Development of VO659 a CAG repeat targeting ASO in development for PolyQ diseases

Scott Schobel, MD, MSc
Chief Medical Officer, VICO Therapeutics

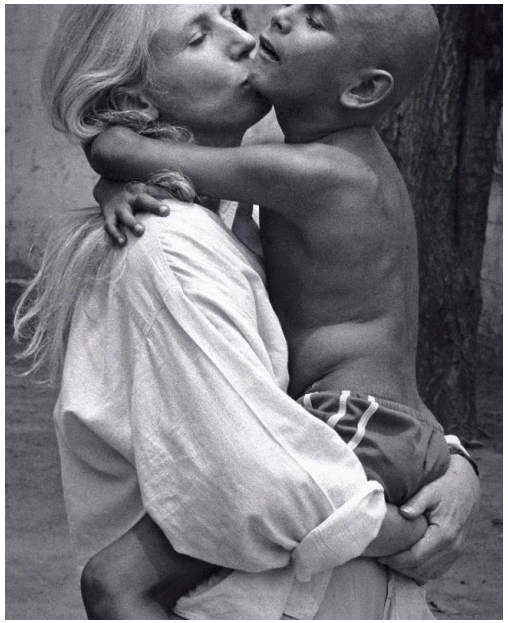
AGI Conference presentation

November 5, 2022

VICO Therapeutics®

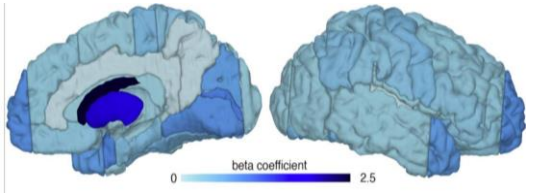
SCA1, SCA3, and HD – monogenic, fatal neurodegenerative diseases with no cure

- **SCA1, SCA3 and HD are caused by CAG repeat expansion** mutations in the *ATXN1*, *ATXN3,* and *HTT* genes, respectively
  - CAG repeat expansion causes **toxic gain-of-function in mutated protein** resulting in neuronal cell death
  - Prevalence of diseases[1-3] **~0.5-1/10,000 in HD and ~1-5/100,000 in SCA** in America/Europe; with 'flip' ratio of HD/SCA prevalence in East Asia/China
    - **At risk population** is estimated as 2-3 fold larger
  - **Onset is in the prime of life** with relentless motor, cognitive, and functional decline
- HD targets the cortex and striatum, whereas SCA1 and SCA3 target the brain stem, spinal cord and cerebellum
- **No disease modifying therapies are available** for SCA1, SCA3, or HD with high unmet need and early mortality
  - The need in children with a high repeat expansion burden and aggressive disease course is extreme



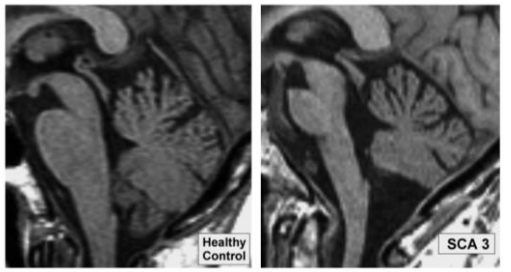
Nancy Wexler, individual with HD gene & pioneer of HD gene discovery, Venezuela project

HD targets the cortex and striatum



Johnson et al 2020

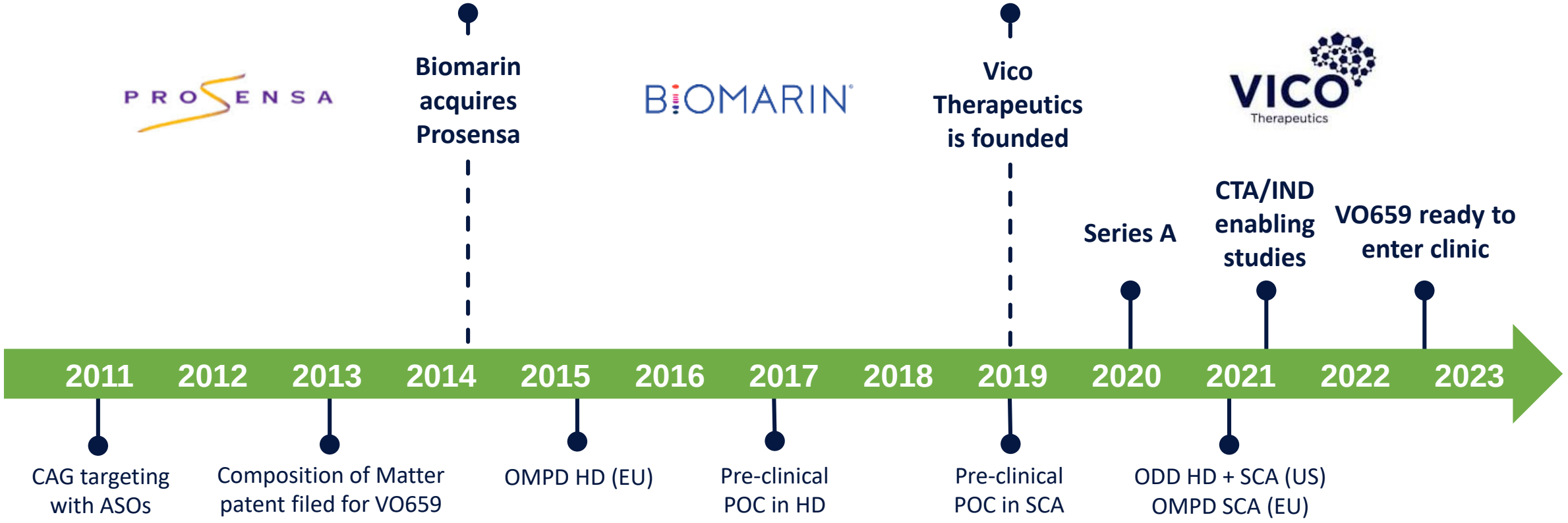
SCA: differential targeting of cerebellum & brain stem



