An alternative to viral vectors for Gene and Cell Therapies, *in vivo*-jetPEI®

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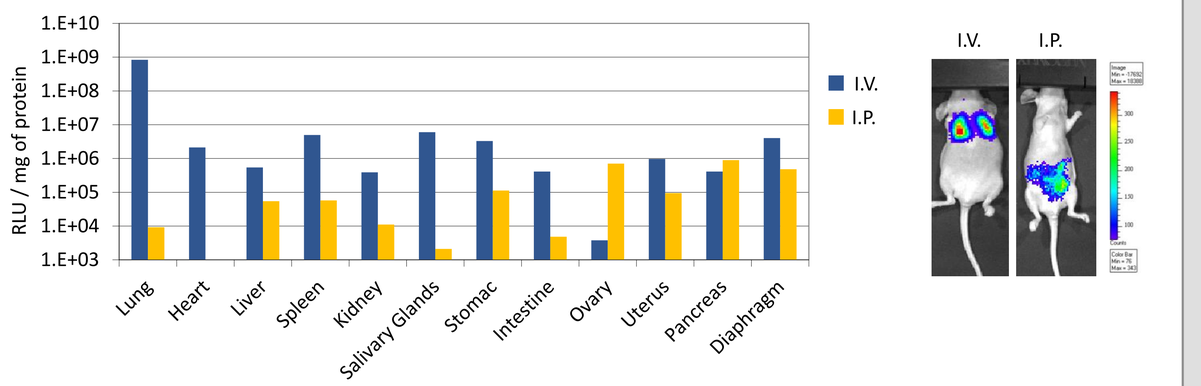
Abstract

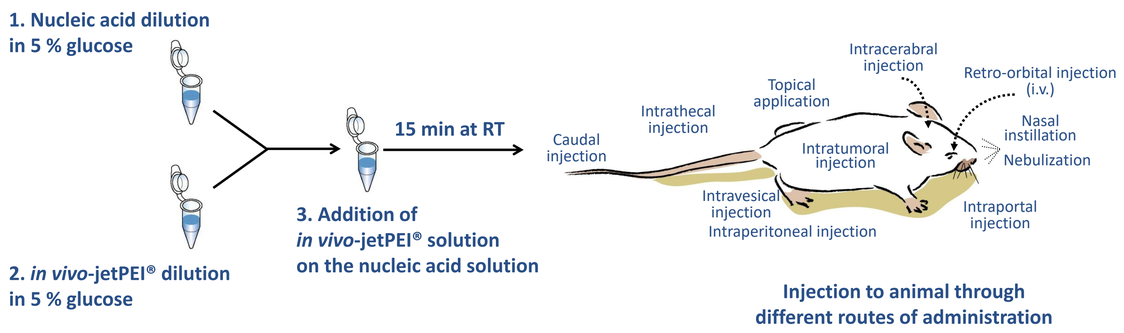
Advanced therapy medicinal products (ATMPs) including gene and cell therapy medicines have emerged as promising treatments for various diseases. These therapies involve the introduction of a therapeutic nucleic acid into the patient's body or patient's cells. *in vivo*-jetPEI®, a cationic polymer-based reagent, is a very powerful non-viral vector to safely and easily deliver nucleic acids *in vivo* to a wide range of tissues through various routes of administrations. *in vivo*-jetPEI® offers high performance in terms of efficiency, reproducibility and robustness. Following *in vivo*-jetPEI®-mediated systemic delivery of nucleic acid, no induction of major pro-inflammatory cytokines and no increase in sera levels of hepatic enzymes is observed, making it a reliable and safe alternative to viral vectors that can elicit an immune response. Nowadays, *in vivo*-jetPEI® is a widely used chemical reagent to deliver nucleic acids in animals and it has been selected as the delivery vector of choice in several drug development programs. To fulfill all the quality requirements associated to its use in Human, Polyplus-transfection® can supply preclinical grade as well as cGMP grade *in vivo*-jetPEI® reagents that are used worldwide for a growing number of preclinical studies and clinical trials based on plasmids or oligonucleotides delivery.

