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NeuroRestore ACD856
Background & data supporting disease modifying effects

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Background: Neurotrophins and ACD856, a clinical stage cognitive enhancer with disease modifying potential

- ACD856 is a novel small molecule positive modulator of Trk receptors enhancing the signaling of neurotrophins, such as Nerve Growth Factor (NGF) and Brain-Derived Neurotrophic Factor (BDNF)
- The neurotrophins has been known for decades to play an essential role in neuronal survival and function as well as in learning, memory and mood
- ACD856 has been tested in a phase 0 micro-dose study, in a phase 1 single ascending dose study and in a phase 1 multiple ascending dose study
- ACD856 demonstrated excellent pharmacokinetic properties and bioavailability. It was safe, well tolerated with good blood-brain-barrier permeability. Quantitative EEG demonstrated evidence of a pharmacological effect in the CNS, suggesting target engagement.
- The role of neurotrophins and the mechanism of action of ACD856 implies that the compound could have disease modifying effects

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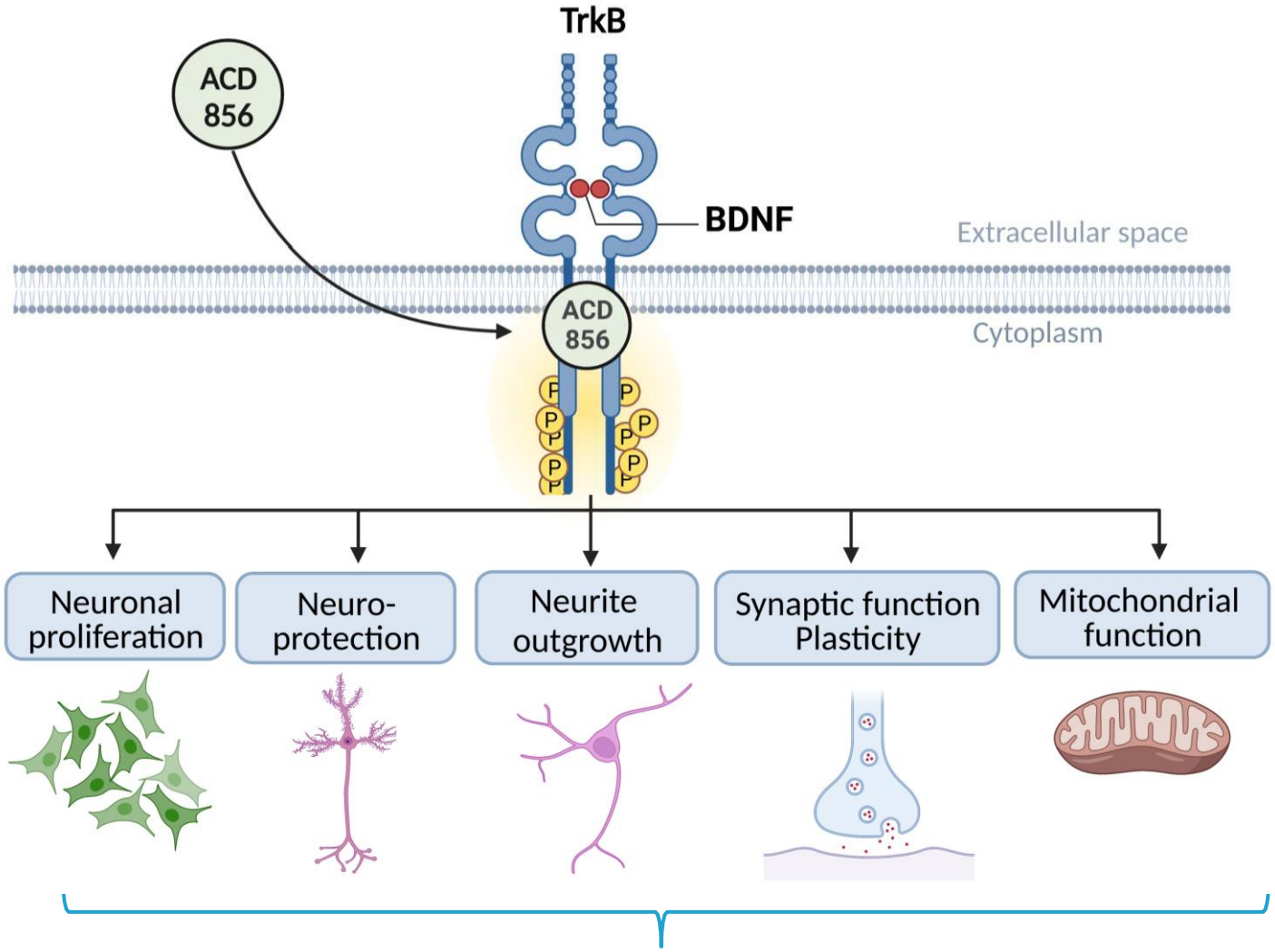
ACD856, mechanism of action supports disease modifying potential

- ACD856 is a novel small molecule positive modulator of Trk-receptors enhancing the signaling of neurotrophins such as NGF and BDNF
- The enhanced signaling leads to short term symptomatic effects with long term benefits
- The long-term effects of ACD856 could include improved neuronal function, increased mitochondrial function and improved cognition.



