Bioinspired chemical evolution of nucleic acid nanomedicines

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It took five decades from first gene transfections to approval of gene therapies as medical drugs. Up to date, >2600 clinical gene therapy trials have been performed, 7 gene therapy products and 6 oligonucleotide drugs received market authorization. In Aug 2018 the FDA approved Patisiran as first siRNA drug. For optimization of precise synthetic carriers for the targeted drug and nucleic acid delivery, our strategy has been to learn from viruses and natural evolution. The process of a bioinspired chemical evolution includes (i) identification of chemical motifs active in specific delivery steps (such as artificial amino acids containing short aminoethylene repeats promoting endosomal escape), (ii) precise assembly of such motifs/micro-domains into defined sequences by automated or semi-manual solid phase-assisted synthesis, (iii) screening for a pre-defined delivery task and selection of top candidates, followed by (iv) random or educated variation and rearrangement into various topologies, providing feedback for a next round of selection. As will be outlined in this presentation, the selected type of cargo (natural products, proteins, therapeutic nucleic acids including pDNA, siRNA, miRNA, PMOs, mRNA, Cas9/sgRNA) directs the optimal motifs and sequences of carriers.

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