A wide variety of targeted organs depending on the administration route



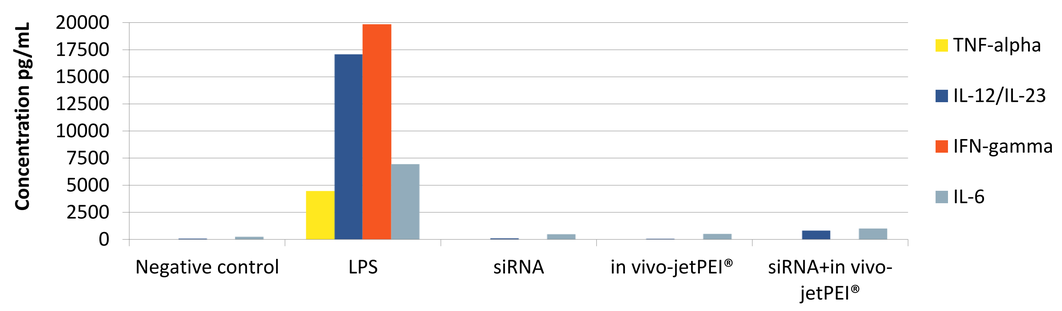
Complexes were formed using 40 µg or 100 µg of luciferase expressing plasmid and in vivo-jetPEI® at an N/P ratio of 8, in 200 µl or 1 ml of 5% glucose and injected either through retro-orbital sinus (IV) or intraperitoneally (IP), respectively. 24 hours after injection, different organs were extracted and luciferase expression was measured or live imaging was performed using IVIS system (Perkin Elmer).

Very easy to handle protocol



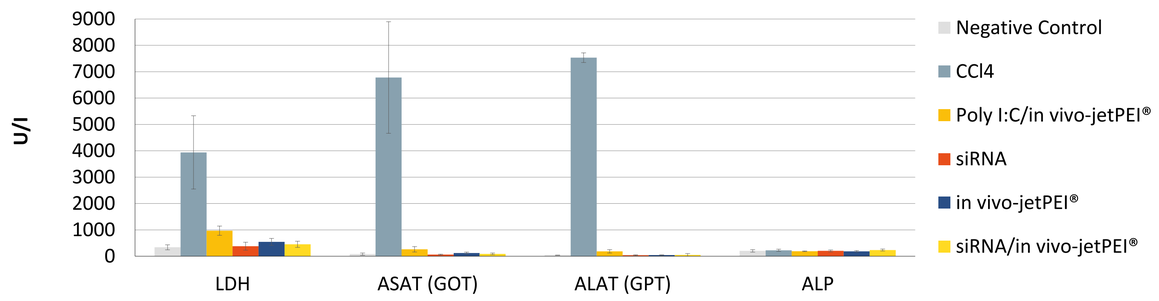
Safe method of delivery, with no major inflammatory response triggered

No pro-inflammatory cytokine expression



Complexes were formed in 200 µl of 5% glucose using 40 µg of luciferase siRNA with in vivo-jetPEI® at an N/P ratio of 8, and injected through retro-orbital sinus. 1 to 6 hours after injection, blood was collected and the level of TNF, IFN and IL-6 was measured by ELISA (n=8). As a positive control, LPS was injected intraperitoneally.

No induction of liver enzyme

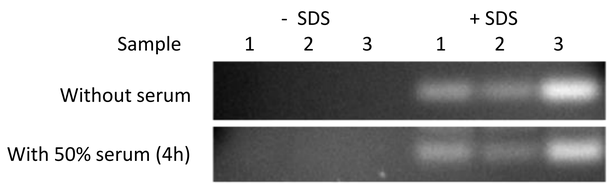


Complexes were formed in 200 µl of 5% glucose using 40 µg of luciferase expressing plasmid with in vivo-jetPEI® at an N/P ratio of 8, and injected through retro-orbital sinus. 24 hours after injection, blood was collected and the level of LDH, ASAT, ALAT and ALP was measured. Each value corresponds to the mean ± SD (n=8). As a positive control, CCl4 was subcutaneously administered.

Bonnet et al., 2008

High stability of complexes formed between nucleic acid and *in vivo*-jetPEI®

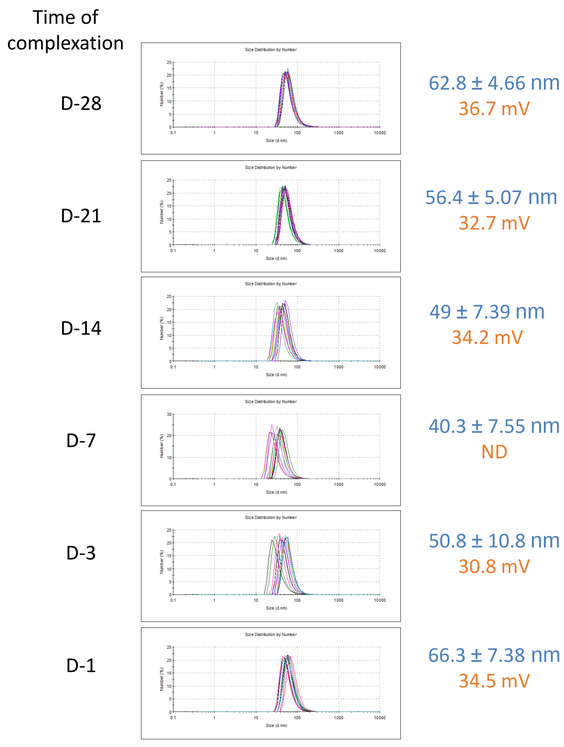
Complexes protect integrity of nucleic acids in presence of serum



