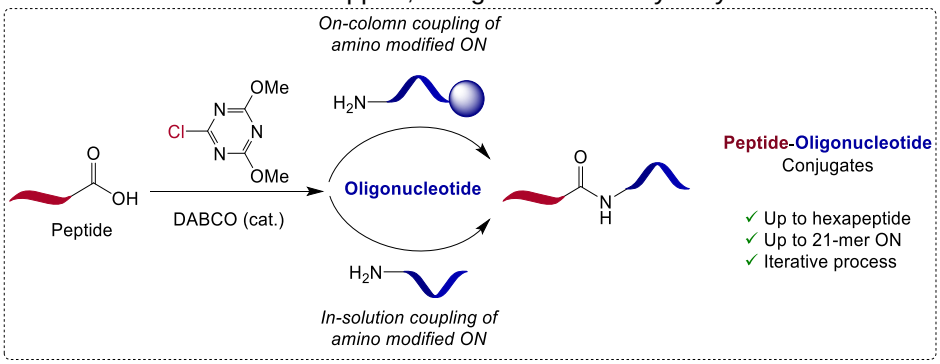
DEVELOPMENT OF PEPTIDE-OLIGONUCLEOTIDE CONJUGATES VIA A CATALYTIC AMIDE COUPLING APPROACH

Marion Gras, Pauline Adler, Michael Smietana
ChemBioNAC, IBMM, CNRS, University of Montpellier, ENSCM, Montpellier, France
marion.gras@etu.umontpellier.fr

Therapeutic oligonucleotides (ONs) are increasingly used for treating diseases often associated with undruggable proteins.[1] However, their effectiveness is limited due to poor cellular uptake, instability in biological fluids, and difficulties to reach the nucleus.[2] To overcome these issues peptide-oligonucleotide conjugates (POCs) have demonstrated their potential to improve the delivery and stability of these bioconjugates in antisense-, siRNAs-, and aptamers-based strategies.[3]
Amongst the numerous strategies to conjugate a peptide to ON fragments, the amide coupling remains one of the most widely used approach, as it mimics the peptide bond. However, forming amides requires large amounts of traditional activating agents such as HATU, DMTMM or EDC.[4] Moreover, there is no universal approach that ensures optimal coupling efficiencies between peptides and oligonucleotides substrates. The development of greener approaches for amide bond formation is therefore of high importance. In the course of our studies, we have developed a novel catalytic and sustainable method for the direct synthesis of amides from carboxylic acids and amines. This approach demonstrates excellent efficiency across a wide range of substrates, without causing epimerization of chiral stereocenters, and is applicable to solid-phase peptide synthesis (SPPS).[5]
Subsequently, this new approach was extended to the synthesis of peptide-oligonucleotide conjugates (POC).[6] In this context, we will present the results of our study dedicated to the synthesis of POC both in aqueous solution and on CPG solid support, using this new catalytic system.



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