VectorY THERAPEUTICS

Precision targeted therapies for neurodegenerative diseases

Pavlina Konstantinova, CSO

DHDRN presentation

23 January 2023

VectorY is developing innovative technology platforms

PRECISION PROTEIN TARGETING AND DEGRADATION

VecTab

Vectorized transformative antibodies

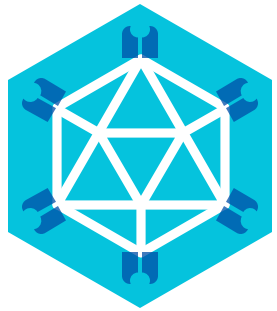
Targeted binding of disease-associated lipids and proteins

VecTron

Vectorized transformative antibody/degron fusion proteins

Pathway specific protein degradation

CNS DELIVERY



VeCaps

VectorY AAV Safe Capsids

Efficient delivery of antibodies intracellularly in CNS, long term expression

MANUFACTURABILITY

ManuVec

Stable, robust, large scale AAV manufacturing, at low COGS

Vectorized antibody pipeline

Therapies for neurodegenerative diseases with high unmet medical need

	PROGRAM / TECHNOLOGY	INDICATION / TARGET	TARGET SELECTION	DISCOVERY	PRE-CLINICAL	IND-ENABLING	PHASE I/II
Proteino-pathies	**VTx-002** *VecTab*	Sporadic ALS TDP-43					
	VTx-003 *VecTab/VecTron*	Huntington's PolyQ, HTT					
	VTx-004 *VecTab/VecTron*	Parkinson's Alpha-Synuclein					
	VTx-005 *VecTab/VecTron*	Undisclosed					
Lipid toxicity	**VTx-001** *VecTab*	Sporadic ALS OxPC					

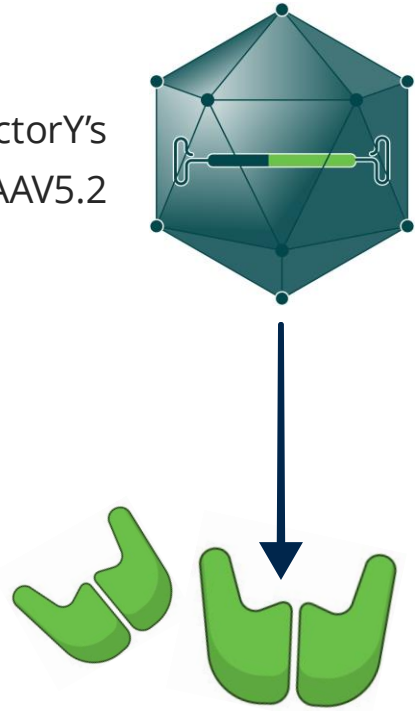
HD treatments have shown POC but significant gap towards viable disease modifying therapy remains

Drug	Company	MOA/Delivery	HTT reduction in R6/2 mice	Disease phenotype impact in R6/2	Clinical translation
AMT-130	uniQure	AAV5-miHTT **Intrastriatal**	**40% aggregate reduction**	Survival; +26 days Rotarod; +56%	**Phase 1/2 – ongoing** **54% mHTT reduction in CSF**
Tominersen	Roche	ASO-HTT **Intrathecal**	**No aggregate reduction** **43% mRNA reduction**	Survival; +23 days	**Phase 3 – discontinued** **Lack of efficacy**
WVE-003	WAVE LIFE SCIENCES	ASO mHTT **Intrathecal**	**NA**	NA	**Phase 1/2 - ongoing**
VY-HTT101	voyager THERAPEUTICS	AAV1-miRNA **Intrastriatal/thalamus**	**NA**	NA	**Phase 1b- recruiting**
V0659	VICO therapeutics	ASO-CAG **Intrathecal**	**15-30% mHTT soluble and aggregated**	Survival; NA Rotarod; 20% Open Field; +30% Brain volume; 0%	NA
C4-scFv	Messer et al	AAV2/1-scFv-C4	**50% aggregate reduction**	NA	NA
INT41	Vybion	AAV6 - INT41	**16-31% aggregate reduction**	Cognitive function; 30% male, 100% female mice	NA
Happ1 **VL12.3**	Southwell et al	AAV1-Happ1 AAV1-VL12.3	**30-60% aggregate reduction**	Survival; none Rotarod; 10-30% (Happ1) BW; none Ventricle enlargement; 50% (Happ1)	NA