Eichler et al 2011

1 - Ruano et al, Neuroepidemiology 2014;42:174–183 2 – Huntington's disease Society of America 3 – European Huntington's disease Network

V0659 is a CAG repeat targeting ASO ready to enter the clinic for SCA1, SCA3, and HD

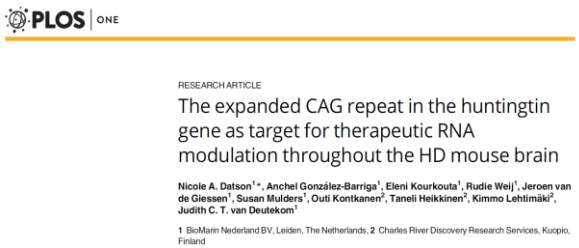



OPEN ACCESS Freely available online PLoS one

Targeting Several CAG Expansion Diseases by a Single Antisense Oligonucleotide

Melvin M. Evers[1], Barry A. Pepers[1], Judith C. T. van Deutekom[2], Susan A. M. Mulders[2], Johan T. den Dunnen[1,3], Annemieke Aartsma-Rus[1], Gert-Jan B. van Ommen[1], Willeke M. C. van Roon-Mom[1]*

1 Center for Human and Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands, 2 Prosensa Therapeutics B.V., Leiden, The Netherlands, 3 Leiden Genome Technology Center, Leiden University Medical Center, Leiden, The Netherlands

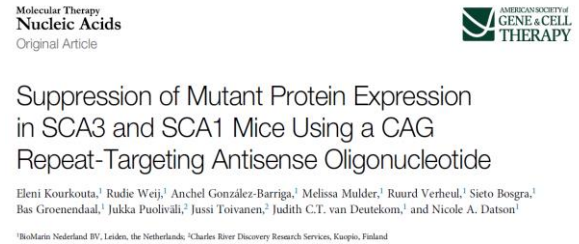

PLOS ONE

RESEARCH ARTICLE

The expanded CAG repeat in the huntingtin gene as target for therapeutic RNA modulation throughout the HD mouse brain

Nicole A. Datson[1]*, Anchel González-Barriga[1], Eleni Kourkouta[1], Rudie Weij[1], Jeroen van de Giessen[1], Susan Mulders[1], Outi Kontkanen[2], Taneli Heikkinen[2], Kimmo Lehtimäki[2], Judith C. T. van Deutekom[1]

1 BioMarin Nederland BV, Leiden, The Netherlands, 2 Charles River Discovery Research Services, Kuopio, Finland


Molecular Therapy Nucleic Acids

Original Article

AMERICAN SOCIETY of GENE & CELL THERAPY

Suppression of Mutant Protein Expression in SCA3 and SCA1 Mice Using a CAG Repeat-Targeting Antisense Oligonucleotide

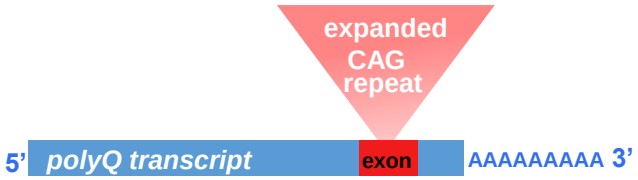
Eleni Kourkouta,[1] Rudie Weij,[1] Anchel González-Barriga,[1] Melissa Mulder,[1] Ruurd Verheul,[1] Sieto Bosgra,[1] Bas Groenendaal,[1] Jukka Puoliväli,[2] Jussi Toivanen,[2] Judith C.T. van Deutekom,[1] and Nicole A. Datson[1]