Results supporting disease modifying effects

- **In vitro**
  - Protection against amyloid-beta induced neurotoxicity
  - Potentiation of neuronal growth and neurite outgrowth
  - Increased levels of BDNF
- **In vivo**
  - Improved memory possibly through increased neuroplasticity
  - Long term antidepressant-like effect via a potential neuroplastic adaption

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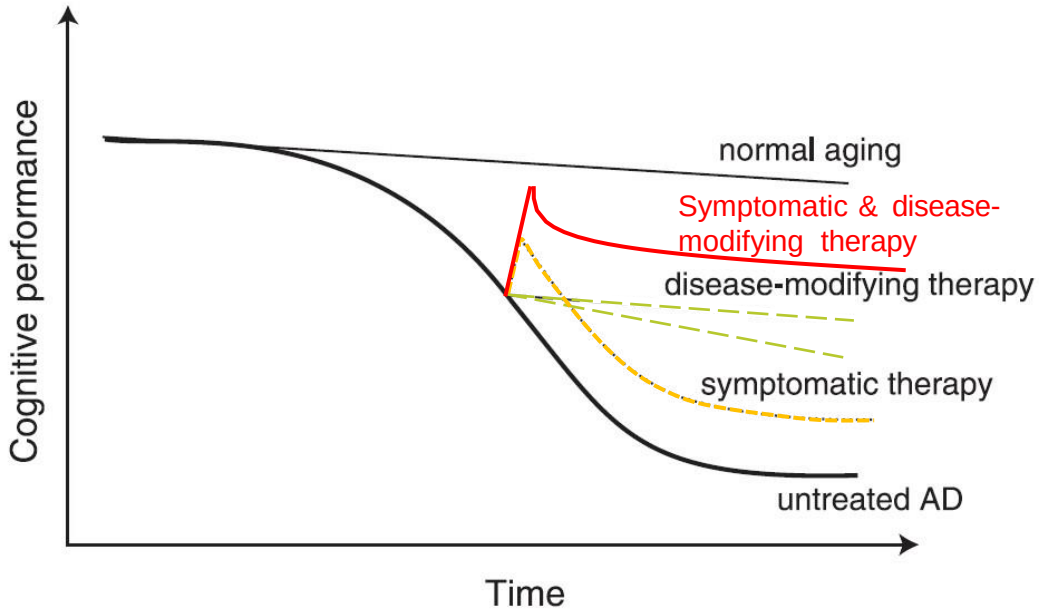
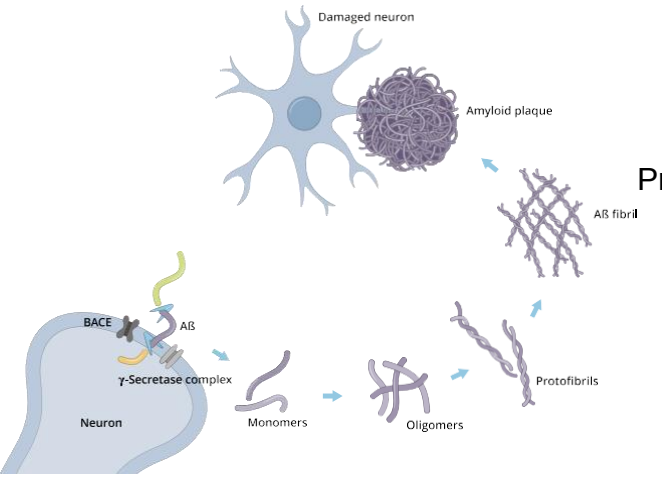
Amyloid toxicity and disease progression

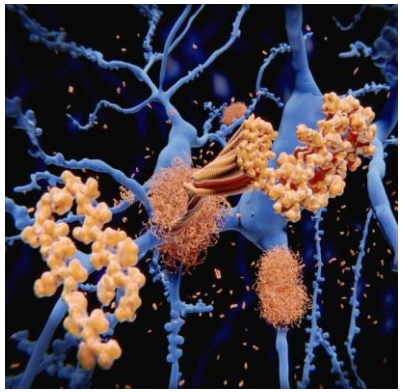
- Key pathological features of the Alzheimer's disease brain:
  - Amyloid plaque
  - Synapse dysfunction
  - Axon withdrawal
  - Mitochondrial dysfunction
- These events are closely correlated with the cognitive dysfunction that is characteristic for Alzheimer's disease.

Preventive, protective or restorative treatment will have a significant impact on disease progression, especially if combined with a symptomatic effect

