D-peptides disrupting α-synuclein aggregates extend survival of mice modeling Parkinson's disease

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Introduction

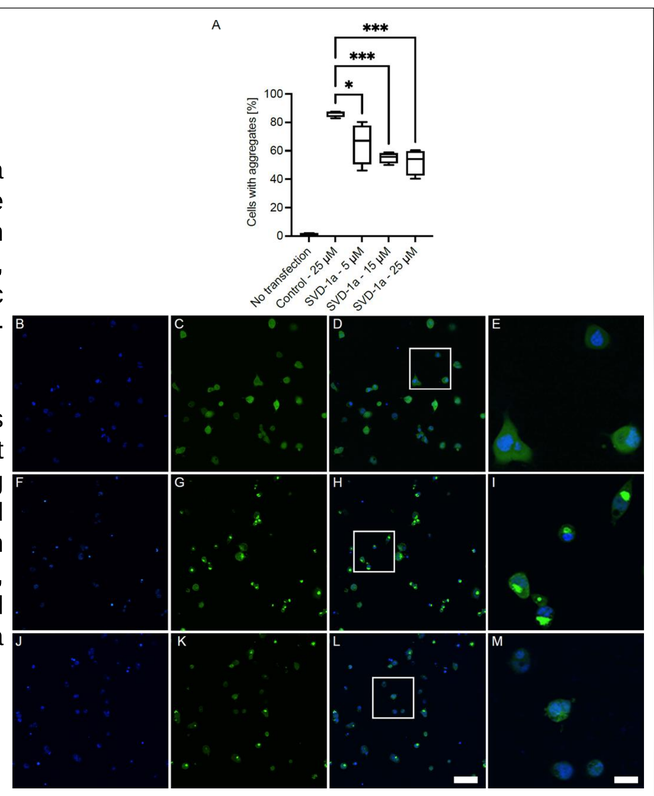
Parkinson's disease (PD) is one of the most common neurodegenerative disorders, affecting approximately 1% of the population over the age of 60. The disease is characterized by a progressive loss of dopaminergic neurons in the substantia nigra, leading to motor symptoms such as tremor, bradykinesia and rigidity, and is caused by pathological misfolding and aggregation of native α-synuclein monomers into toxic oligomers and fibrils. Despite the high burden of disease, only symptomatic treatment is currently available, not a cure. The development and testing of new therapeutics is therefore essential to address this problem.

Here, we tested two all-D-enantiomeric peptides, developed to target and disassemble toxic α-synuclein species by stabilizing the monomeric conformation, for their potential to prevent or slow down disease progression in vivo in a mouse model of PD.

Background

The two all-D-peptides SVD-1 & SVD-1a were identified by mirror image phage display. The compounds then went through further selection and optimization rounds, e.g. to ensure their ability to dissolve toxic α-syn oligomers and to cross the blood-brain-barrier.

Left: In a cell assay using HEK293T cells expressing α-synA53T–YFP[1], treatment with SVD-1a at concentrations ranging from 5 to 25 µM significantly reduced seeding of α-syn aggregation (**A**). Shown are images of non-transfected cells (**B-E**), cells transfected with α-syn fibrils (**F-I**) and cells transfected with α-syn fibrils+SVD-1a (**J-M**).



Study design

Mouse model: TgM83$^{+/-}$ mice express human α-syn with the A53T mutation and only develop PD-like pathology and disease when inoculated with α-syn fibrils.[2,3,4]

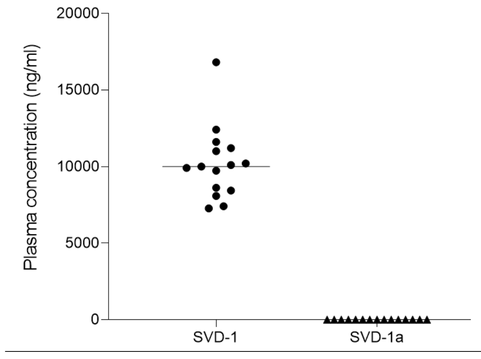
Inoculation: Adult mice were challenged intraperitoneally with 50 µg α-syn fibrils

Treatment:

- Start: 1 week post challenge
- Duration: 12 weeks
- Route of administration: subcutaneous
  SVD-1: daily s.c. injections
  SVD-1a & placebo: s.c. pump
- Dosage: 10 mg/kg/d

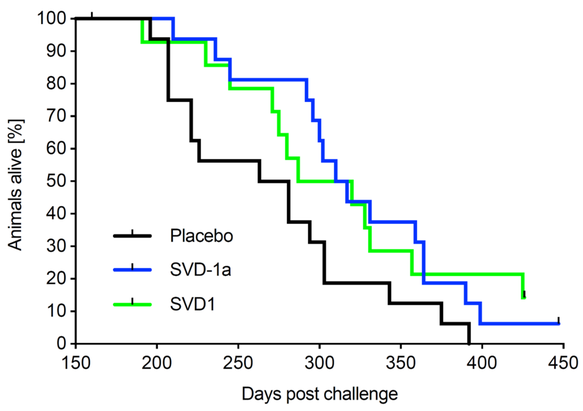
End of study: Appearance of signs of neurological disease

Plasma levels at the end of treatment



Plasma samples collected at the end of the 12-week-treatment period display peptide concentrations of ~10.000 ng/ml for SVD-1 treated animals. SVD-1a-levels were below the lower level of quantification.
These differences may be a result of the different forms of drug-administration.

