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Dynamic Nanocarriers for RNA Delivery and Genome Editing

Abstract: By end of 2024, 33 gene therapies and 35 RNA therapies are approved as medical drugs. Dynamic and targeted intracellular delivery of RNA still remains a key requirement. We focus on a bio-inspired chemical evolution strategy of delivery carriers. By incorporation of artificial amino acids such as tetraethylene pentamino succinic acid or lipo amino fatty acids (LAF) into xenopeptides (XPs), double pH-responsive nucleic acid carriers have been designed for potent intracellular delivery of mRNA in vitro and in vivo. Enhanced endosomal escape turned out to be a key factor for RNA delivery.

An pH-dependent polarity of LAF was implemented by a central tertiary amine, which disrupts the hydrophobic character once protonated, resulting in drastic pH-dependent change in the distribution from lipid phase (physiological pH 7.4) to lipid/water interface (endosomal pH 5.5). Unique dynamic ultrastructures assemblies are revealed by SAXS and molecular dynamics calculations. Activity was maintained even in full serum and at extremely low dosage of only ~2 nanoparticles/cell. Applications include mRNA expression in several organs upon systemic administration, in vivo gene silencing by siRNA-LNPs with superior activity in liver endothelial cells or, when including targeting ligand cRGDfk, in tumor endothelial cells. Furthermore, chemical evolution of lipo-XPs resulted in potent carriers for CRISPER mediated genome editing, either via Cas9 mRNA/sgRNA or Cas9 protein/sgRNA RNPs, triggering therapeutic genome editing of immune check-point genes in cancer or in vivo editing of dystrophin. Up to >50% homology directed repair (HDR) was obtained in cell cultures treated with Cas9/dsgRNA in combination with donor DNA template.

Keywords: Cas9, Genome Editing, LNP, mRNA, Nanoparticle, Polyplex

Biography: Prof. Ernst Wagner is Chair of Pharmaceutical Biotechnology, Department Pharmacy, LMU Munich (since 2001). He was Director Cancer Vaccines, Boehringer Ingelheim 1992-2001 (world-wide first polymer-based gene therapy in 1994), 1987-1995 Group Leader at IMP Vienna and Vienna University Biocenter, 1985-1987 postdoc at ETH Zurich, 1985 PhD (TU Vienna). He is Academician of European Academy of Sciences, Controlled Release Society (CRS) College of Fellows, Honorary Professor at U of Sichuan. He authored ≥ 524 publications, with ≥ 54 800 citations, h-index 117 (GS).