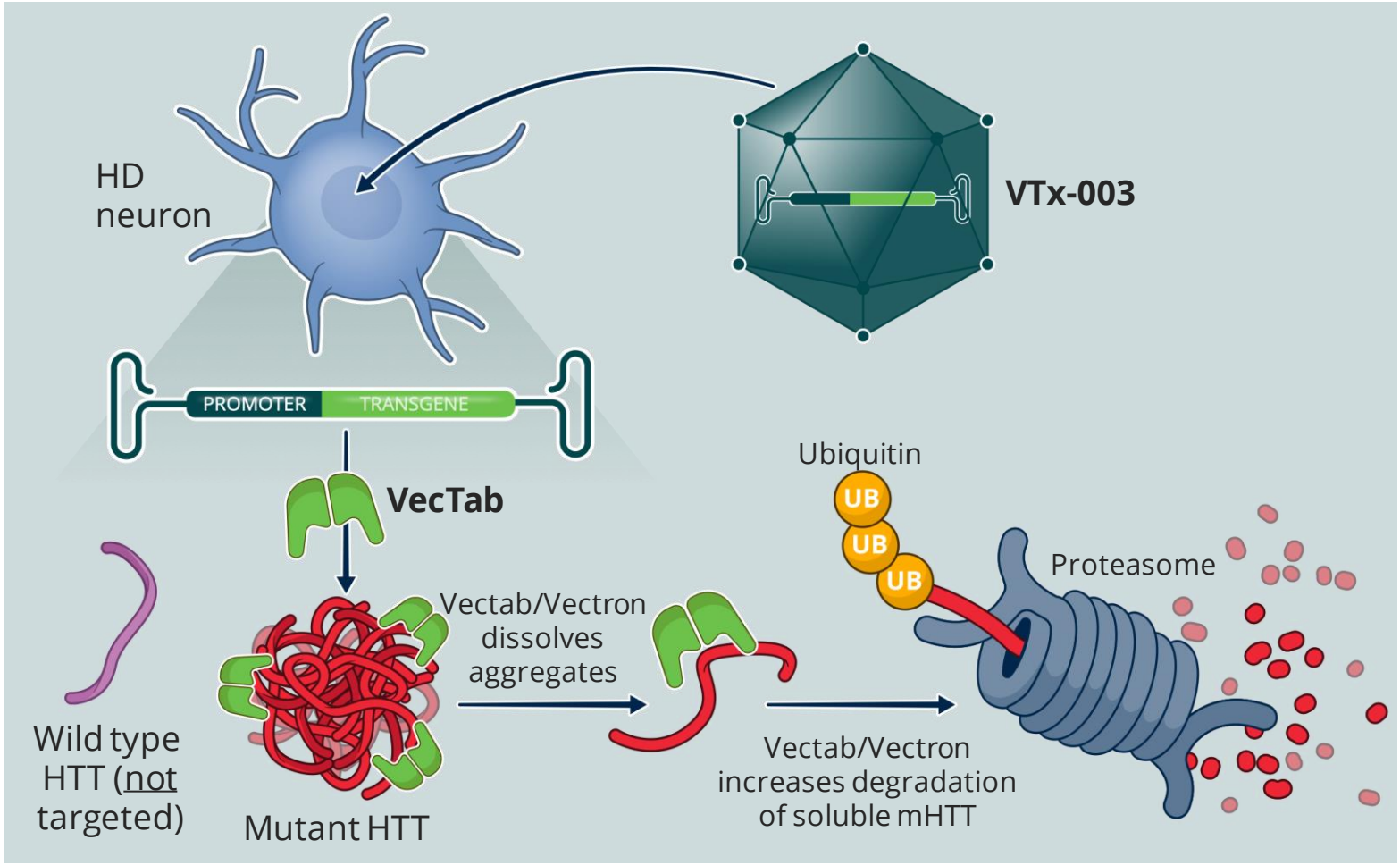
VTx-003 program selectively targets mutant HTT

