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Targeting for success: mechanistic insights into microRNA-based gene therapy for Huntington disease

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List of abbreviations

3'UTR	3' untranslated region
AAV	adeno-associated virus
AGO	argonaute protein
ASO	antisense oligonucleotide
ATXN	ataxin gene
BBB	blood brain barrier
CAG	cytomegalovirus immediate-early enhancer fused to chicken β -actin promoter
cDNA	complementary DNA
CED	convection-enhanced delivery
CMV	cytomegalovirus
CNS	central nervous system
CRISPR	clustered regularly interspaced short palindromic repeats
CSF	cerebrospinal fluid
CT	computed tomography
dsDNase	double-strand DNase
EV	extracellular vesicle
FDA	food and drug administration
FL-HTT	full length HTT
GAPDH	glyceraldehyde 3-phosphate dehydrogenase gene
gc	genome copies
gDNA	genomic DNA
GFAP	glial fibrillary acidic protein
GFP	green fluorescent protein
HD	Huntington disease
HTT	huntingtin
HTTex1	exon 1 HTT
iPSC	induced pluripotent stem cells
ITR	inverted terminal repeat



Appendix

MAP2	microtubule-associated protein 2
miATXN3	<i>ATXN3</i> targeting microRNA
MRI	magnetic resonance imaging
mHTT	mutant huntingtin protein
miHTT	<i>HTT</i> targeting microRNA
miRNA	microRNA
NFL	neurofilament light chain
NHP	nonhuman primate
PK	pharmacokinetic
PolyA	polyalanine
PolyQ	polyglutamine
Pre-miRNA	precursor miRNA
Pri-miRNA	primary miRNA
qPCR	quantitative real-time polymerase chain reaction
rAAV	recombinant AAV
RISC	RNA-induced silencing complex
RNAi	RNA interference
RT-qPCR	reverse transcription quantitative real-time PCR
SCA	spinocerebellar ataxia
SEC	size exclusion chromatography
shRNA	short hairpin RNA
siRNA	small interference RNA
SNP	single nucleotide polymorphism
tgHD	transgenic minipig model for HD
vDNA	vector DNA
VG	vector genome
wtHTT	wild-type HTT
ZFP	zinc finger protein



Curriculum vitae

Marina Sogorb Gonzalez was born on 7th July 1992 in Burgos, Spain, where she graduated at high school IES Comuneros de Castilla in 2010. After her graduation, she moved to Salamanca to initiate her bachelor studies in Biotechnology at University of Salamanca, Spain. In 2012-2013, she participated in the “Erasmus Program” as an exchange student in Comenius University, Bratislava, Slovakia. Her final thesis was under the supervision of Dr. Marina Holgado Madruga, where she performed a literature review titled “Optogenetics and its application”. It was during this time that she discovered her passion for the brain and translational research.

In 2014, Marina moved to the Netherlands, to study the master’s degree in Neuroscience at the Vrije Universiteit (VU) in Amsterdam, where she specialized in Clinical Neurosciences. Following her interest in the field of applied sciences, in 2016, she performed a one-year internship at the Research Department of uniQure B.V, Amsterdam, under the daily supervision of Dr. Jana Miniarikova and Dr. Pavlina Konstantinova. During this time, she was introduced to the field of Huntington disease and contributed to investigating miRNA-based gene therapies. In October 2017, Marina received her Master of Science degree with *Cum Laude* distinction.

With the goal to further contribute to the development of gene therapies for neurodegenerative diseases, in January 2018, she enrolled in a PhD position at Leiden University Medical Center (LUMC) under the supervision of Prof. Dr. Sander van Deventer, and funded by uniQure B.V. The experimental work presented in this thesis was performed at uniQure, Amsterdam, under the daily supervision of Dr. Melvin Evers. From 2018 to 2020, Marina investigated novel mechanisms of action of microRNA-based gene therapies relevant for the treatment of Huntington disease. She presented at numerous scientific conferences and contributed as a co-inventor in two patent applications regarding her work at uniQure.

In February 2021, while finalizing her doctoral studies, Marina started working as a Scientist Translational Biology at VectorY B.V, a recent gene therapy start-up based in Amsterdam. With the supervision of Dr. Pavlina Konstantinova, CSO at VectorY, and her promotor Prof. Dr. Sander van Deventer, she finalized writing this thesis and interpreting the results. At VectorY, Marina contributes to the *in vivo* studies and preclinical development of novel therapeutics with vectorized antibodies, applying her knowledge in the field while learning new challenges.

Marina is a creative, enthusiastic and proactive scientist with a great interest in neuroscience. She aims to contribute to the development of curative therapies for brain diseases.



List of first-author presentations

- 2018** HD Dutch Meeting, Amsterdam, The Netherlands. Poster presentation
- 2019** RNA & Oligonucleotide Therapeutics, Cold Spring, NY, USA. Oral presentation
- 2019** ASGCT, Washington, DC, USA. Poster presentation
- 2019** HD Dutch Meeting, Groningen, The Netherlands. Poster Presentation
- 2020** CHDI, Palm Springs, LA, USA. Poster presentation
- 2020** AAN, Virtual, Poster presentation
- 2020** ASGCT, Virtual, Poster presentation



List of publications

Morais R*, **Sogorb-Gonzalez M***, Bar C, Timmer NC, van der Bent ML, Wartel M, Vallès V. Functional intercellular transmission of miHTT via extracellular vesicles: an in vitro proof-of-mechanism study. *Cells* (2022); 11(17):2748. *These authors contributed equally to this work.

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Valles A*, Evers MM*, Stam A, **Sogorb-Gonzalez M**, Brouwers CC, Vendrell-Tornero C, Acar-Broekmans S, Paerels L, Klima J, Bohuslavova B, Pintauro R, Fodale V, Bresciani A, Liscak R, Urgosik D, Starek Z, Crha M, Blits, B, Petry H, Ellederova Z, Motlik J, van Deventer SJ, Konstantinova P. Widespread and sustained target engagement in Huntington s disease minipigs upon intrastriatal microRNA-based gene therapy. *Science Translational Medicine* (2021); 13(588). *These authors contributed equally to this work.

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Martier R, **Sogorb-Gonzalez M**, Stricker-Shaver J, Hübener-Schmid J, Keskin S, Klima J, Toonen LJ, Juhas S, Juhasova J, Ellederova Z, Motlik J, Haas E, van Deventer SJ, Konstantinova P, Nguyen HP, Evers MM. Development of an AAV-Based MicroRNA Gene Therapy to Treat Machado-Joseph Disease. *Molecular Therapeutics - Methods & Clinical Development* (2019); 15: 343–58.

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Patent applications

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Van Deventer SJH, Evers MM, **Sogorb-Gonzalez M**, Konstantinova PS, Valles-Sanchez A. Targeting mis-spliced transcripts in genetic disorders. WO-2021053018-A1. Patent filed by UniQure IP BV on September 16th, 2020.



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