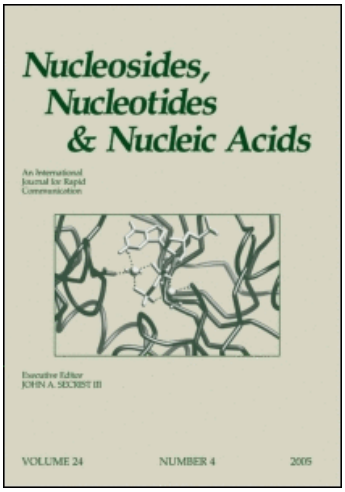

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Synthesis of Oligonucleotide-Peptide PEG-Conjugated: The EGG (Oligonucleotide)-Chicken (Peptide) Dilemma?

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ABSTRACT

The synthesis of a peptide-PEG-oligonucleotide chimera is compared when starting from the peptide or from the oligonucleotide sequence.

Key Words: Peptide; Oligonucleotide; Conjugate; Polyethylene glycol.

It is well known that the use of oligonucleotides as therapeutics is limited by their poor cellular uptake and low cellular distribution. A possible solution is a backbone modification that, however, could be toxic. A chemical conjugation can be alternatively investigated to maximise the recognition events demanded for an efficient delivery and to avoid heavy toxic effects. As new conjugating agents a wide choice of polymers has been proposed to improve binding to complementary target, hybridisation speed and nuclease resistance. Among the polymers, poly(ethylene glycol), or PEG, was recently adopted since it puts together peculiar synthetic advantages for the conjugation with an almost complete lack of toxicity and

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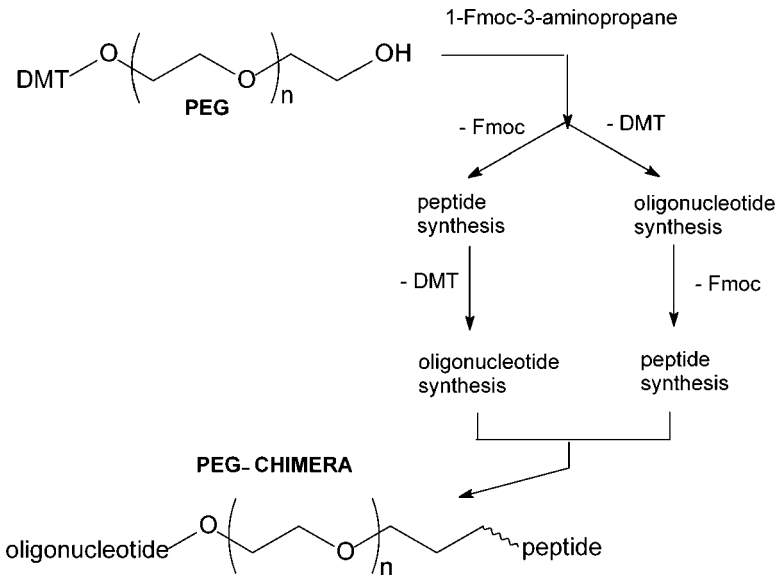

Figure 1. Scheme of the synthesis.

immunogenicity;[1] as a consequence, PEG is widely used as a linker in a wide series of bioconjugates.[2]

On the basis of our previous experience on the use of PEG as soluble support,[3] we decided to explore the synthesis of a mixed PEG-conjugates carrying on the same polymer an oligonucleotide, as eventually demanded for antisense applications, and a peptide sequence to specifically interact with cellular receptors, enhancing cellular recognition and absorption.[4] Recently, a new protocol for the liquid-phase synthesis of PEG-conjugates was reported,[5] taking advantage from a new procedure for the preparation of pure, selectively protected polydispersed PEG polymers.[6] Using the new selectively protected DMT-PEG-OH both as synthetic support as well as a conjugating moiety, two biopolymers, that is an oligonucleotide and a peptide, can be built up in two different orders on the same PEG chain, as depicted in the Fig. 1.

To decide for the better procedure we synthesized the same sample, a tetranucleotide-PEG-tripeptide, starting from the oligonucleotide, or from the peptide, respectively. The oligonucleotide was d(TACG), that is the simplest and shortest sequence made from all the four natural deoxyribonucleotides, while the peptide was Z-D-Phe-L-Phe-Gly, as the simplest sequence active toward receptors of the cell surface.[7] The two products were obtained in a quite high amount, with average yield values comparable to those of the classical solid-phase procedures. The two chimeras were purified by IE HPLC and characterized by ^{1}H NMR: the chromatographic and spectrographic patterns resulted almost super imposable and fully compatible with the expected compounds.

From the overall comparison of the two synthetic procedures applied to the sample sequences, it was not possible to decide which is the best procedure for the synthesis of these chimeras.

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Consequently, the classical dilemma, which came before, the egg (oligonucleotide) or the chicken (peptide), remains unanswered.

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