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

MAP2	microtubule-associated protein 2
miATXN3	*ATXN3* targeting microRNA
MRI	magnetic resonance imaging
mHTT	mutant huntingtin protein
miHTT	*HTT* 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 chomatograohy
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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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**.

Acknowledgements

Ok, it's time to close this chapter. This PhD journey has been definitely challenging but above all, worthy. When I look back, I could have never imagined how much I would learn and grow in these years. It is indeed a character-building experience. After the first three years of excitement playing in the lab, hard work and falling in love with science, I took the decision to keep growing in my professional career and I embarked myself in a new project. It wasn't an easy decision to make and it added extra challenges to the final stages of this PhD journey. Nevertheless, here I am. And luckily, I didn't have to do it all alone. I would like to thank all the people who have accompanied me during this journey, contributing to my work, helping me grow or sharing fun moments together.

Dear **Sander,** thank you for always supporting my work and giving me the opportunity to share it with others, for your patience reminding me that I would one day finish and for standing up for me when I needed. Your knowledge is endless and your curiosity truly motivating. Most of the content in this thesis is thanks to your creative ideas which taught me to broaden my knowledge and think outside of the box. Also, thank you for organizing the best trip ever to Burgos.

Dear **Pavlina,** you have always challenged me, you made me GROW in capital letters. Thank you for always making time to critically review my work and giving me the most valuable feedback. I also appreciate that you also helped me making Amsterdam a home and trusted me with cute Cuppie. I wouldn't be here without your support and I am very grateful to keep sharing my scientific career with you.

Dear **Melvin,** I started this journey with you and I will always be grateful for your support. Thank you for your guidance, supporting my work and keeping up with my enthusiastic ideas. As a good team player, you were always looking for ways to enable collaborations and bring the projects further. Dear **Astrid**, thank you for your substantial contribution to this thesis. I am very grateful we got to work together in so many projects. Thank you for your advises and sharing your knowledge with me. I learned so much from you, both professionally and personally.

Dear **Carlos,** you were the most important person of this journey, my little brother. For sure I wouldn't be here without you. Your energy, your curiosity and your friendship made this journey much, much better. I learned a lot from you and I really enjoyed our brainstorm sessions together (Bamboooo forever). I have no doubt that you will do a great job in your PhD adventure and I hope to be part of it as well. And together with **Pablo**, thank you for bringing so much joy in my life, for taking care of me with the best meals and always making me laugh. Dear **Fanny,** my student and also my friend, I admired your motivation

and patience to learn. I had a lot of fun working with you and growing together. Thank you for your contribution to this thesis.

Dear **Jana**, my mentor, my flatmate, my friend, my "not-only love". I started this journey with you even before I knew that one day I would get here, when we were searching for exosomes in the exosomes! Thank you for building a strong scientific basis in me and for showing me that science is more fun when approached with lots of curiosity and also humor. I learned from you to have a global vision and the importance of creating a solid story, even with just few graphs of data. Thank you very much for helping me grow in all aspects of my life and for sharing so many moments together. And together with **Rudy** and **Kasia**, thank you for the sport sessions, fun moments and for always taking care of me when I needed.

Dear **Loreto,** so many years together and I feel so lucky to keep growing close to you. Thank you for always being there and for reminding me who I am when I get lost. Who would have told us that two biotech students would have gotten this far and survived in Dutch lands. Dear **Sanne** thank you for our fun Manguito&Mangon adventures, and for always being there as my friend. Thank you for your positive energy, your humor and for helping me make The Netherlands my home during these years. You became my family here and I will always be grateful for that. Dear **Gio**, also good things happened during covid times, thank you for your friendship and for the best advises during our sport sessions. Dear **Alessia**, friends at first sight. Thank you for your friendship, sweet hugs and best Italian recipes. I miss you. Dear **Carmen**, I am so happy you came into my life, and that it feels like we grew up together. Thank you for supporting me during the end of this journey, also as my paranymph and best organizer! Can't wait to share more moments together.