Optimized humanized
HTT-scFv DNA cassette

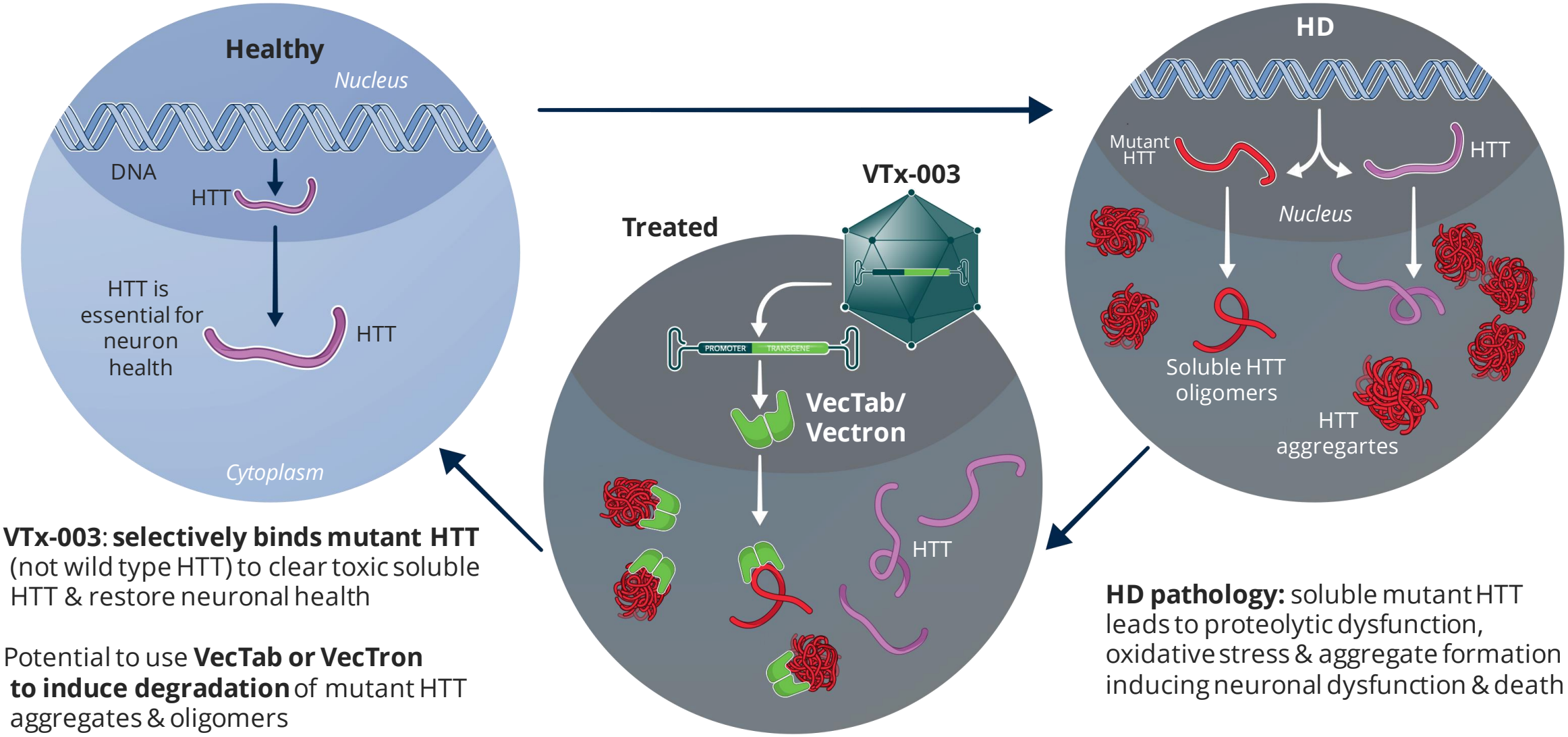
VectorY's
AAV5.2



scFv selectively binds to mutant HTT to clear or degrade mutant HTT with VecTab or VecTron technology



VTx-003 dissolves mutant HTT aggregates, degrades toxic soluble monomers, preserves wt HTT



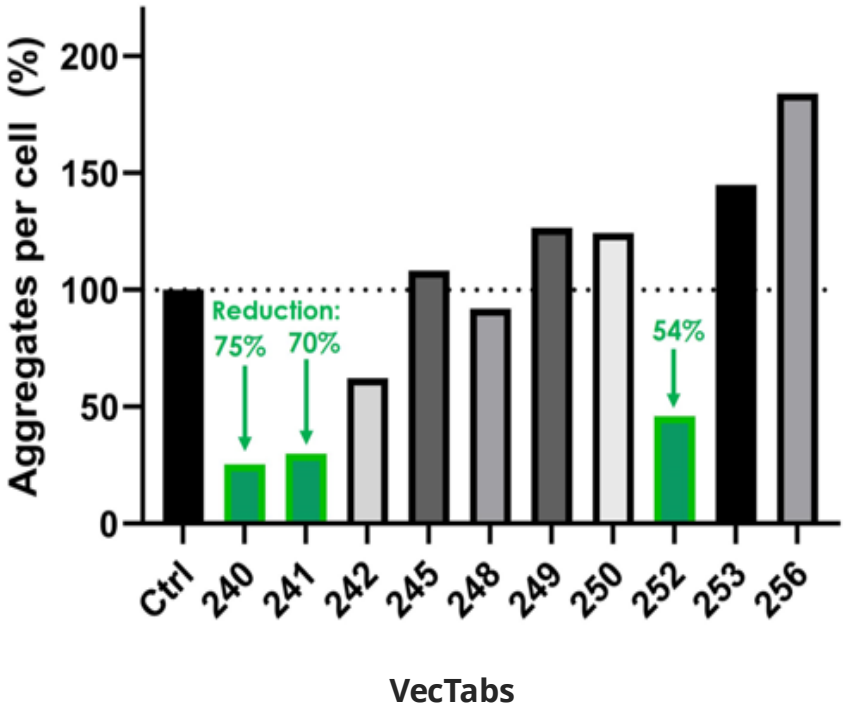
VTx-003: **selectively binds mutant HTT** (not wild type HTT) to clear toxic soluble HTT & restore neuronal health

Potential to use **VecTab or VecTron to induce degradation** of mutant HTT aggregates & oligomers

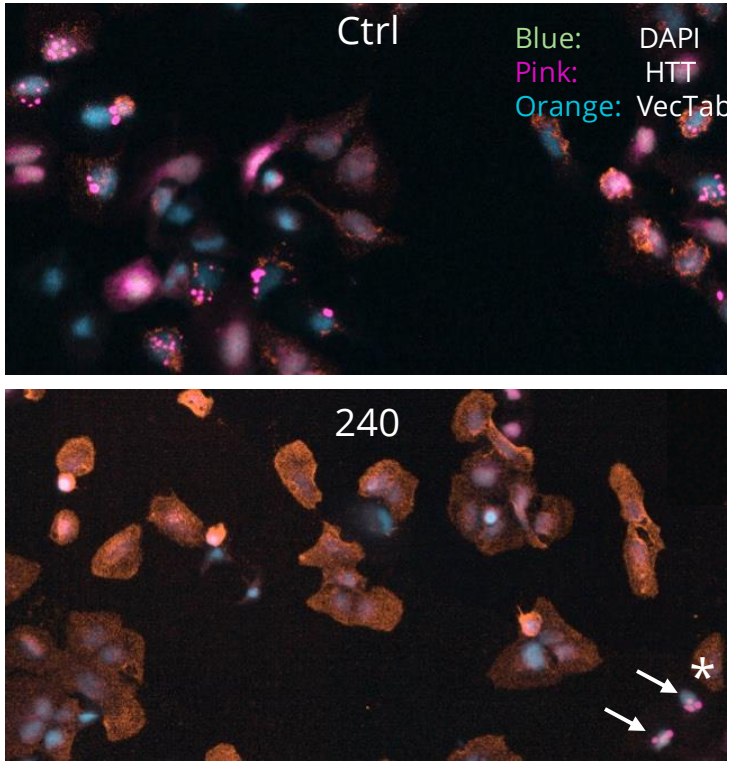
HD pathology: soluble mutant HTT leads to proteolytic dysfunction, oxidative stress & aggregate formation inducing neuronal dysfunction & death