[1]BioMarin Nederland BV, Leiden, the Netherlands; [2]Charles River Discovery Research Services, Kuopio, Finland

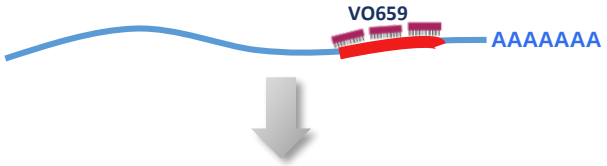
VICO Therapeutics

VO659 has two mechanisms of action: Inhibition of translation (SCA1/HD) and splicing (SCA3)

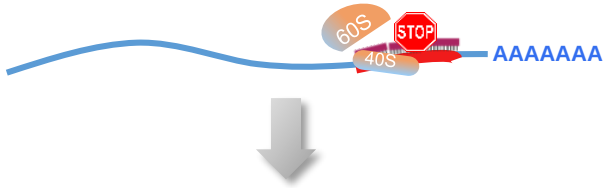
Inhibit Translation
Huntington's disease and SCA1



- VO659 binds to CAG repeat in mutant (pre)mRNA

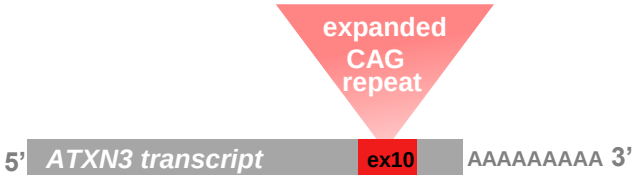


- steric hindrance of mutant polyQ protein synthesis

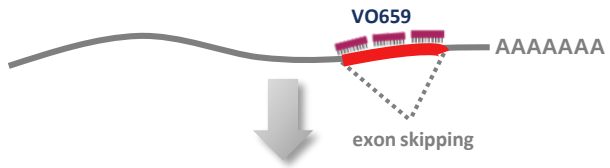


- reduced levels of mutant polyQ protein

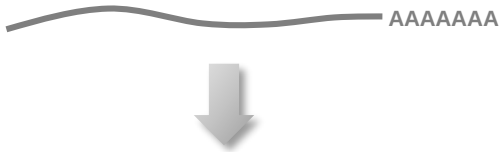
Splicing
