2nd European CMT Specialists Conference
Antwerp, 23-25 October 2025

Poster P19

Efficacy of PLGA nanoparticles for Schwann cell targeted gene delivery

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The unique properties of nanoparticles (NPs) and their ability to cross blood-brain-barrier (BBB) make them an attractive vehicle for the treatment of neurological diseases. In our previous studies we showed that gene replacement delivered by adeno-associated viral (AAVs) vectors including AAV9 and AAVrh10 can partially rescue the demyelinating neuropathy in different models of Charcot-Marie-Tooth (CMT) disease. Although AAVs proved to be efficient, certain properties may limit their potential for clinical translation. These issues motivated us to develop a potentially safer and more targeted gene delivery approach for Schwann cells through the development of targeted NPs for the treatment of peripheral demyelinating neuropathies.

We created conjugated and non-conjugated PLGA NPs encapsulating a plasmid expressing the reporter gene EGFP driven by the Schwann cell specific myelin protein zero (MPZ) promoter. Targeting was achieved by conjugation of the NP to a tripeptide that has the ability to bind on a protein located on the abaxonal outer membrane of Schwann cells, in order to facilitate binding of the NP to the cell of interest. NPs were delivered in adult mice by lumbar intrathecal injection at the dose of 60 mg/kg. We examined possible toxicity in peripheral organs and EGFP expression in Schwann cells in PNS tissues including lumbar roots and sciatic nerves, comparing targeted to non-targeted NPs.

We detected EGFP in perinuclear cytoplasm of a subset of Schwann cells in lumbar roots and sciatic nerves but at low expression rates. Neither the conjugated nor the non-conjugated NPs resulted in any inflammatory responses in the peripheral tissues examined including the liver, indicating that this approach is safe.

In conclusion, we have developed a safe and promising approach for Schwann cell targeting to deliver gene therapies for demyelinating CMT neuropathies. Further optimization is needed in order to achieve higher expression rates in the cells of interest.

This work was co-funded by CMTA-MDA (MDA 952763), awarded to AK