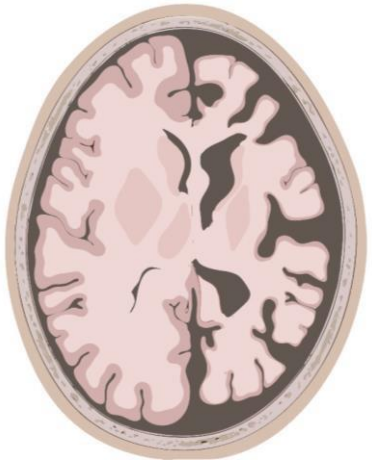




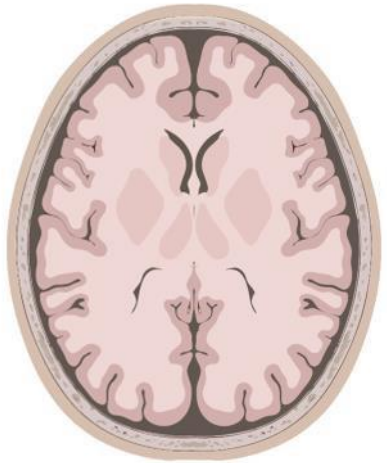
Preventive



Protective

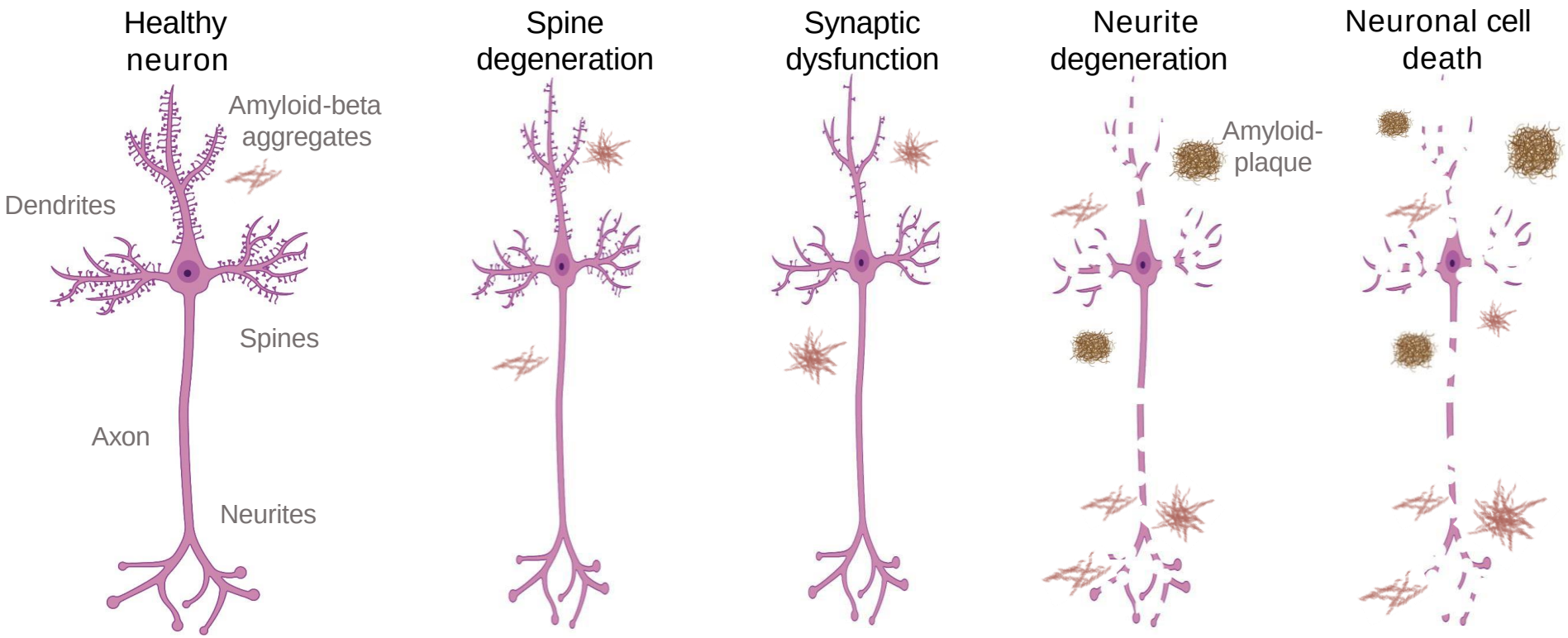


Restorative



Amyloid-beta induced neurotoxicity

The life and death of a neuron



Neuronal function

Neuroprotective effects of ACD856

Synaptic dysfunction
Neurite degeneration
Neuronal cell death

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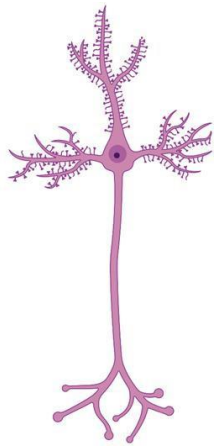
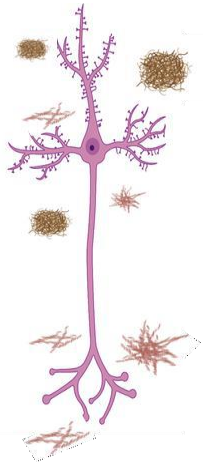
ACD856 and amyloid-beta induced neurotoxicity

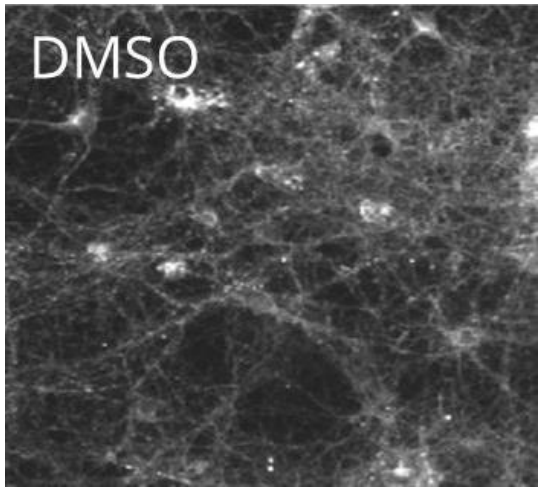
- Vehicle (DMSO) or $A\beta_{1-42}$ was added to neurons, with or without ACD856
- The neuronal content of a synaptic protein (SNAP25) was quantified by microscopy