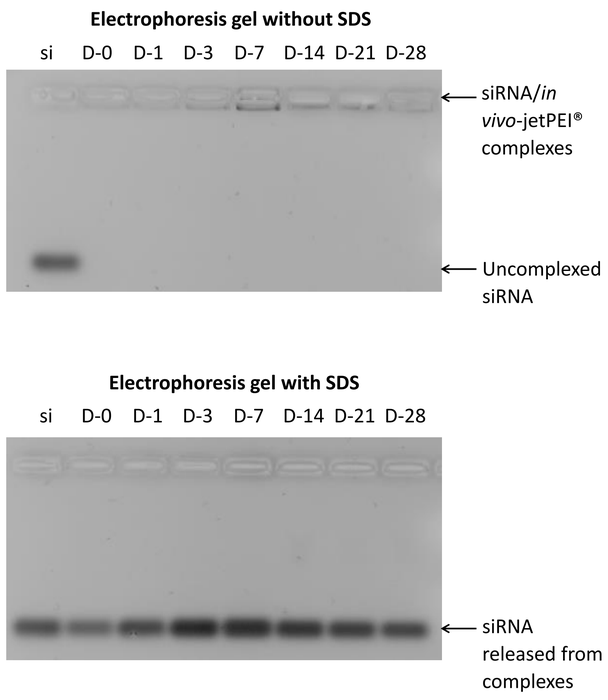
Complexes were formed at a constant N/P ratio of 8 and incubated for 4 hours at room temperature either in 5% glucose without serum or in 5% glucose with 50% of serum. After incubation, complexes were analyzed by gel electrophoresis (Left part), or treated with SDS to release siRNA from the complexes and then analyzed by gel electrophoresis (Right part).

Nucleic acid/in vivo-jetPEI® complexes are very stable over time

Size and charge of complexes over time

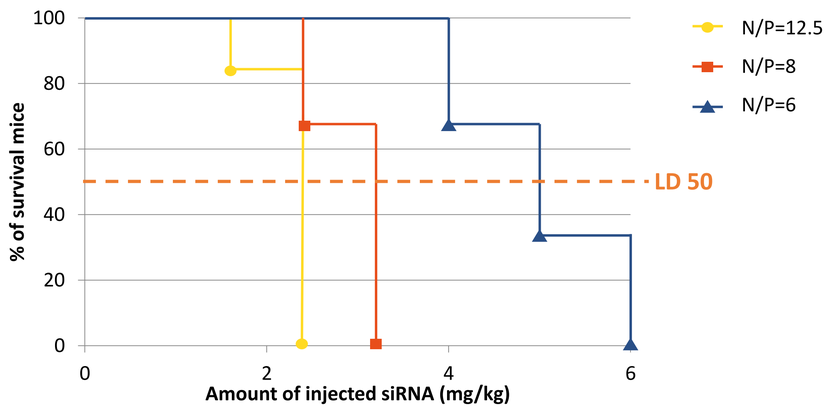


Integrity of nucleic acid over time



Complexes were formed at 200 µg/ml of siRNA and at an N/P of 8. Complexes size was measured by Dynamic Light Scattering and charge was measured using a zeta sizer after 1, 3, 7, 14, 21 and 28 days of incubation at 4°C (Left panel). After different times of incubation at 4°C, complexes were analyzed by gel electrophoresis with (Right panel, bottom part) or without SDS treatment to monitor siRNA integrity (Right panel, top part).

Dose response survival study of siRNA/*in vivo*-jetPEI® complexes



Mice were treated via intravenous injection with increasing amounts of siRNA delivered with in vivo-jetPEI® at an N/P ratio of 12.5, 8 and 6 (n=6 per group). Percentage of survival is represented depending on the amount of siRNA.

Bonnet et al., 2013

in vivo-jetPEI® for clinical trials in Human

- Manufacturing of *in vivo*-jetPEI® in compliance with US and EU **GMP guidelines** since 2007.
- Several clinical trials worldwide using *in vivo*-jetPEI® for the delivery in human of **different types of nucleic acids** (DNA, siRNA, oligonucleotides…) (Buscail et al., 2015; Sidi et al., 2008; Matouk et al., 2013).
- Different administration routes can be used, including **systemic delivery**
- Used in different applications such as in cancer therapy, immunization, modulation of blood-brain barrier.
- *in vivo*-jetPEI® mediated delivery of nucleic acids can be used as a treatment in **combination with chemotherapy.**
- One project entering **Phase III** in 2018.

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