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Dynamic combinatorial approach as synthetic strategy for the formation of non-viral vectors for gene therapy

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The next level in **Drug Discovery** is the easy building and self-generation of multifunctional nanostructures from commercially available or "easy to prepare" units, which will further self-assemble in a complex, tunable and multifunctional materials, suitable for very specific targeted drug delivery. Many functional platforms have been rationally designed with the hope of mimicking the complicated DNA histone machinery. However, DNA and target cells are highly variable and rational design is limited to a relatively small number of components and a high number of synthetic steps. One possible solution to this problem is to employ a dynamic screening approaches. In presented work adaptive dynamic vectors based on polyethylene glycol, cationic moiety components and in some cases squalene derivative, which are reversibly connected to core centres are prepared and tested as vectors for DNA transfection. Depending on their tuneable composition, these modular vectors dynamically self-adapt to their DNA targets, allowing the rapid screening of most effective vectors, optimally matched to DNA 3D surrounding space. Our strategy allows easy and efficient identification of adaptive vectors with high DNA complexation ability, good transfection efficiency, and well tolerated by mammalian cells. This work was supported by Horizon 2020 WIDESPREAD 2-2014: ERA Chairs Project no 667387 and a grant of the Romanian National Authority for Scientific Research and Innovation, CNCS/CCCDI – UEFISCDI, project number PN-III-P3-3.6-H2020- 2016-0011, within PNCDI III.

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