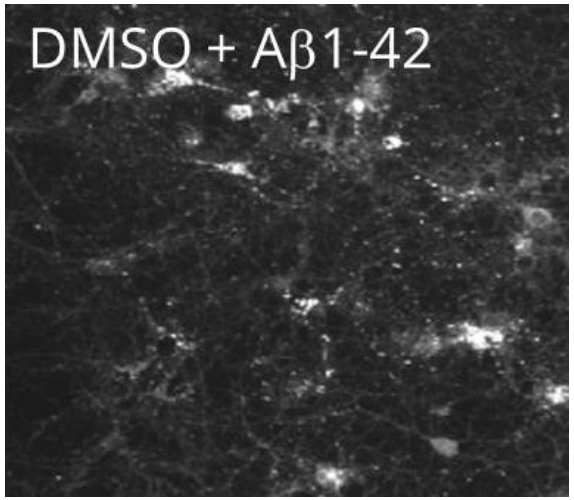


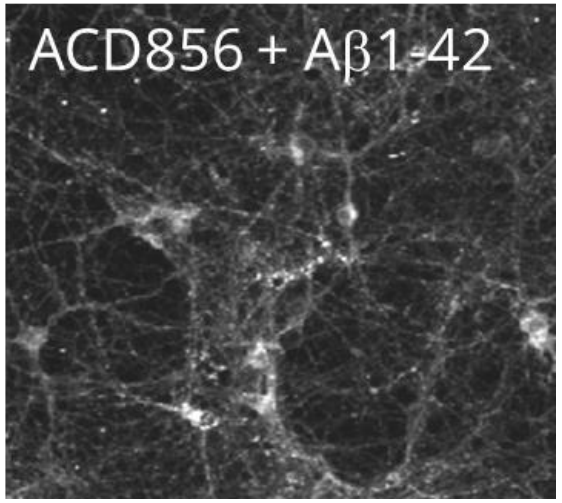
$A\beta_{1-42}$

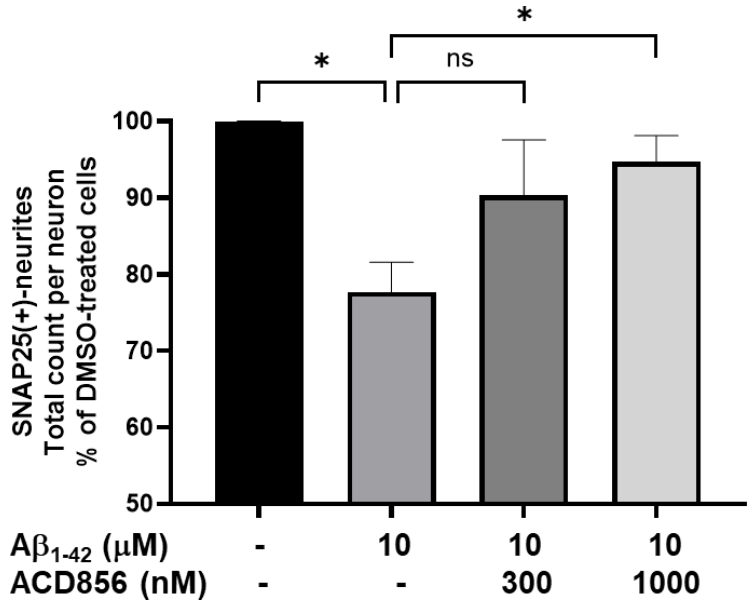
ACD856 + $A\beta_{1-42}$











ACD856 is protective against $A\beta_{1-42}$-induced neurotoxicity

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Results supporting disease modifying effects

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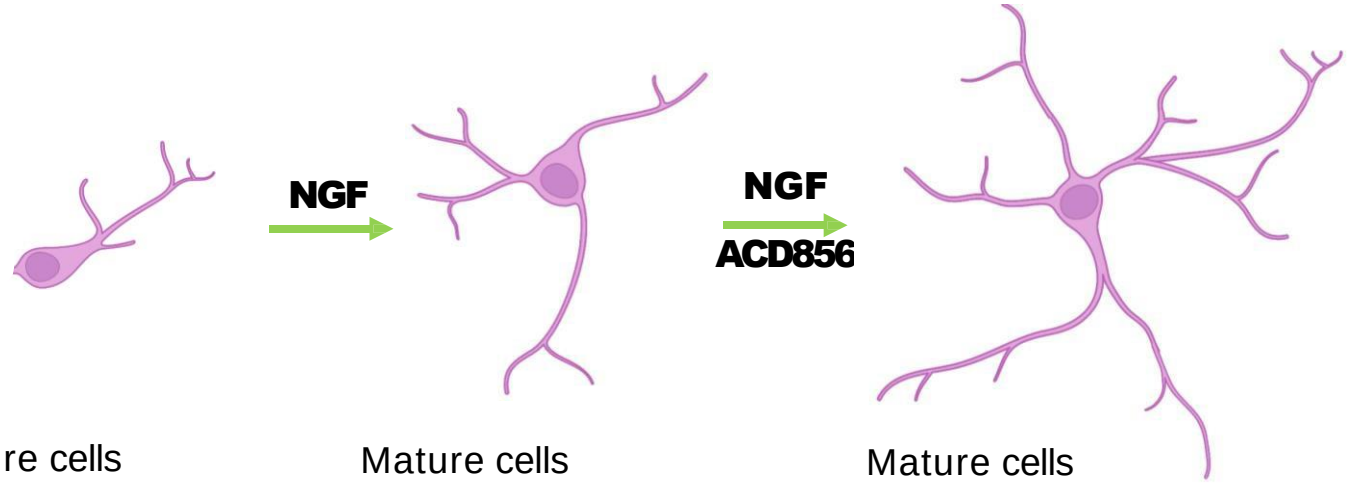
ACD856 and neurite outgrowth