SCA3



- VO659 binds to CAG repeat in mutant pre-mRNA



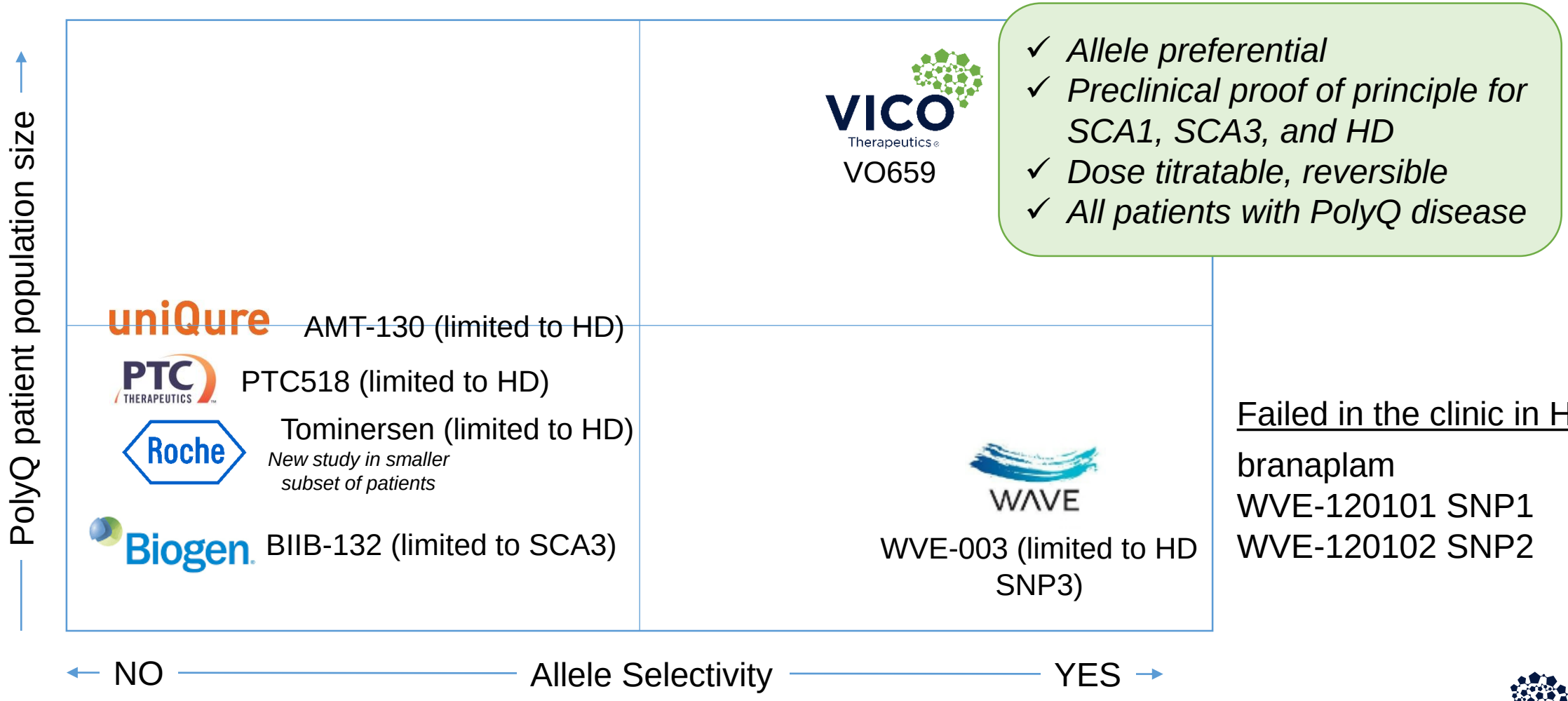
- mRNA lacking expanded polyQ region



- truncated ATXN3 protein (ΔpolyQ isoform)
- reduced levels of full length mutant ATXN3 protein

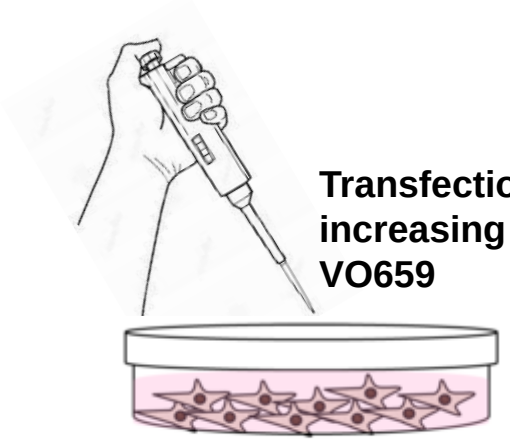
VICO Therapeutics®

VO659's allele-preferential MOA can be used in all people with PolyQ diseases regardless of individual genetic background



Clinical stage RNA therapeutic strategies being developed for HD and SCA3

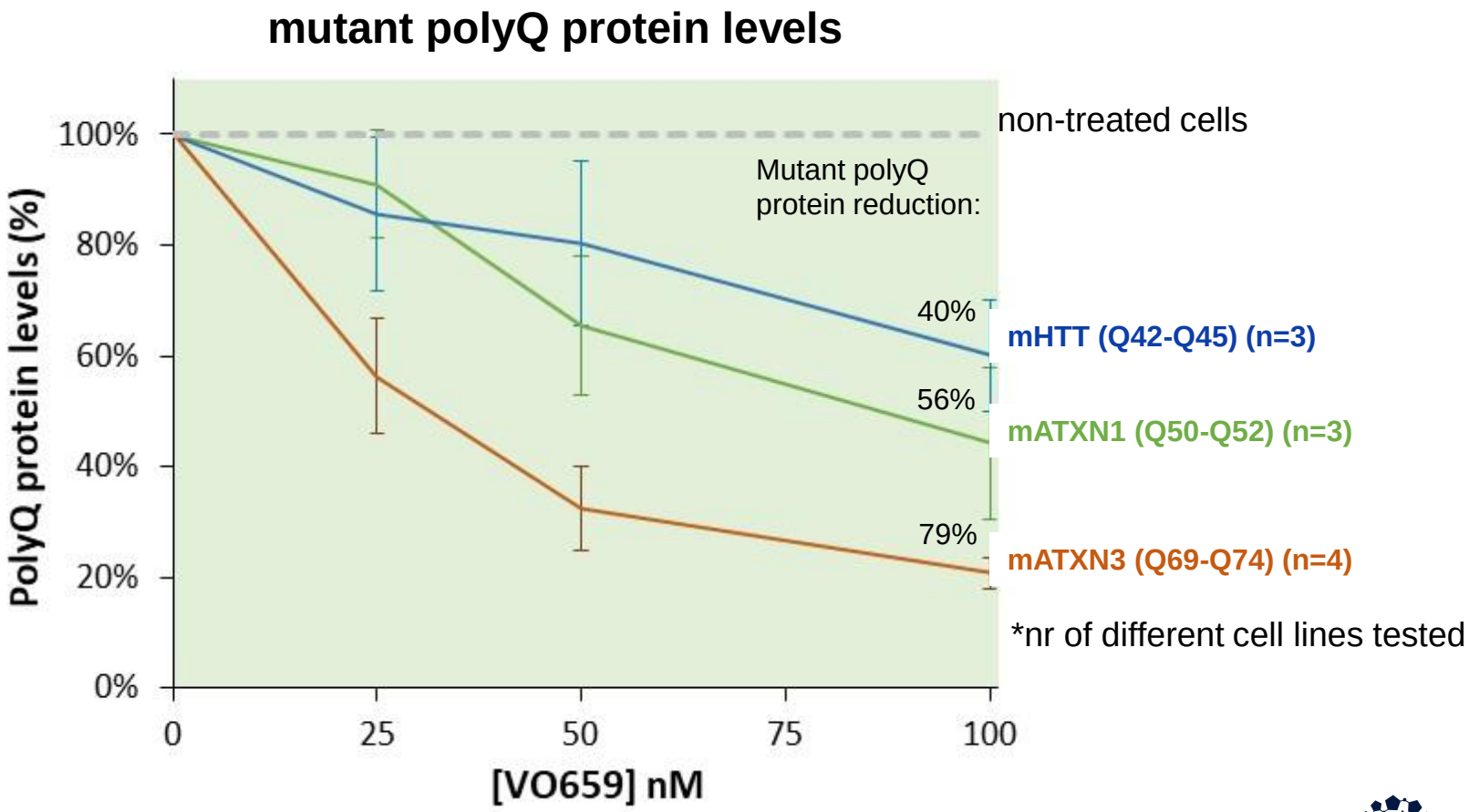
VO659 significantly reduces mutant ATXN1, ATXN3 and HTT protein levels in patient fibroblasts



