97. Polymeric Nanoparticle Platform Technologies

(SaxoCell)

Asset Overview

Product Type	Nanoparticle
Disease Area	Oncology
Indication	Pancreatic Cancer
Current Stage	Lead Optimization
Target	-
MoA	high complexation efficiency & improved biological KD efficiency
Brief Description	• Therapeutic gene silencing by RNA interference relies on the safe and efficient in vivo delivery of small interfering RNAs (siRNAs). Polyethylenimines are among the most studied cationic polymers for gene delivery. • For several reasons including superior tolerability, small linear PEIs would be preferable over branched PEIs, but inventors show poor siRNA complexation. Their chemical modification for siRNA formulation has not been extensively explored so far. • Inventors generated a set of small linear PEIs bearing tyrosine modifications (LPxY), leading to substantially enhanced siRNA delivery and knockdown efficacy in vitro in various cell lines, including hard-to-transfect cells. The tyrosine-modified linear 10 kDa PEI (LP10Y) is particularly powerful, associated with favorable physicochemical properties and very high biocompatibility. • Systemically administered LP10Y/siRNA complexes reveal antitumor effects in mouse xenograft and patient-derived xenograft (PDX) models, and their direct application into the brain achieves therapeutic inhibition of orthotopic glioma xenografts. LP10Y is particularly interesting for therapeutic siRNA delivery.
Intellectual Property	DE102020114183A1
Publication	Tyrosine-modified linear PEIs for highly efficacious and biocompatible siRNA delivery in vitro and in vivo. Nanomedicine: Nanotechnology, Biology and Medicine. (2021)
Inventors	Achim Aigner, Alexander Ewe, Michael Karimov

Highlights

- The tyrosine-modification addresses, and positively affects, three important parameters in parallel: the complex stability, which is markedly enhanced and now sufficient for siRNA delivery, cellular uptake, which benefits from enhanced interaction of the polymer with the cell membrane, and intracellular siRNA release into the right compartment as another key process for siRNA activity.
- Comparably large complexes (i.e., several hundred nm in diameter) still showed very profound transfection efficacy in vitro.
- Beyond the positive effects of tyrosine modification on physicochemical complex properties described here, leading to enhanced biological efficacy, complexes may further benefit in the in vivo situation.

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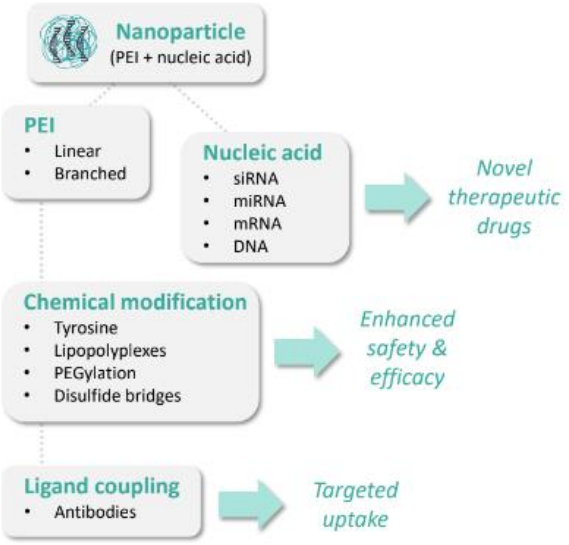
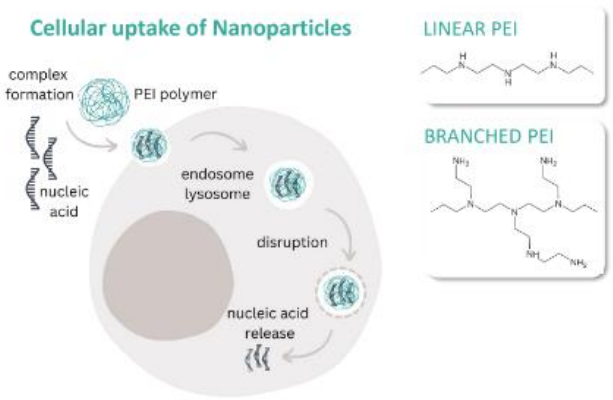
Key Data

Polymer-based Nanoparticles for the delivery of nucleic acids in vitro & in vivo

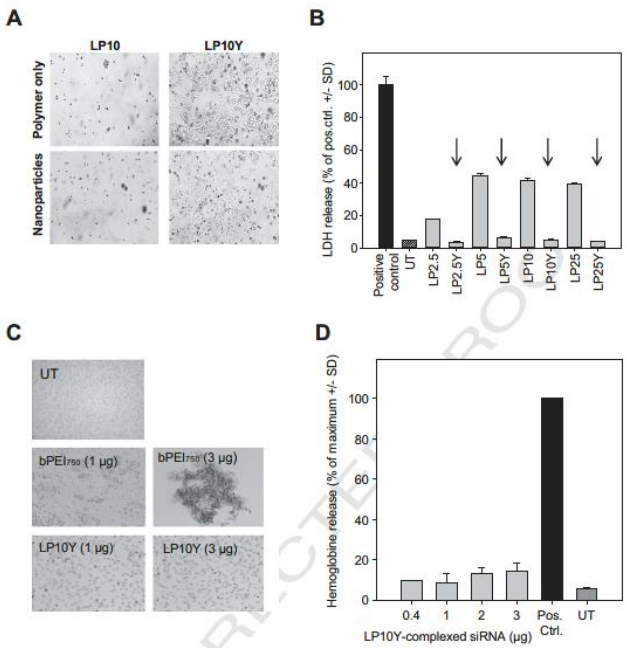




1. Nanoparticle formation - *Nucleic acids protected from degradation*
2. Cellular internalization - *Endocytosis*
3. Intracellular nanoparticle release - *Escape from the endo-/lysosome*
4. Release of nucleic acids - *at their site of action*

PEI = Polyethylenimine

Analysis of LP10Y/siRNA biocompatibility.



(A) Microscopic images of H441-luc cells 3 days after treatment with 10 kDa PEI or its tyrosine-modified derivative (upper panel), or the respective siRNA complexes derived thereof (lower panel). (B) LDH release assay for the assessment of cytotoxicity. H441-luc cells were transfected with complexes based on the various polymers and LDH levels were measured in the supernatant. Black bar: positive control (100% release); UT: untreated cells; arrows: complexes based onto tyrosine-modified PEIs. (C) Microscopic pictures from an erythrocyte aggregation assay after treatment with complexes as indicated. (D) Hemoglobin release from erythrocytes after treatment with LP10Y/siRNA complexes at various amounts. Black bar: positive control; UT: background level of untreated erythrocytes.