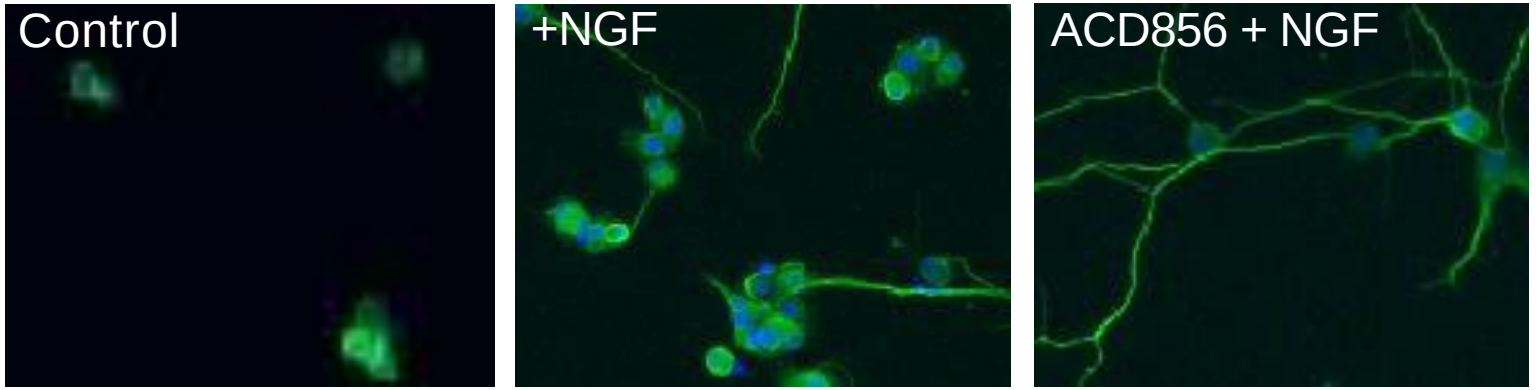
- Neurotrophins like NGF and BDNF are important for neurite outgrowth and neuronal proliferation
- Effects of ACD856 on cell number and neurite outgrowth was studied in immature neuronal-like cells

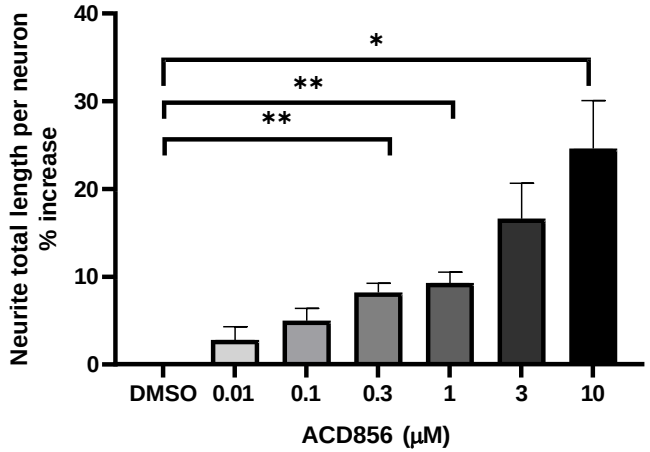


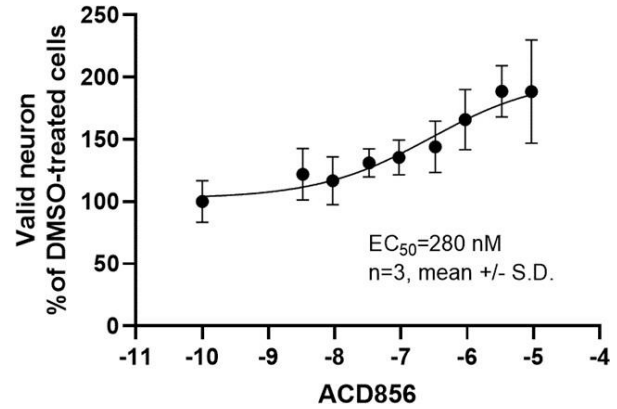
Immature cells
Low degree of neurites

Mature cells
Medium degree of neurites

Mature cells
High degree of neurites







ACD856 increase neuronal growth and neurite formation suggesting a potential for neurorestorative effects

