Therapeutic RNAi-based gene therapy for neurodegenerative disorders : slowing down the ticking clock

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List of abbreviations

AAT	alpha1-antitrypsin
AAV	adeno-associated virus
AD	Alzheimer's disease
AGO	argonaute
ALS	amyotrophic lateral sclerosis
ASOs	antisense oligonucleotides
ATXN	ataxin gene
BAC	bacterial artificial chromosome
BBB	blood brain barrier
C9orf72	chromosome 9 open reading frame 72
CA	Cornu Ammonis
CAG	cytomegalovirus immediate-early enhancer fused to chicken β-actin promoter
Cas9	CRISPR-associated system 9
CMV	cytomegalovirus
CRISPR	clustered regulatory interspaced short palindromic repeats
CSF	cerebrospinal fluid
DCN	deep cerebellar nuclei
DG	Dentate Gyrus
DM1	myotonic dystrophy type 1
DMD	Duchenne muscular dystrophy
DPRs	dipeptide repeat proteins
DRG	dorsal Root Ganglia
DSBs	DNA double strand breaks
EPO	erythropoietin
FISH	fluorescence in situ hybridization
FTD	frontotemporal dementia
FUS	fused in sarcoma
GA	glycine-alanine
gc	genome copies
GDNF	glial cell-derived neurotrophic factor
GFP	green fluorescent protein
GP	glycine-proline
GR	glycine-arginine
GS	GeneSwitch
HD	Huntington's disease
HDR	homology-directed repair
HP1α	heterochromatin protein 1α
HSV	herpes simplex virus

HTT	huntingtin gene
ICV	intracerebroventricular
IFN	interferon
IGF	Insulin-like growth factor
iPSC	induced-pluripotent stem cells
Istr	Intrastriatal
IT	intrathecal
ITH	intrathalamic
ITRs	inverted terminal repeats
IV	intravenously
Kb	kilobase
Luc	luciferase
MBNL1	muscleblind-like 1
MFP	mifepristone
mi*ATXN3*	*ATXN3* targeting microRNA
miC	*C9orf72* targeting microRNA
miR-451a or miR-451	microRNA-451a
miRNA	microRNA
MJD	Machado-Joseph disease
mRNA	messenger RNA
NGS	next generation sequencing
NHEJ	nonhomologous end-joining
NHP	nonhuman primate
Nt	nucleotide
PA	proline-alanine
PARN	poly(A)-specific ribonuclease
PD	Parkinson's disease
piRNAs	piwi-interacting RNAs
polyA	polyalanine
PolyQ	polyglutamine
PR	proline-arginine
pre-miRNA	precursor microRNA
pri-miRNA	primary microRNA
rAAV	recombinant adeno-associated virus
RAN	translation repeat-associated non-ATG translation
RISC	RNAi-induced silencing complex
RNAi	RNA interference
RNAse H	ribonuclease H
RT-PCR	real-time polymerase chain reaction
RT-qPCR	quantitative real-time polymerase chain reaction

rtTA	transactivator-protein
SCA	spinocerebellar ataxia
shRNA	short hairpin RNA
siRNA	small interfering RNA
SMA	spinal muscular atrophy
SMN	survival motor neuron
SN	substantia nigra
SNP	single nucleotide polymorphism
SNpc	SN pars compacta
SNrc	pars recticulata
SOD1	superoxide dismutase1
TALENs	transcription activator-like effector nucleases
TARDBP	transactive response DNA-binding protein of 43 kDa
TDP-43	transactive response DNA-binding protein 43
UIM	ubiquitin-interacting motifs
UTR	untranslated region
VTA	Ventral Tegmental Area
ZFNs	zinc-finger nucleases

List of publications

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Curriculum Vitae

Raygene Martier was born on 11-02-1987 in Willemstad, Curaçao. In 2005 he graduated from high school Maria Immaculata Lyceum, Curaçao with a focus on natural sciences. After his graduation, he moved to the Netherlands and started the Bachelor study Biotechnology at Van Hall Larenstein en Noordelijke Hoge School Leeuwarden. During his Bachelor studies he did two different internships. The first internship was under supervision of Dr. Johanna (Hannie) Westra at the University Medical Center Groningen, department of Rheumatology and Clinical Immunology where he studied the role of Hypoxia Inducible Factor-1α in patients with rheumatoid arthritis. The second internship was under supervision of Dr. Jeroen Guikema at the University of Massachusetts Medical School, Department of Molecular Genetics and Microbiology (USA) where he studied the role of the DNA repair protein Ataxia Telangiestacta Mutated Kinase in intrachromosomal recombination of the immunoglobulin heavy chain genes. In the second half year of this internship he also studied the function of the enzyme Activation Induced Cytidine Deaminase. He obtained his bachelor degree in 2009 with a major in Biomedical Sciences.

In 2011 he enrolled in the master program Biomolecular Sciences at VU University (Vrije Universiteit) Amsterdam where he also did two internships. The first master internship was under supervision of Prof. Ewa Snaar-Jagalska at the Institute of Biology Leiden (IBL), department of Molecular cell Biology. Here he studied the immune response of ewing sarcoma implants/engrafts in zebrafish and also gained experience in generation of zebrafish transgenic lines. His last internship was at Crucell (Johnson & Johnson) in Leiden where he worked on the development of Hepatitis A virus micro neutralization assay under supervision of Dr. Amanda Versteilen. He obtained his master degree in 2013 with majors in Molecular Biology and Biological Chemistry.

In 2013, he joined uniQure as a Research Technician in the New Therapeutic Target Discovery department under supervision of Dr. Pavlina Konstantinova. He worked on the development of regulated gene expression systems for gene therapy. He also had a supporting role in various other preclinical studies within the company, focusing on the development of microRNA-based and gene replacement gene therapies to treat genetic disorders. In 2015, he started his PhD at Leiden University. The work described in his thesis was performed at uniQure under daily supervision of Dr. Pavlina Konstantinova and his promoter Prof. Sander van Deventer. Besides his scientific work, he had the opportunity to work closely together with uniQure's IP department where he became fascinated about the importance of a strong IP portfolio for the economic value of the company. In January 2019, he started as Junior Scientist and IP support at uniQure and in October 2019 he joined Vereenigde Octrooibureaux (V.O) as trainee patent attorney in the section life sciences.

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