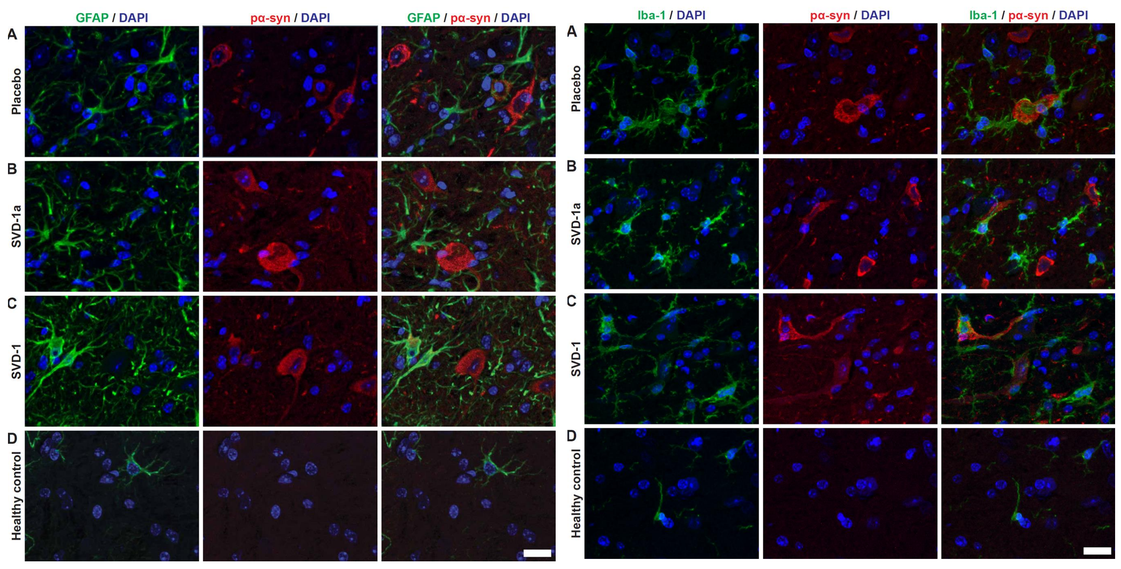
SVD-1a-treated TgM83$^{+/-}$ mice show extended survival



Mice treated with SVD-1a showed a significantly (P = 0,0454) extended life span in comparison to placebo-treated animals.

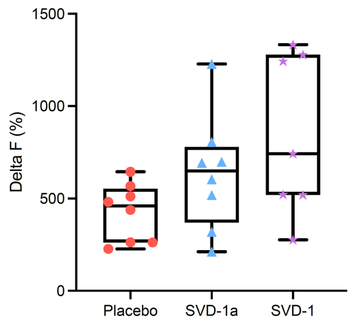
Treatment with SVD-1 did not significantly extend survival.

Sick TgM83$^{+/-}$ mice show severe astrogliosis and microgliosis in the CNS

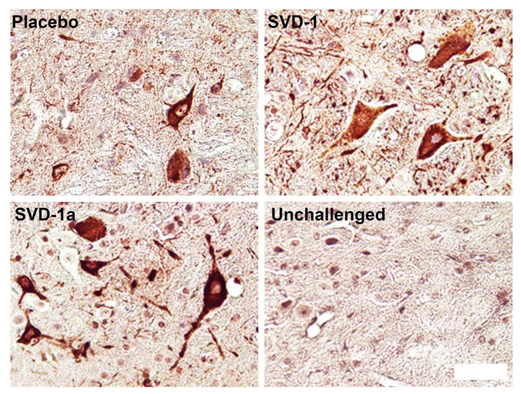


Immunofluorescence staining shows astrocytic gliosis (**left panel**) and microgliosis **(right panel**), indicating neuroinflammation in the CNS of sick animals. Nuclei were stained with DAPI (blue), phosphorylated α-syn with the pSyn#64 antibody (red), astrocytes with an antibody to GFAP (green), and microglia with an antibody to Iba1 (green). Scale bar = 20 µm.

Sick TgM83$^{+/-}$ mice accumulate pathologic α-synuclein in the CNS



TR-FRET-analysis of brain homogenates of peptide- and placebo-treated animals revealed an accumulation of pathological α-syn in the CNS of diseased mice.



Brainstem sections stained with the pSyn#64 antibody against phosphorylated α-syn display neuronal and neuritic deposits of pathologic α-syn aggregates. Unchallenged mice did not exhibit neuropathology. Scale bar = 20 µm.

Conclusions & Outlook

Subcutaneous administration of SVD-1a significantly prolonged survival, compared to placebo-treated controls. In consequence, SVD-1a holds potential as a drug candidate for the treatment of synucleinopathies. In upcoming studies, SVD-1 & SVD-1a and their improved versions will be tested for their therapeutic potential upon oral administration in the TgM83$^{+/-}$ PD model. Additionally, investigating whether these peptide could reverse existing pathology would be of interest.

References

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