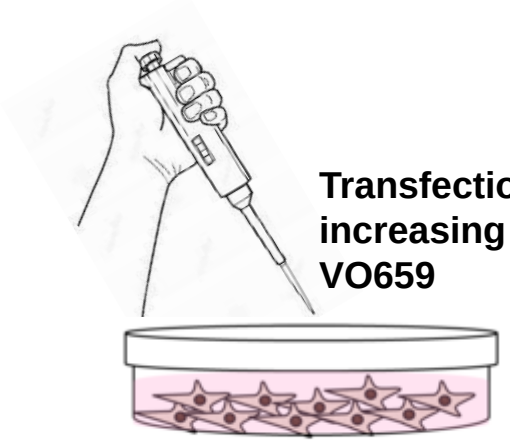
Transfection with increasing amount of VO659

HD, SCA1 and SCA3 patient fibroblasts

- Cells harvested at t=96 hrs after transfection
- Protein lysates subjected to capillary Wes analysis to quantify HTT protein levels



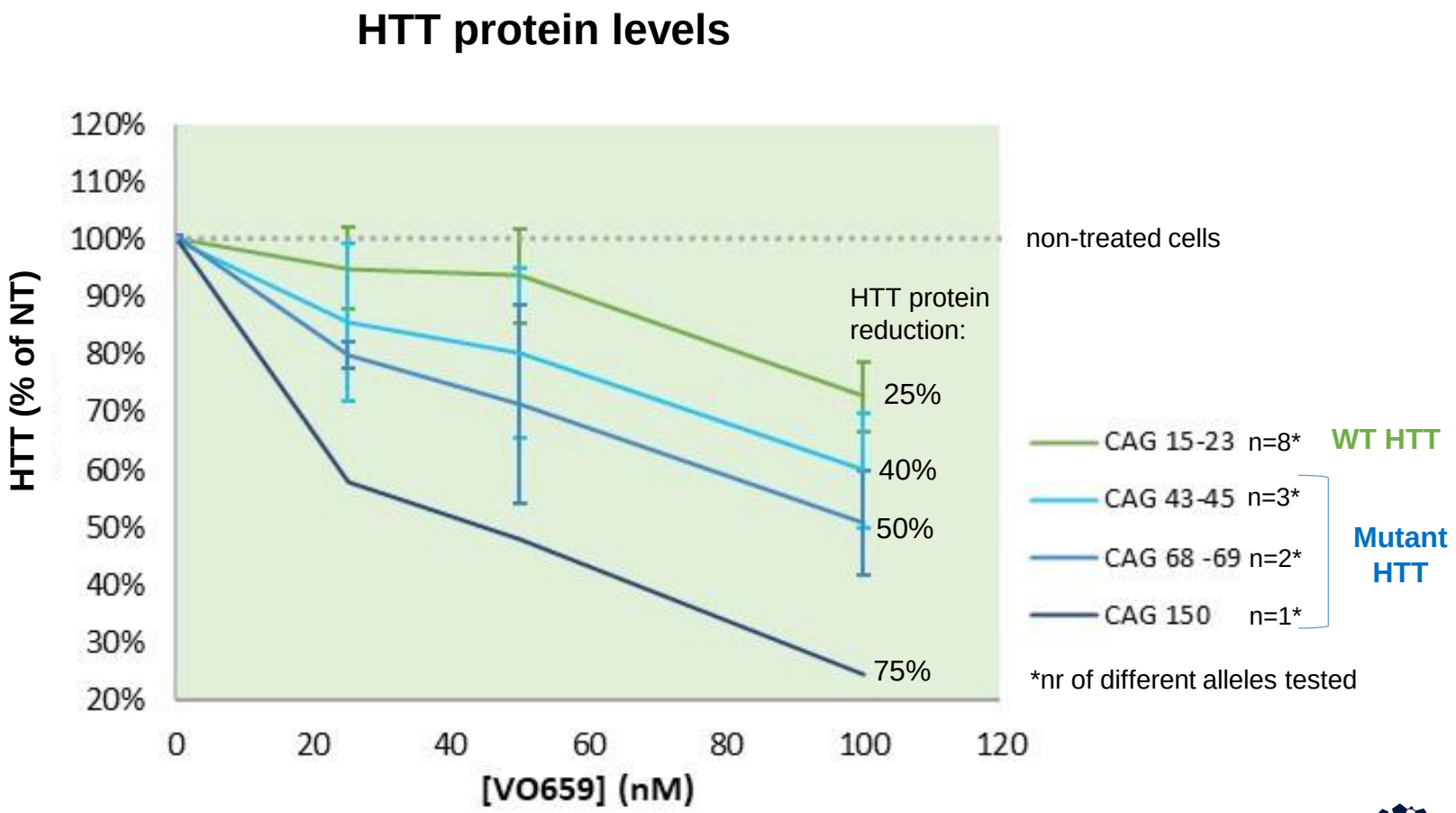
