Targeting Neurodegenerative Diseases with Priavoid's Peptide Drug Development Platform

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Publication on α-syn targeting all-D- npj | parkinson's disease

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Objectives and Introduction

Priavoid GmbH advances clinical and preclinical drug development programs for neurodegenerative diseases by developing **oral all-D-peptides** designed to **detangle toxic oligomers**. Our mission is to deliver disease-modifying therapies that target the root causes of **neurodegeneration**.

Our **Peptide Drug Development Platform** consistently yields active D-enantiomeric peptides **acting as pharmacological chaperones** and detangle protein aggregates into native monomers.

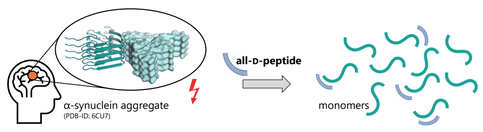


Figure 1: Priavoid develops orally available all-D-peptides that detangle neurotoxic oligomer species to inhibit and reverse disease-specific protein aggregation in neurodegenerative disorders.

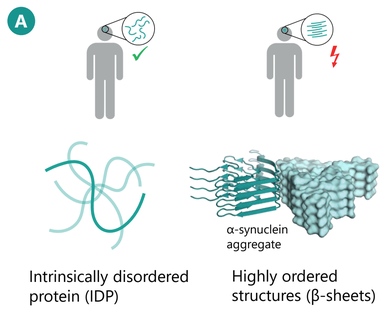
Here, we present our **platform with focus on cell permeability studies** expanding our scope to intracellular drug targets and show case the identification of a cell permeable all-D-peptide ligand that addresses **intracellular α-synuclein**, the disease-driving protein in **Parkinson's Disease** (PD).

About Priavoid

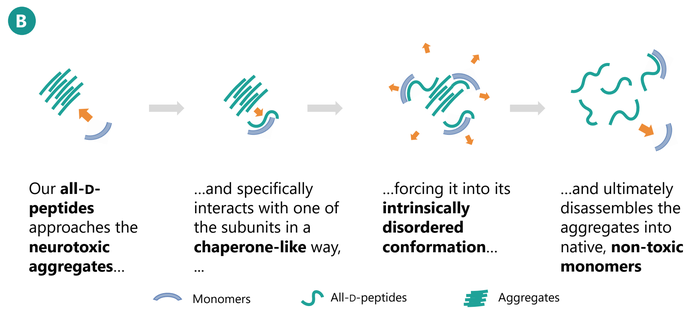
- Founded in 2017 and located in Düsseldorf
- Thirty-two highly skilled employees
- One phase II clinical trial against Alzheimer's
- One partnership ready drug development program
- Six preclinical programs - four addressing high-burden neurodegenerative disorders

PRImus-AD

Peptide Drug Platform Technology



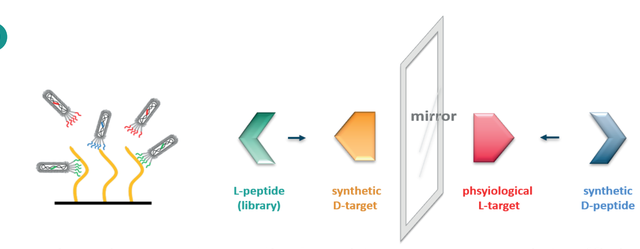
Protein aggregation is a hallmark of various neurodegenerative disorders.



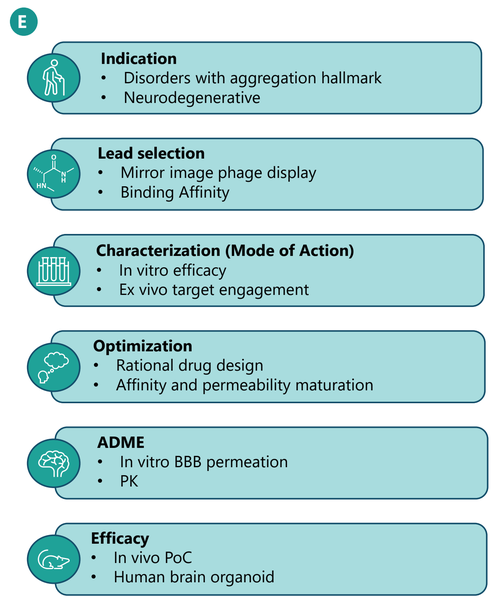
Our compounds act as chaperone-like detanglers and effectively disassemble neurotoxic aggregates.