VecTabs reduce HTT intracellular aggregates in cells

HTT VecTabs reduce HTT exon 1 aggregates *in vitro*

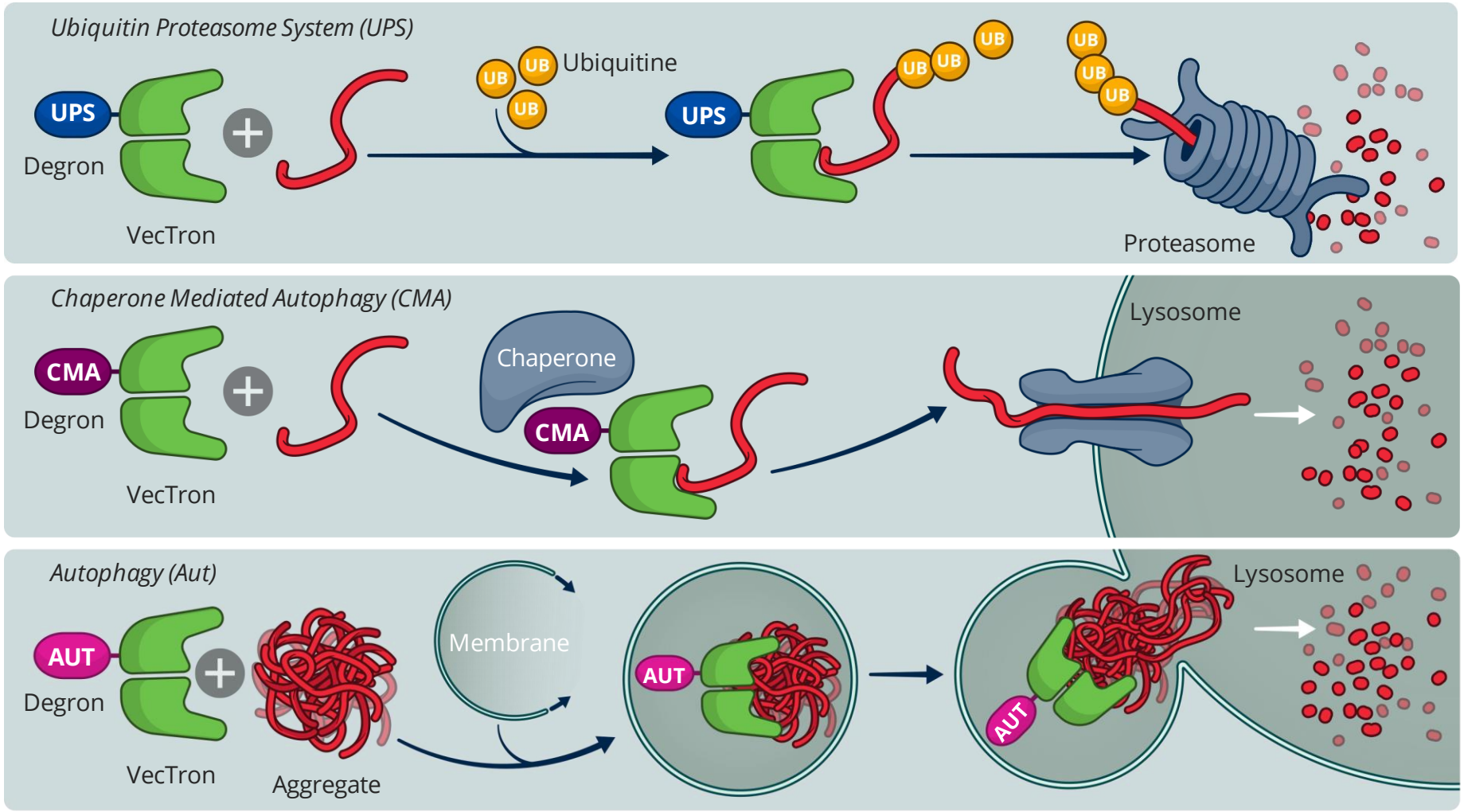


HTT VecTabs specifically reduce aggregates, not total HTT levels in U2OS cells



*Arrow = Aggregates still visible in non-transfected cells

VecTron technology directs protein-aggregate degradation to disease specific pathways