VO659 reduces mutant HTT protein levels in an allele-preferential and CAG repeat length dependent manner



Transfection with increasing amount of VO659

HD patient fibroblasts

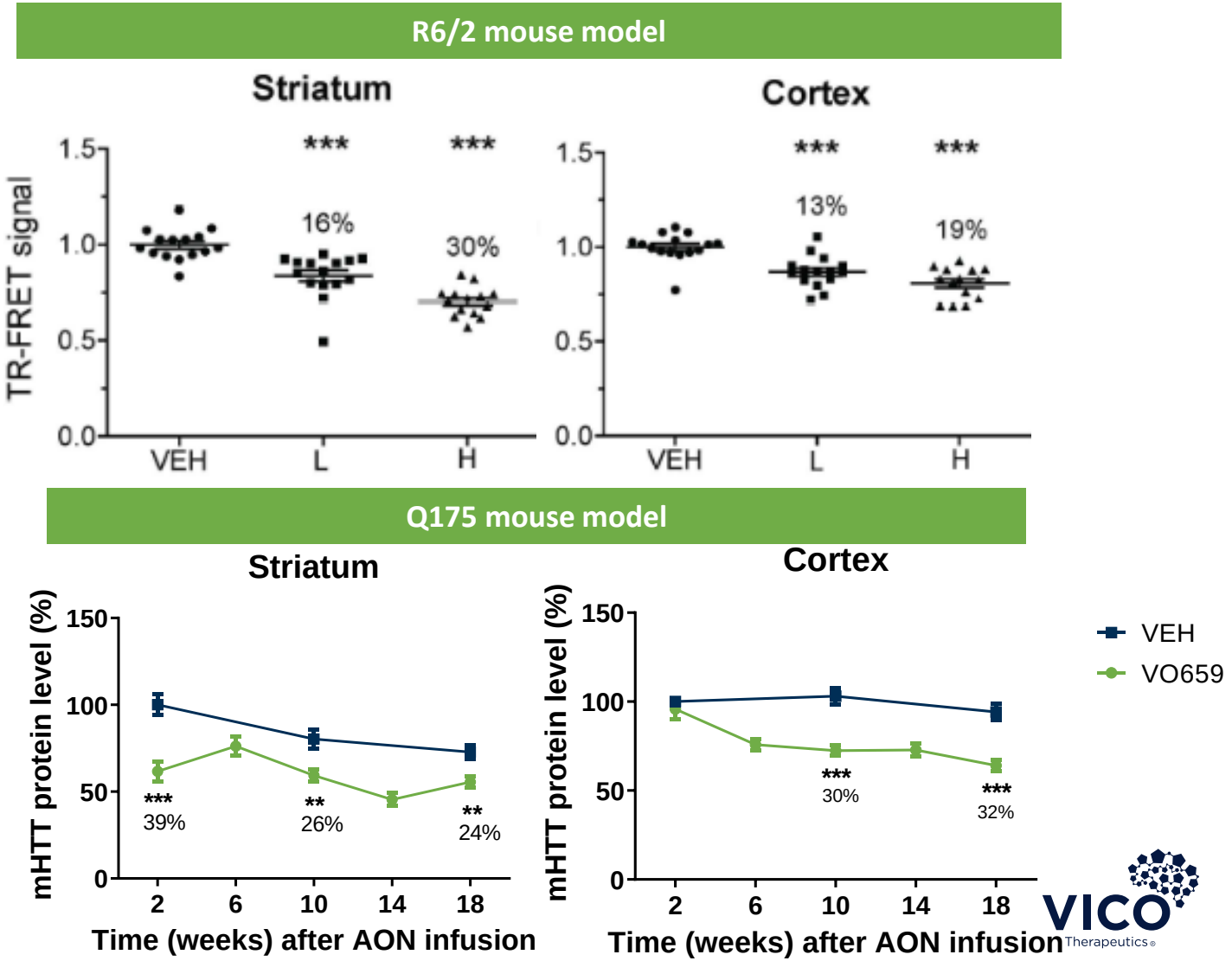
- Cells harvested at t=96 hrs after transfection
- Protein lysates subjected to capillary Wes analysis to quantify HTT protein levels