Dear **Sonay**, thank you for your positive energy, for teaching me the best tricks in the lab and for making the best shakshuka. Thank you for always being there, in the good and challenging times. I miss working with you. Dear **Cynthia,** thank you for your kindness and always being willing to help me and others. Thank you for your support as a colleague and as a friend during these years. Dear **Raygene**, thank you for your input and advises. I always learned a lot from your experience and our discussions together. I am happy that we keep working closely together. Dear **Kimberly**, I truly admire your perseverance and solid work. Thank you for your scientific input and helpful advises. Dear **Lisa**, we are so lucky to have you to support the research team with positive energy and dedication. Thank you for being always keen to help me. I admired you as a person and I am very thankful to have you as a friend. Dear **Giorgia, Furkan, Hendrina, Morgane, Anouk, Lieke, Roberto, Tom, Bas, Lodewijk, Vanessa, Ying Poi, Paula, Sumiati, Jolanda L., Lisa S., Anna, Iolanda, Ellen, Alise, Monique, Laura, Marsha, Kostas, IT dept, IP dept, uniQure runners,** and many more! You made my days in the lab and in the office much more fun. Moreover, it was very special for

me that most of you came to visit my hometown Burgos in Spain. Thank you for your infinite support and for keeping up with my enthusiasm all those years. I will always look back with fondness to those moments. To all **uniQurians**, I admire the work you do and your vision to develop therapies for patients. I am very proud of having being part of your achievements.

Dear **VectorYans**, your creativity and teamwork to build a start-up from scratch gave me a big push to finish this journey. Thank you for your trust, support and motivation. Thank you (not thank you) for keeping asking me about my thesis and becoming part of this adventure as well. Special thanks to **Wouter, Menno, Martino, Christina, Marco, Lisette, Barbara, Alies, Tony, Etsuko, Jolanda, Svetlana, Roland, Andreia, Linda, Farangis, Shilpita, Charlotte, Ruud, Sofia, Kwankwan, Melanie, Giulia, Rob, Saskia, Alexander**, and many more people that joined us on the way. I look forward to achieving great successes together and to deliver therapies for devastating neurodegenerative diseases.

I also would like to thank the scientific collaborators I had the opportunity to work with for their input and time. Special thanks to **Rienk Nieuwland** and his team for their technical input regarding isolation of extracellular vesicles; **Zdenka, Jan, Jiri, Helena** and **Stefan** from PIGMOD Centre (Libechov, Czech Republic) for being very welcoming hosts during my visits; **Sabine** and **Eric Reits** from Amsterdam UMC for opening their doors to me; **Nicholas Caron** from UBC (Vancouver, Canada), **Gillian Bates** and **Christian Landles** from UCL (London, UK) for performing experiments to detect HTT exon 1 protein.

My dear **friends from Spain,** thank you for showing me that friendship is not measured in km away, or months without seeing each other. Thank you for waiting for me with your arms open every time I come back, no matter how express my visits are. To my dear **salsa friends,** life is definitely much better dancing and I am very lucky I got to meet you during these years. Thank you for all the dances, hard trainings and fun trips. Recharging batteries is better with you.

Dear **Tiago**, I am so grateful you walked next to me during the last two years. Thank you for transforming difficulties into growth in such a peaceful manner. Your calmness, trust and love it's what help me to keep going with "one rabbit at a time". I truly admire your infinite curiosity and creativity, it's very unique and also contagious! We are definitely the coolest team and I can't wait to keep growing together.

A **mis padres**, **mi hermano**, **mi hermana, cuñados**, **sobrinos, tíos** y **abuelos**, gracias por educarme, por enseñarme vuestros valores humildes, por demostrarme que las cosas sólo se consiguen con esfuerzo. Sois y siempre seréis mi mayor admiración. Gracias por apoyarme en mis decisiones, por celebrar mis logros, y por esperarme con una comilona y miles de abrazos cuando vuelvo para veros. No es fácil teneros lejos tantos años pero siempre siento vuestro cariño muy muy cerca. Os quiero.