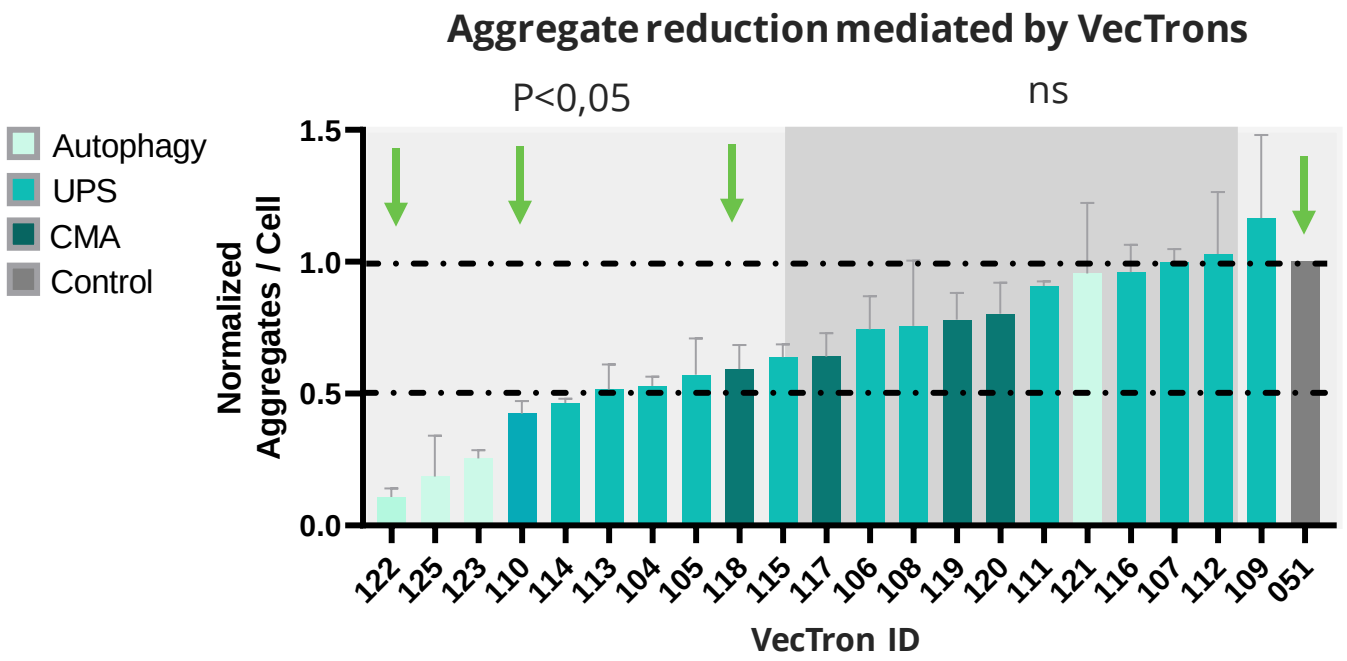
UPS VecTron® degrades soluble toxic proteins (e.g. HTT)

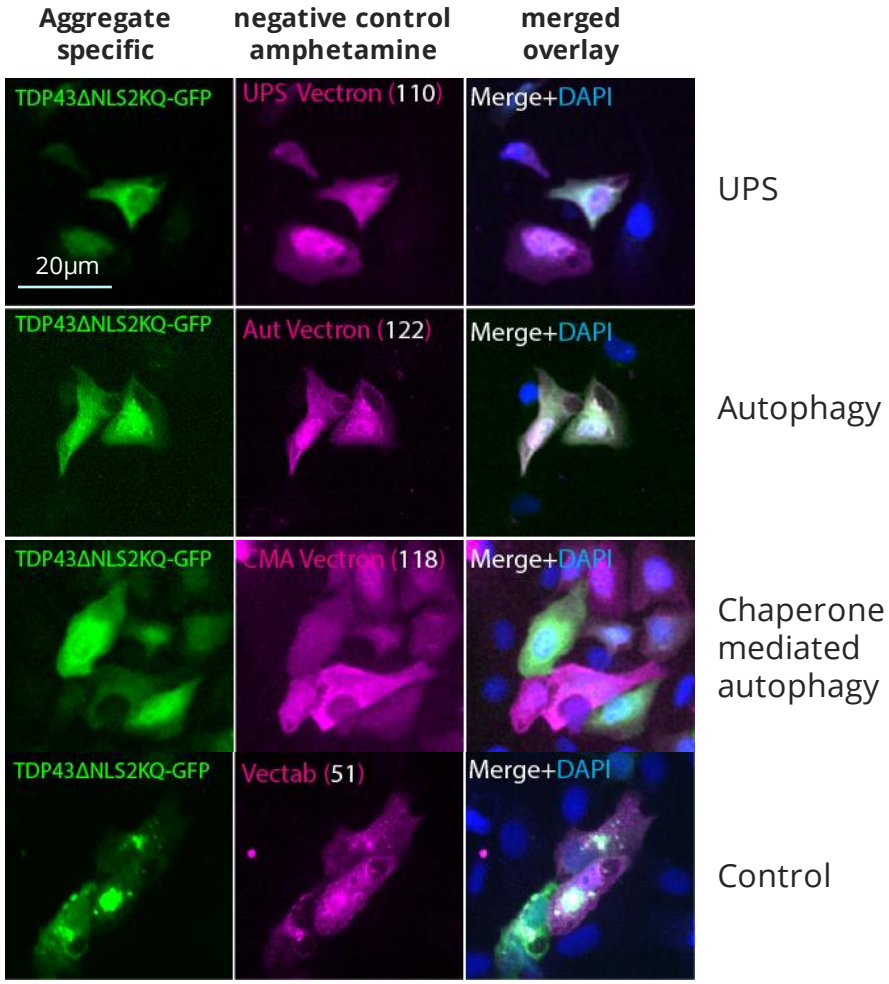
CMA VecTron® degrades soluble toxic proteins (e.g. αSyn)