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The importance of BDNF in brain function and memory

- BDNF stimulates neuroplasticity and synaptic function
- BDNF levels are increased in an activity-dependent manner. Exercise increase BDNF levels and it is believed to be one of the reasons for well-being after training
- Several lines of evidence point to the involvement of BDNF in Alzheimer's disease and in depression
- The BDNF-Val66Met polymorphism is associated with cognitive impairment and worsened amyloid pathology in Alzheimer's disease
- Carriers of ApoE4 and BDNF-Val66Met alleles have increased amyloid-beta pathology compared to non-carriers

BDNF-Val66Met heterozygotes

30% reduced BDNF secretion

- Increased rates of decline in memory
- Increased CSF Tau and p-Tau
- Reduced hippocampal glucose metabolism

"To date, this is the only genetic factor found to moderate downstream effects of amyloid-ß levels in autosomal dominant Alzheimer's disease."

Bateman et al, Brain, 2016

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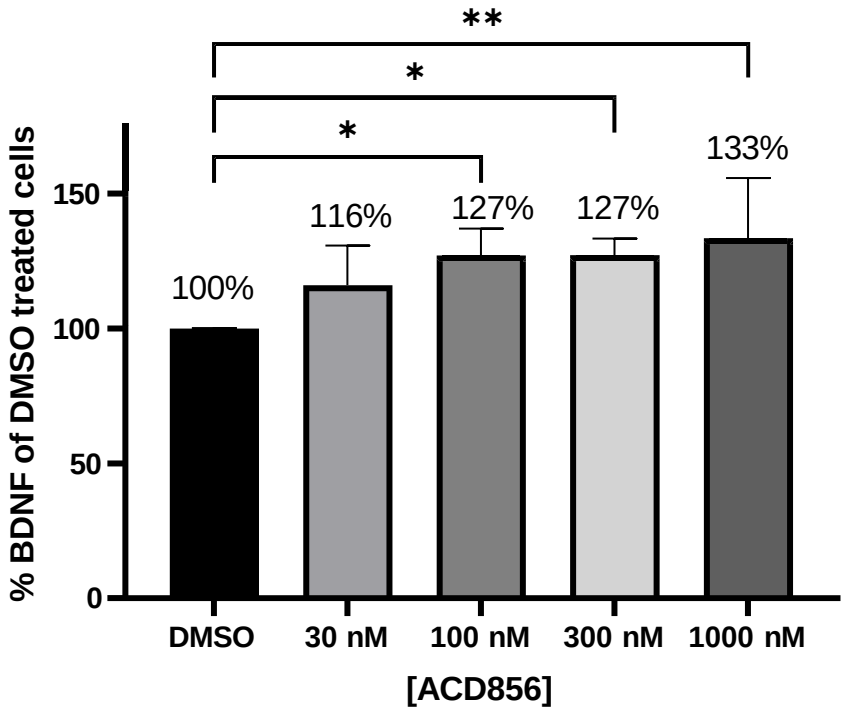
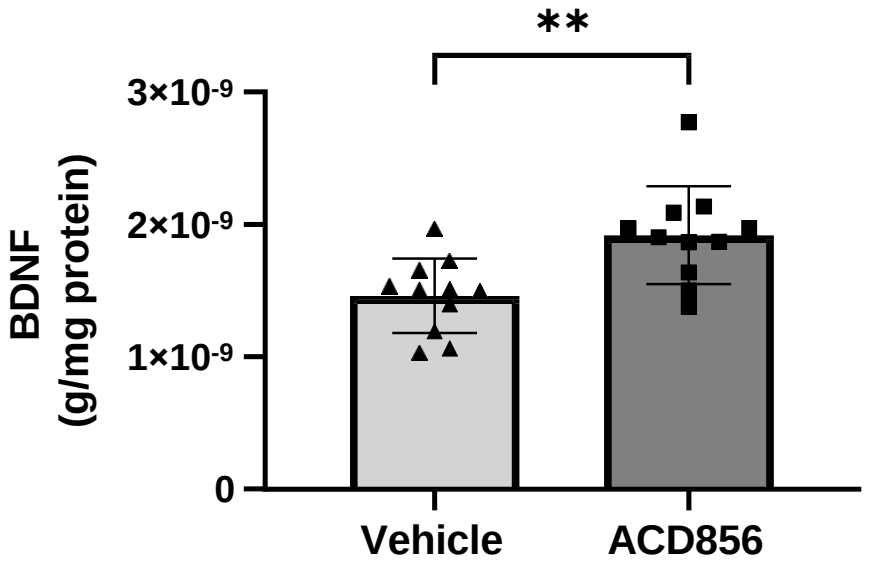
Effects of ACD856 on BDNF levels

- Cortical neurons were incubated with ACD856 for 6 hours
- Old animals were administered ACD856 once daily for 4 weeks

ACD856 increase BDNF levels in cortical neurons



ACD856 increase BDNF in brains of old mice



ACD856 significantly increase the levels of BDNF.