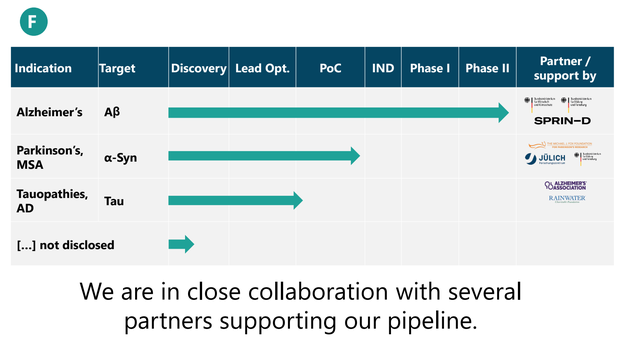
Peptide and target form a stable intrinsically disordered complex.



Mirror image phage display aids to generate high affinity initial screening hits – peptides that consist of D-amino acids.



We advance our peptide platform through the complete preclinical development.



We are in close collaboration with several partners supporting our pipeline.

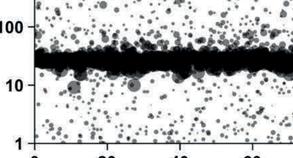
All-D-peptides

- Proteolytically stable and orally available
- Metabolic stability
- Very good safety profile
- No demand for modified building blocks
- Low immunogenic risk
- Extra- and intracellular application

Advancing Parkinson's Therapy with PRI-101

Indication

α-Synuclein forms aggregates



PD Patients

- 8.5 million worldwide and rising every year.
- Many live 15–30 years after diagnosis.
- Dopaminergic neuron loss in the substantia nigra.

Patients suffer major disability

- Motor symptoms (muscle rigidity, tremor, twitching movements etc.)
- Non-motor symptoms (cognitive decline, mood disorders etc.)

Standard of care

- Symptomatic treatment (dopamine)
- Deep brain stimulation (surgery)

Lead selection

PRI-101 binds α-synuclein target

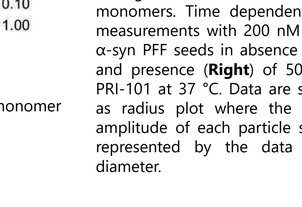


Figure 2: SPR with immobilized PRI-101. α-Syn was injected for 100 s at 30 µl/min ranging from 30 to 500 nM. The interaction was fitted with a 1:1 kinetic interaction model.

Characterization (mode of action)

PRI-101 inhibits seeded aggregation

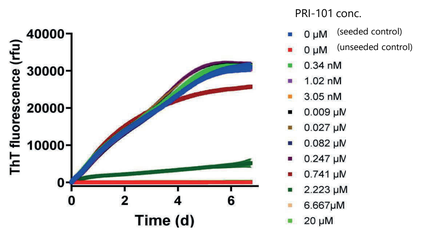


Figure 3: PRI-101 eliminates seeding activity of small α-syn PFFs (50 nM monomer eq.). Before addition of α-syn (20 µM) monomers, fibrils and peptide (up to 20 µM) were incubated for 20 h (n = 4, Read-out: Tht fluorescence).

Seeded aggregation in α-synA53T-YFP cells stopped

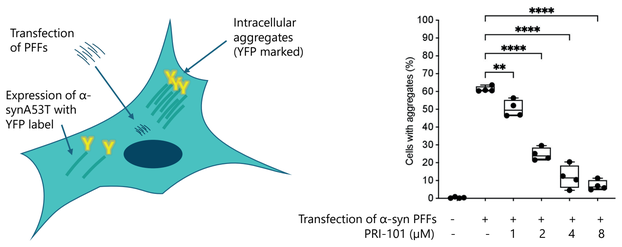


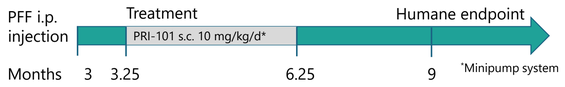
Figure 4: Left: HEK293T cells expressing α-syn monomer are transfected with α-syn PFFs to induce intracellular aggregation. **Right:** Addition of PRI-101 to cell culture medium at low µM concentration is inhibiting seeding capacities of PFFs.

DLS measurement with pre-formed α-syn fibrils (PFFs) reveals disintegration of seeds by PRI-101

Figure 5: PRI-101 reduces the particle size of α-syn small PFFs through stabilization of monomers. Time dependent DLS measurements with 200 nM small α-syn PFF seeds in absence (**Left**) and presence (**Right**) of 500 nM PRI-101 at 37 °C. Data are shown as radius plot where the signal amplitude of each particle size is represented by the data point diameter.

Efficacy

Survival prolonged in TgM83+ (α-synA53T) mice



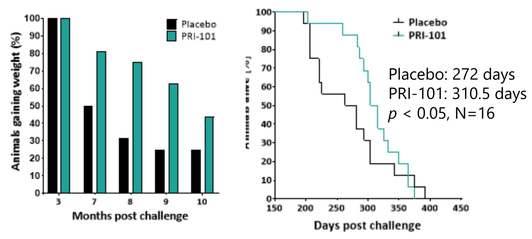


Figure 6: TgM83+ mice carrying a A53T α-syn mutation were injected with α-syn fibrils (PFFs) to induce protein aggregation at 3 months. After short time PRI-101 at 10 mg/kg daily was dosed s.c. using implanted mini-pumps for 3 month. PRI-101 treatment delays weight loss and prolongs the survival of TgM83+ mice.