Autophagy VecTron® degrades large aggregates (e.g. HTT)

VecTron technology converts a non-degrading VecTab into a proteolytic pathway-specific degrader

- VecTrons comprise a non-degrading VecTab combined with different degrons
- Degron library was expanded and combined with different VecTabs

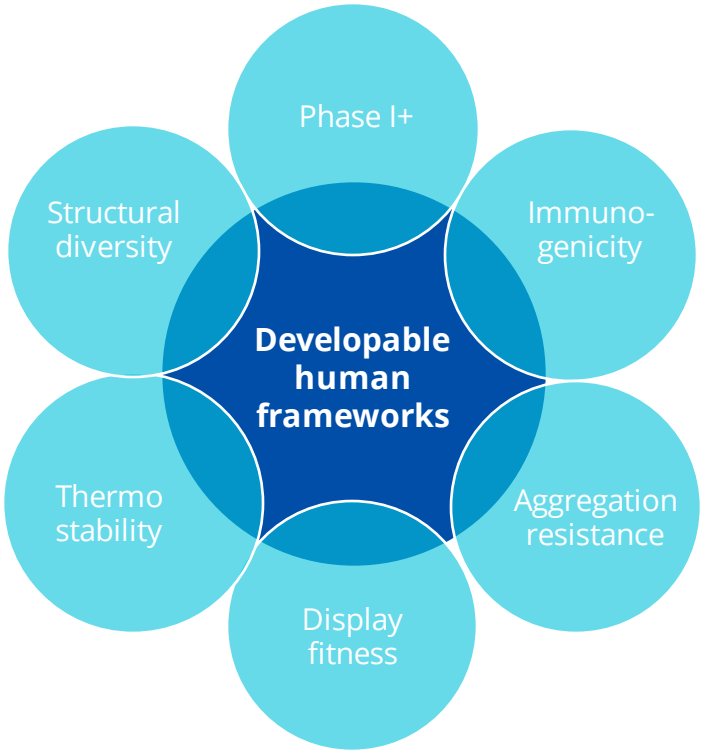




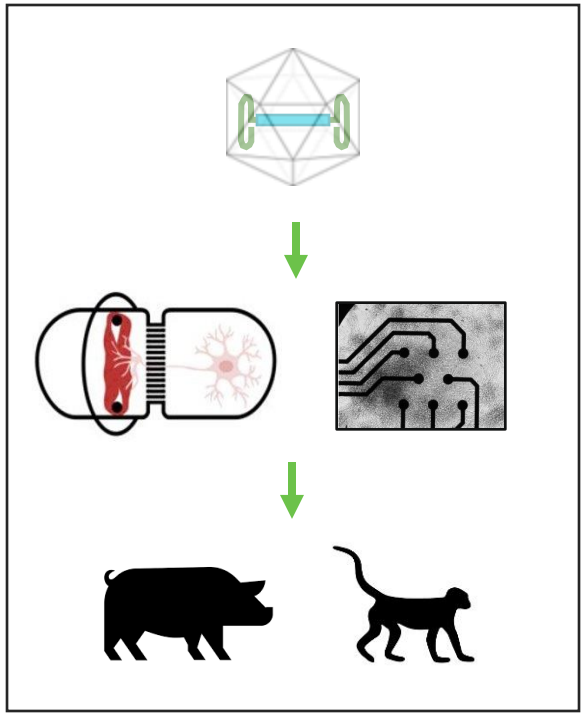
Protein aggregate analysis (**left**) of images (**right**) of cells transfected with aggregate specific and control VecTrons

VectorY has unique antibody expertise and know how enabling the VecTab and VecTron platforms

Sequence analysis → Library creation → Library panning → Binding characteristics → Validation at VectorY