BDNF improves synaptic function and cognition

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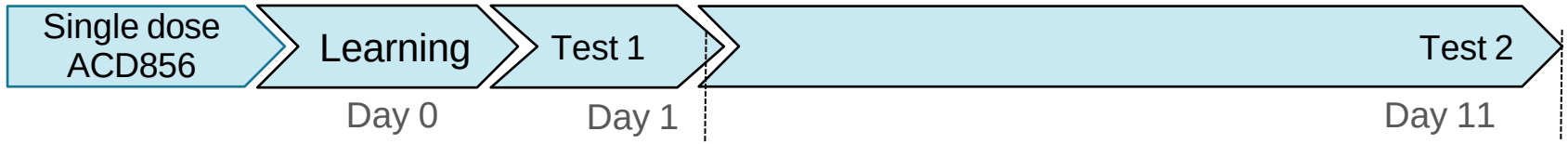
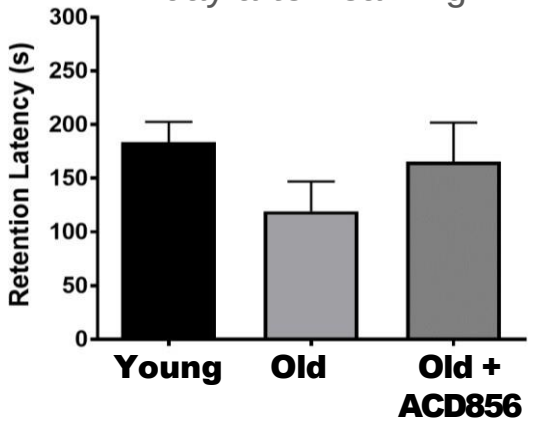
ACD856 and aged-induced memory impairment

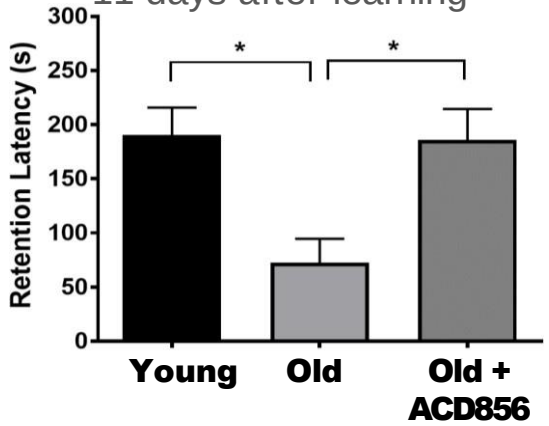
- Old animals were used to study effects of ACD856 on age-induced memory impairment
- Two memory tests were performed at one or eleven days after a learning task



Memory test #1,
1 day after learning



Memory test #2,
11 days after learning



ACD856 improves age-induced memory impairment to a level similar to young animals

LEARN **STORE** **REMEMBER**

A single dose of ACD856 can improve the ability to both learn, store and remember information.
Repeated administration of ACD856 suggest improved neuroplastic adaption leading to better memory

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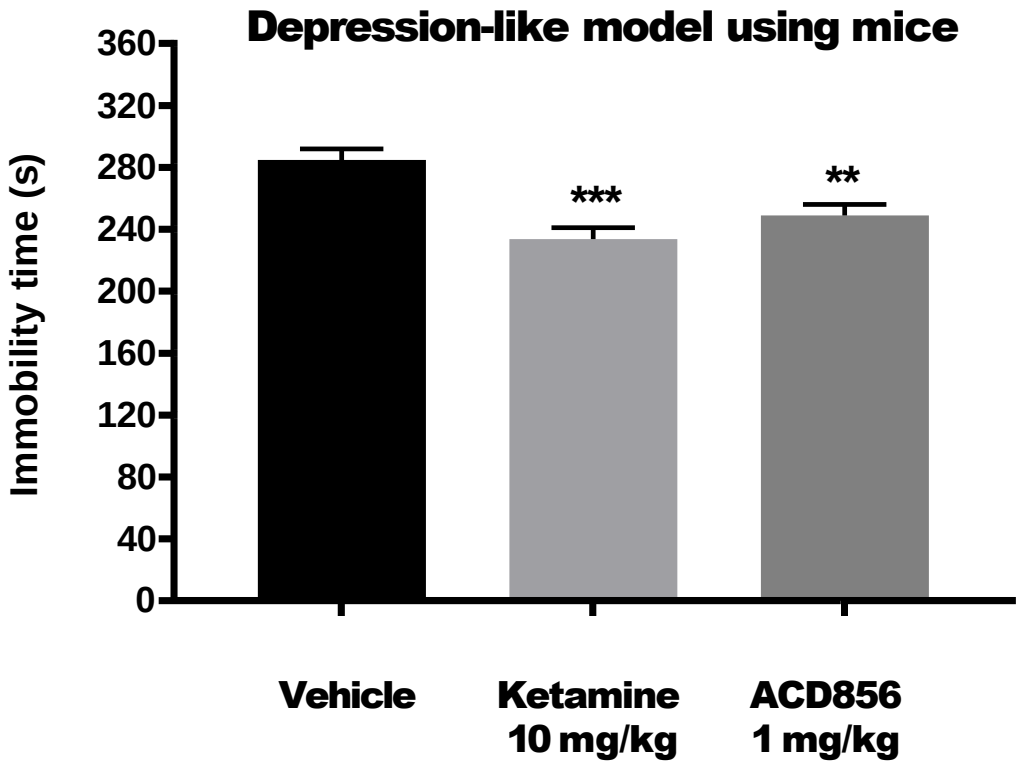
ACD856 and sustained antidepressant-like effects

