MicroRNA-based gene therapy for Huntington's disease : Silencing the villain

Miniarikova, J.

LIST OF ABBREVIATIONS

3'UTR	3' untranslated region
AAV	adeno-associated virus
AD	Alzheimer's disease
Ago	Argonaute protein
BBB	blood brain barrier
CAG	cytomegalovirus immediate-early enhancer fused to chicken β-actin promoter
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
dsRNA	double-stranded DNA
gDNA	genomic DNA
GFAP	glial fibrillary acidic
GFP	green fluorescent protein
HD	Huntington's disease
HTT	huntingtin
ICV	intracerebroventricular
ITR	inverted terminal repeat
miRNA	microRNA
MRI	magnetic resonance imaging
NGS	next generation sequencing
NHP	nonhuman primate
Nt	nucleotide
ORF	open reading frame
pA	polyadenylation signal
PD	Parkinson's disease
PK/PD	pharmacokinetic/pharmacodynamic
polyQ	polyglutamine
pre-miRNA	precursor miRNA
pri-miRNA	primary precursor miRNA

qRT-PCR	quantitative real-time polymerase chain reaction
RNAi	RNA interference
RNAse H	ribonuclease H
RT-PCR	real-time polymerase chain reaction
shRNA	short hairpin RNA
siRNA	small interfering RNA
SNP	single nucleotide polymorphism
SOD1	superoxide dismutase 1
ss-siRNA	single-stranded silencing RNA
3'UTR	3' untranslated region

CURRICULUM VITAE

Jana Miniariková was born on 26-07-1988 in Bratislava, Slovakia. In 2003, she entered Bilingual High School Metodova in Bratislava, Slovakia with a focus on Natural Sciences. She graduated with a majority of subjects in French. In 2008, she started her bachelor studies in Biology at Comenius University in Bratislava, Slovakia. She graduated with a major in Genetics. During these studies, she lived one year in Málaga, Spain as an exchange student having all subjects thought in Spanish. In 2012, she moved to Rotterdam, Netherlands to study Molecular Medicine at Erasmus Medical Center Rotterdam. During her internship at the Department of Hematology, she investigated the biology of cellular microRNAs and their roles in hematologic malignancies. During these studies, she realized the clinical applicability of microRNAs to treat genetic disorders. In 2014, she pursued actions to translate the basic knowledge into a preclinical development as a doctoral researcher at Leiden University Medical Center, Leiden, Netherlands. The work described in this thesis was performed at uniQure, Amsterdam, Netherlands under a daily supervision of Dr. Pavlina Konstantinova and her promoter Prof. Dr. Sander J. van Deventer. In 2018, while approaching to her graduation date, she joined ttopstart, Utrecht, Netherlands. As a ttopstart consultant, she appreciates the opportunity to combine science, business, creativity and innovation, while reaching a wide audience. She yearns to work with the brightest mind to reinvent biotech and contribute to the society.

LIST OF PUBLICATIONS AND PATENTS

Martier, R, Liefhebber, J, Evers, MM, van der Zon, T, Snapper, J, **Miniarikova, J**, *et al.* MicroRNAs targeting C9ORF72 have the potential to reduce gain of toxicity in ALS and FTD patients. *Submitted to Mol. Ther. Nucleic Acids.*

Evers, MM, **Miniarikova, J**, Juhas, S, Vallès, A, Bohuslavova B, Juhasova, J, Kupcova, H *et al*. **(2018)**. AAV5-miHTT gene therapy demonstrates broad distribution and strong mutant huntingtin lowering in a Huntington's disease minipig model. *Mol. Ther.* ***26****(9):2163-2177.*

Miniarikova, J, Evers, MM and Konstantinova, P (**2018**). Translation of MicroRNA-Based Huntingtin-Lowering Therapies from Preclinical Studies to the Clinic. *Mol. Ther.* **26**: 947–962.

Miniarikova, J, Zimmer, V, Martier, R, Brouwers, CC, Pythoud, C, Richetin, K, *et al.* (**2017**). AAV5-miHTT gene therapy demonstrates suppression of mutant huntingtin aggregation and neuronal dysfunction in a rat model of Huntington's disease. *Gene Ther.* **24**: 630–639.

Cambon, K, Zimmer, V, Martineau, S, Gaillard, M, Jarrige, M, Bugi, A, **Miniarikova, J**, *et al.* (**2017**). Preclinical Evaluation of a Lentiviral Vector for Huntingtin Silencing. *Mol. Ther. Methods Clin. Dev.* **5**: 259–276.

Miniarikova, J, Zanella, I, Huseinovic, A, van der Zon, T, Hanemaaijer, E, Martier, R, et al. (**2016**). Design, Characterization, and Lead Selection of Therapeutic miRNAs Targeting Huntingtin for Development of Gene Therapy for Huntington's Disease. *Mol. Ther. Nucleic Acids* 5: e297. *Selected as 'the best of 2016' in the journal of Molecular Therapy: Family of Journals.*

Konstantinova P and **Miniarikova J**. RNAI INDUCED HUNTINGTIN GENE SUPRESSION. Patent filed on Dec 23, 2015. de 15817385.6-1401.

LIST OF PRESENTATIONS

2014 **NVGCT**, Lunteren, The Netherlands, Poster presentation
2014 **EHDN**, Barcelona, Spain, Poster presentation
2014 **ESGCT**, The Hague, The Netherlands, Poster presentation
2015 **ESGCT**, Helsinki, Finland, Oral presentation
2015 **OTS**, Leiden, The Netherlands, Poster presentation
2015 **HD Dutch Meeting**, Groningen, The Netherlands, Oral presentation
2016 **Small RNA meeting**, Keystone, CO, USA, Poster presentation
2016 **EHDN**, The Hague, The Netherlands, Poster presentation
2017 **CHDI**, St Julian's, Malta, Poster presentation

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