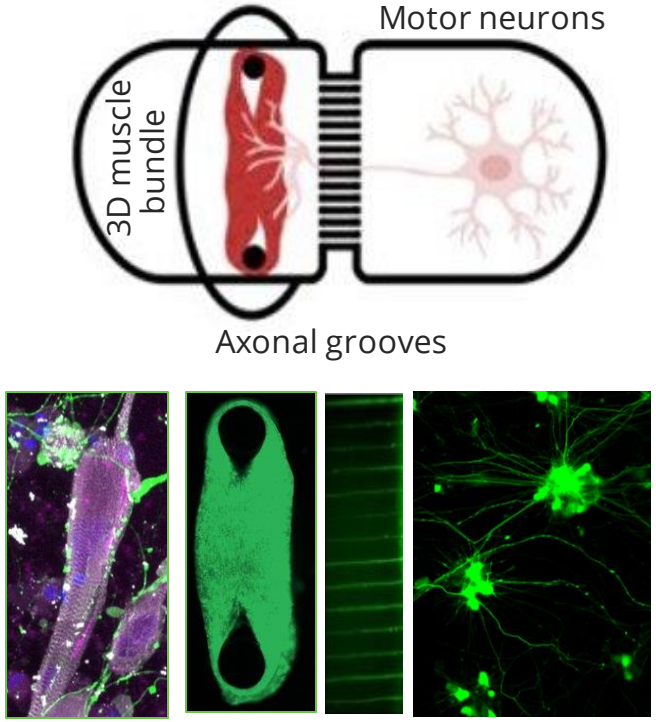


Lead candidate testing

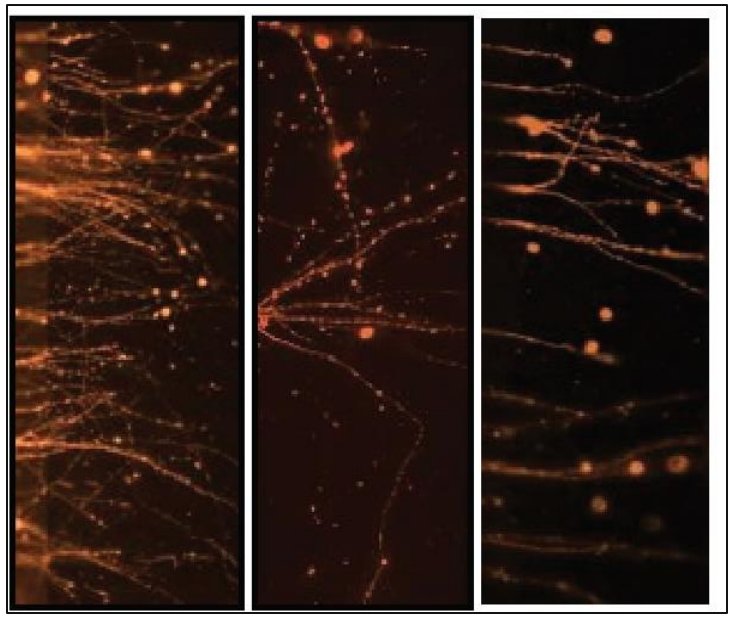


VectorY is pioneering iPSC-derived and electrophysiology disease models for demonstration of MoA

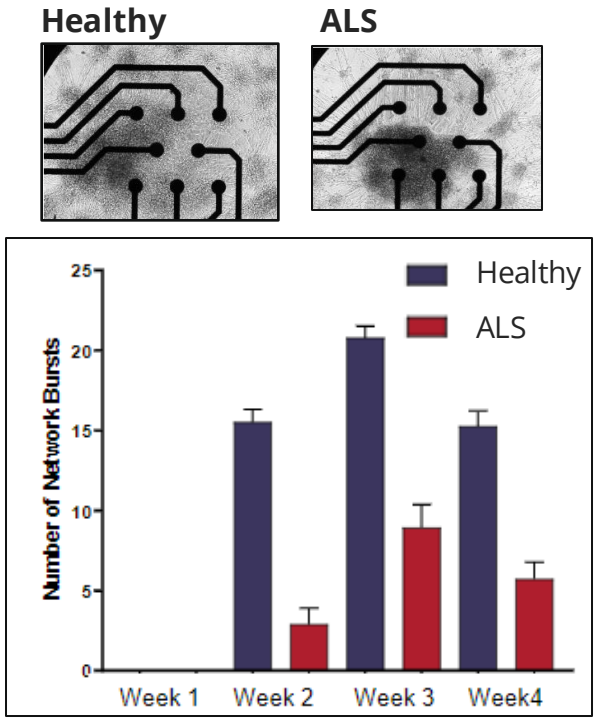
3D functional neuro-muscular junction (NMJ) device transduced with AAV5.2-GFP



OxPC-induced distal axonal pathology is recovered by VTx-001 treatment



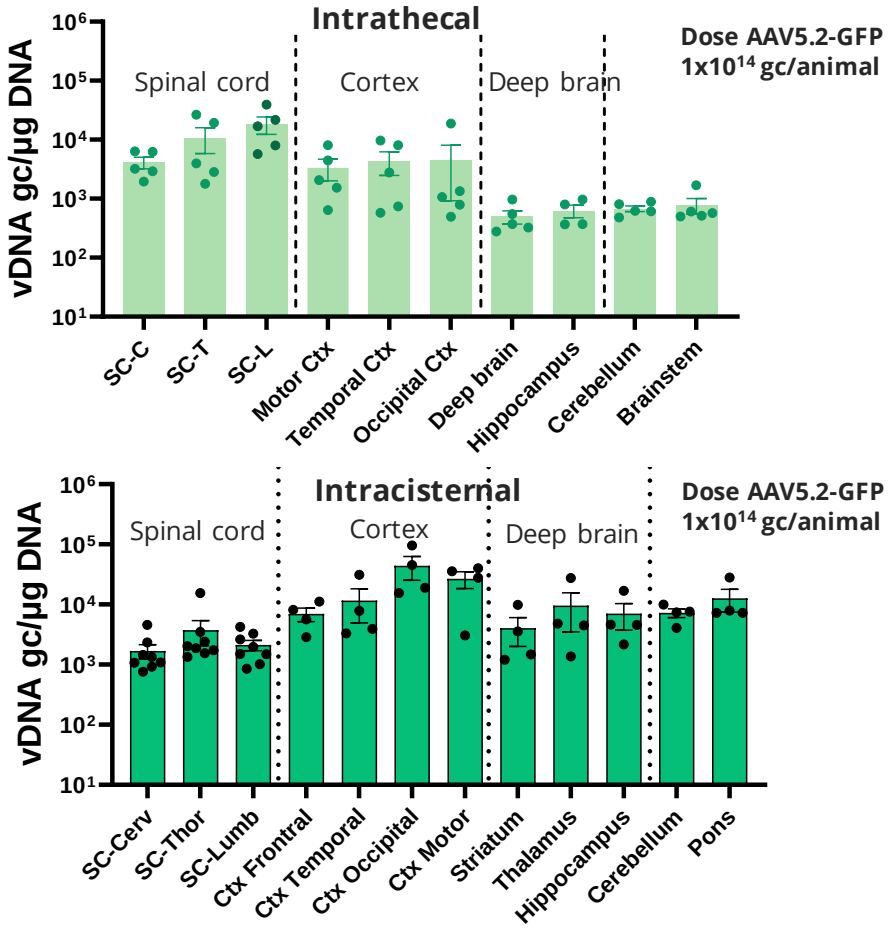
High throughput electrophysiology device for functional damage of ALS motor neurons