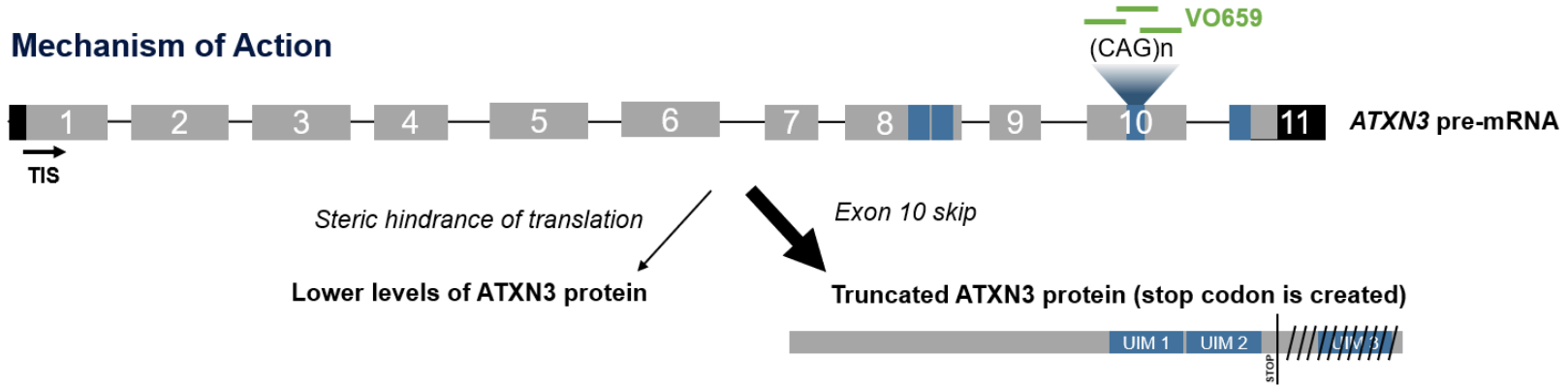
Data obtained in 6 different HD and 1 healthy control cell line

In vivo proof of concept in HD: Significant reduction of mutant HTT protein levels in R6/2 and Q175 models

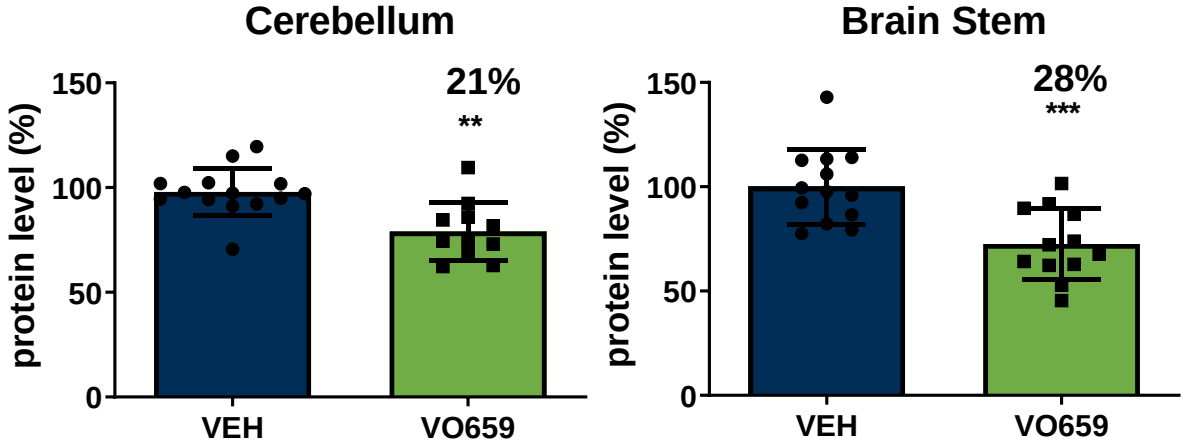
- **Mutant HTT protein levels are significantly reduced in two in-vivo models of HD with VO659 exposure, providing in-vivo proof of steric hindrance mechanism**
- **Levels are still significantly reduced in striatum and cortex 18 weeks post-last-injection when measured in Q175 model, suggesting potent and long-lived PK/PD effect**



