Exploring D-peptides as a Nanovector for Nucleic Acid Delivery

Andrea Banfi[1], Lucia Salvioni[1], Biancamaria Petrucci[1], Davide Prosperi[1]

E-mail: a.banfi17@campus.unimib.it

[1] Università degli Studi Milano-Bicocca

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Abstract:

The development of efficient delivery systems for nucleic acid-based cancer therapies is an ongoing challenge. Lipid-based nanocarriers are widely used; however, they present limitations, including poor specificity, toxicity, and instability under physiological conditions. Peptide-based systems are emerging as promising alternatives due to their tunable properties. Nevertheless, their clinical application is hindered by susceptibility to proteases and limited stability.

In this study, we investigate the potential of D-peptides, protease-resistant synthetic peptides composed exclusively of D-amino acids, as nanovectors for nucleic acid delivery. Due to their inverted chirality, D-peptides demonstrate remarkable resistance to protease activity while retaining biological functionality. Among various constructs, we selected a promising sequence characterized by the presence of charged amino acids, which enable the complexation of negatively charged nucleic acids. Using both manual and automated synthesis methods, we produce nanoparticles, which were subsequently characterized in terms of size, cargo capacity, and biological capabilities. Finally, we evaluated their penetration and delivery efficiency in tumour cell models of interest.