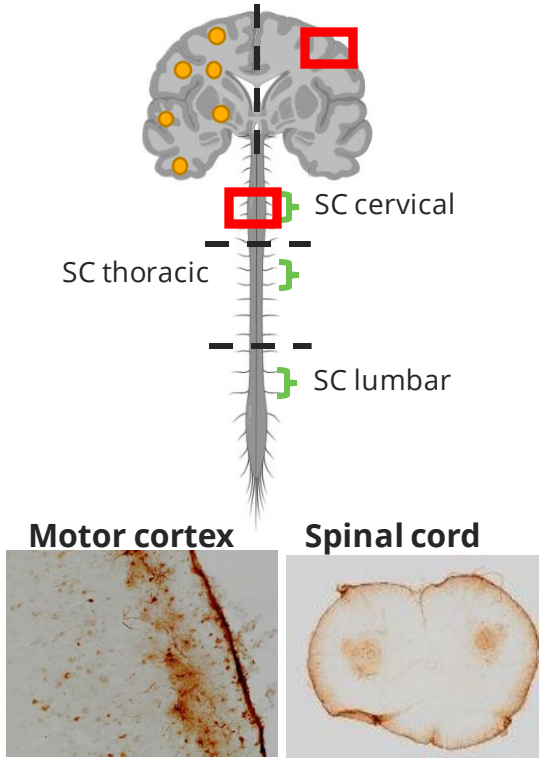


"Successful disease-attenuating therapies tested in transgenic models harbouring ALS-associated gene mutations have failed to translate to the clinic, ***suggesting that genetic models may not necessarily reflect pathophysiological mechanisms underlying sporadic amyotrophic lateral sclerosis (sALS)****".* Wong KJ et al. Brain Commun 2022

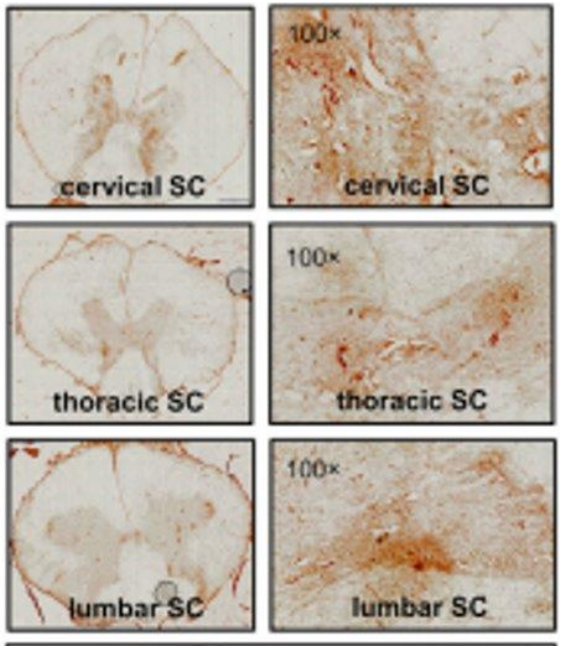
AAV5.2 vector effectively transduces target areas in mice, rats, pigs and NHP

VectorY's AAV5.2 transduces CNS at therapeutically relevant levels estimated by clinical dose prediction model





Comparable to CNS transduction in large animals with clinically validated AAV5.2



Evers and **Konstantinova**; Mol Ther, 2018*

***AAV5.2 bidoistribution also shown in:** Samaranch et al, Gene Therapy 2017, Martier R and **Konstantinova**; Mol Ther, 2019, Valles and **Konstantinova**; Sc TranslMed 2021, Spronck and **Konstantinova**; Brain Science, 2021, Pietersz and **Konstantinova**; Gene Therapy, 2021, Pietersz and **Konstantinova**; Journal of Neurosci Meth, 2022

Key program achievements

VTx-003 (HTT in HD)

✓Molecular MoA validated *in vitro*

✓***In vivo* POC** with HTT-VecTab in R6/2 mouse model

- ✓Best-in-class clearance of mutant HTT-aggregates in striatum
- ✓Motor deficit improvement

✓Improved VecTabs and VecTrons identified, to further improve upon observed best-in-class activity

The VectorY Talent Pool!!

Location	: Amsterdam Science Park
Staff	: 65+
PhDs	: 30
Nationalities	: 15

VectorY Therapeutics

Science Park
Matrix Innovation Center 408
1098 XH Amsterdam

info@vectorytx.com
+31 (0)20 226 80 20
vectorytx.com
vectorytx1