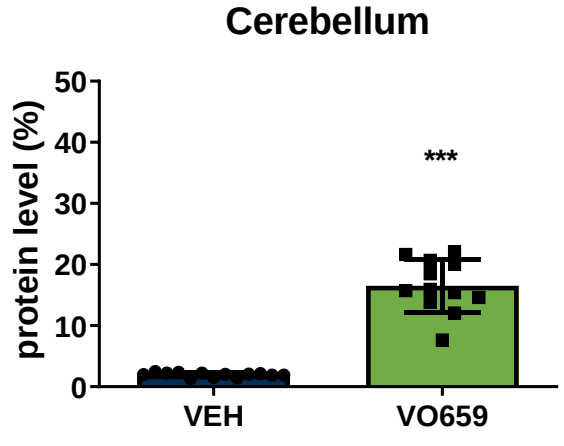
VO659 reduces mutant ATXN3 protein and generates functional ΔpolyQ ATXN3 isoform via exon 10 skipping

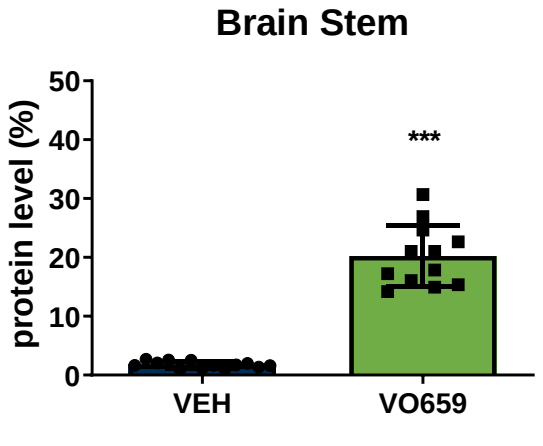


Mutant ATXN3 protein levels



ΔpolyQ ATXN3 isoform levels





Kourkouta et al 2019

Repeated IT dosing of VO659 is well tolerated in NHPs

- Repeated administrations of VO659 via intrathecal injection in a 13-week GLP toxicology study was well tolerated by cynomolgus monkeys
  - Findings are well characterized, non-adverse, and described in the literature for AONs
  - No observed adverse effect level (NOAEL) permits testing in humans across a dose range that is anticipated to be pharmacologically active
- Clinical study is in planning and start-up phase with first patient anticipated in early 2023 timeframe

VICO Therapeutics®

Zooming out to the VICO pipeline: novel RNA modulators for genetic neurological disorders

Product / Disease	Target	Approach	Discovery	Non clinical	Phase 1/2	Pivotal
VO659 – Huntington's disease	CAG repeat expansion	Inhibit translation				
VO659 – SCA1	CAG repeat expansion	Inhibit translation				
VO659 – SCA3	CAG repeat expansion	Splicing				
Rett Syndrome	Mecp2-R255X	RNA editing				
Familial Alzheimer's disease (FAD)	PSEN1	Degradation				
Undisclosed		Activation				

VICO Therapeutics

Summary: VO659 and the journey ahead

- ✓ **VO659 is differentiated with best-in-class potential for Poly-Q diseases**
  - ✓ First clinical-stage new molecular entity targeting CAG repeat underlying the cause of disease pathogenesis in all PolyQ diseases
  - ✓ Proof of concept *in vitro* and *in vivo* established for SCA1, SCA3, and HD
  - ✓ Large animal safety studies supportive of first in human study across a dose range that is anticipated to be pharmacologically active
- ✓ **We are relentlessly focused on monogenic neurodegenerative diseases,** taking lessons learned from the field forward in ASO development
  - ✓ Approach pursues highest unmet need areas first, with clinical urgency
- ✓ **A large thanks and warm hello to the investigator and patient community. We look forward to robust collaboration on the VO659 program and beyond**

VICO Therapeutics®

VICO Therapeutics®