- Mice were treated with ACD856 once daily for 5 days
- ACD856 was tested for antidepression-like effect 3, 5 or 7 days after the last dose



Repeated dosing of ACD856 leads to a sustained antidepressant-like effect lasting up to one week

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Summary of preclinical results – potential for disease modification

ACD856:

- ✓ Protects against amyloid-beta induced neurotoxicity
- ✓ Enhance neurite outgrowth and neuronal proliferation
- ✓ Increase the levels of BDNF in cortical neurons and in brains of aged mice
- ✓ Improves memory impairment, presumably via increased synaptic function/plasticity
- ✓ Demonstrate a sustained antidepressant-like effect

ACD856 has several short-term effects leading to memory improvement.

The presented long-term effects suggest a new potential disease modifying effect.

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Conclusions

- The preclinical data suggest a new potential use of ACD856
- The effect of ACD856 on BDNF levels are very encouraging and supports that ACD856 can improve learning and memory in multiple ways
- Neuroprotective and neurorestorative effects are add-on effects to the symptomatic effects previously seen with ACD856

The new presented data introduce a potential for disease modifying treatment to the already established symptomatic effects of ACD856.

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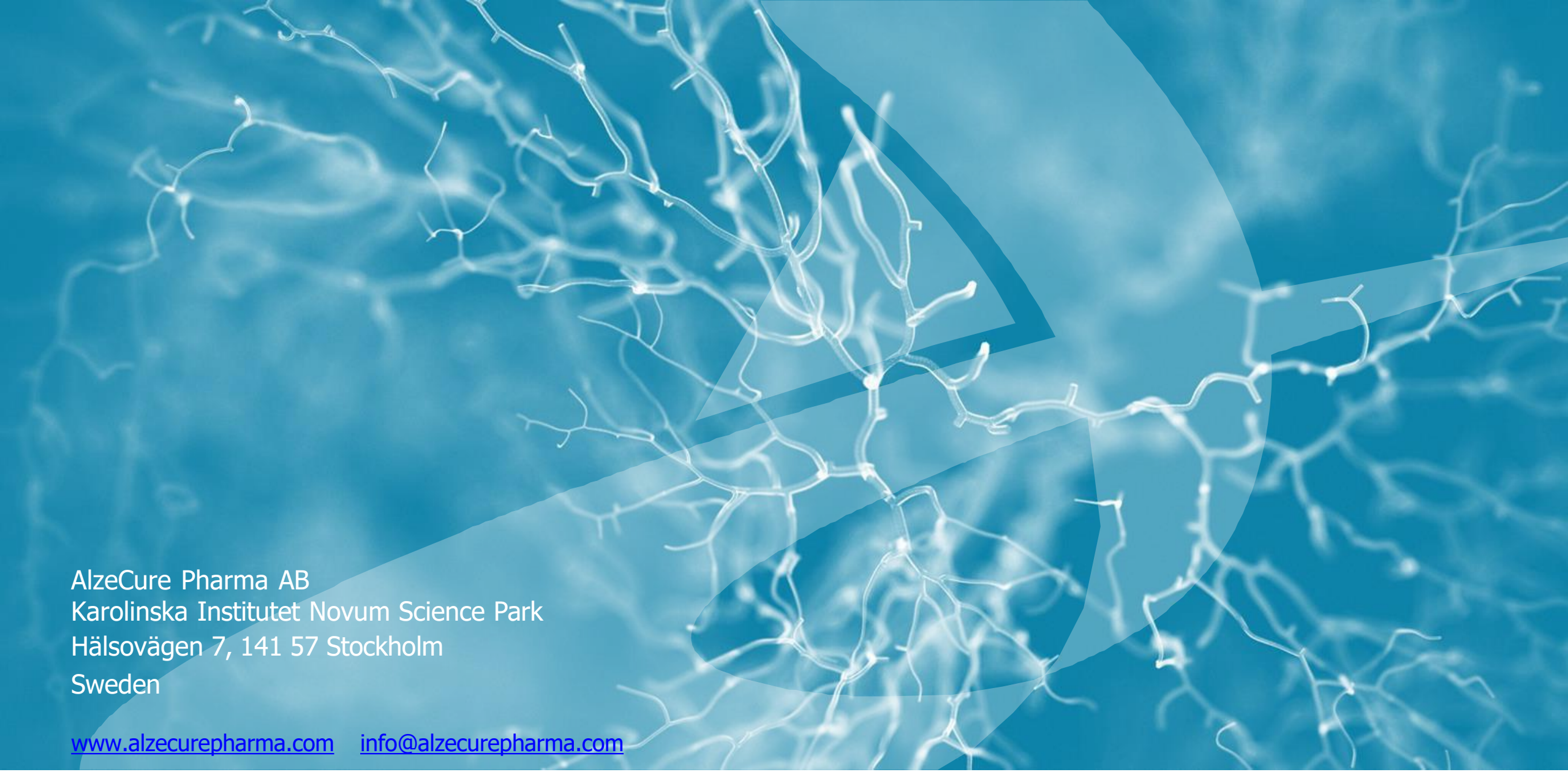

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