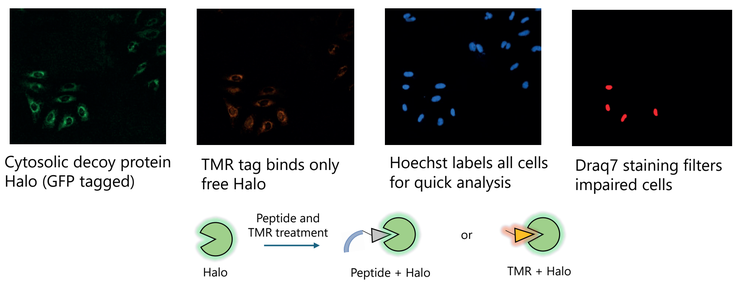
Highlights of PRI-101

	Property	Parameter	PRI-101
In vitro	Binding affinity	SPR (kinetic fit) [K_d]	1 nM
	Seeded aggregation	Inactivation of seeds [EC_{50}]	1.4 µM
	Intracellular aggregation	Reduction of aggregation [IC_{50}]	1.6 µM
ADME	Cell permeability	CAPA assay [EC_{50}]	4.3 µM
	Mouse PK	Brain uptake	Sufficient
PD	Ex vivo target engagement	Reduction of aggregates (human PD brain)	72%
	In vivo seeding/spreading	Prolongation of survival	38 d
Safety	Safety panel	Off-target binding assay	No off-target hits

Cellular Permeability

Optimization

Chloroalkane Penetration Assay (CAPA) analyzed by fluorescence microscopy



Cytosolic localization of PRI-101

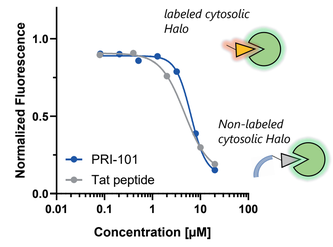


Figure 7: Left: Principle of CAPA. Cells producing cytosol localized Halo protein (green) are treated with tagged Peptide (grey) and TMR-tagged Halo protein ligand. Only free Halo protein reacts with TMR and shows orange signal. TMR fluorescence intensity is anti-proportional to cytosolic localized peptide concentration. Hoechst labels all nuclei and Draq7 staining is used to analyze and filter membrane disturbing peptides. **Right:** Halo ligand tagged PRI-101 is tested in HeLa cells using the CAPA system. Peptides were incubated with cells in OptiMEM for 24 h.

Focus screening library changing amino acid residues to improve permeability

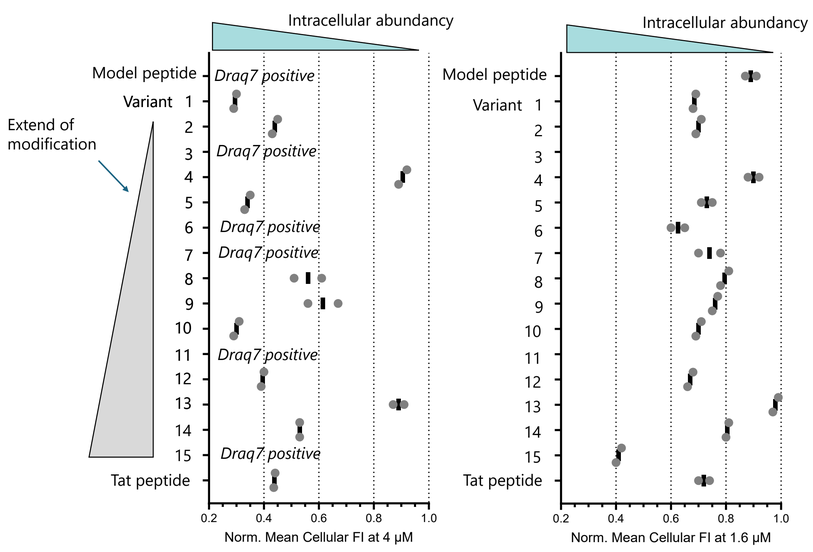


Figure 8: Example data of a small peptide library, synthesized with single, double and triple aa mutations. CAPA can be used to determine quickly their intracellular localization rates. Halo expression levels are accounted for by GFP signal and TMR fluorescence intensity is normalized to maximum and minimal TMR signal. Draq7 positive conditions with impaired cells can be excluded (example data with n = 2).

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