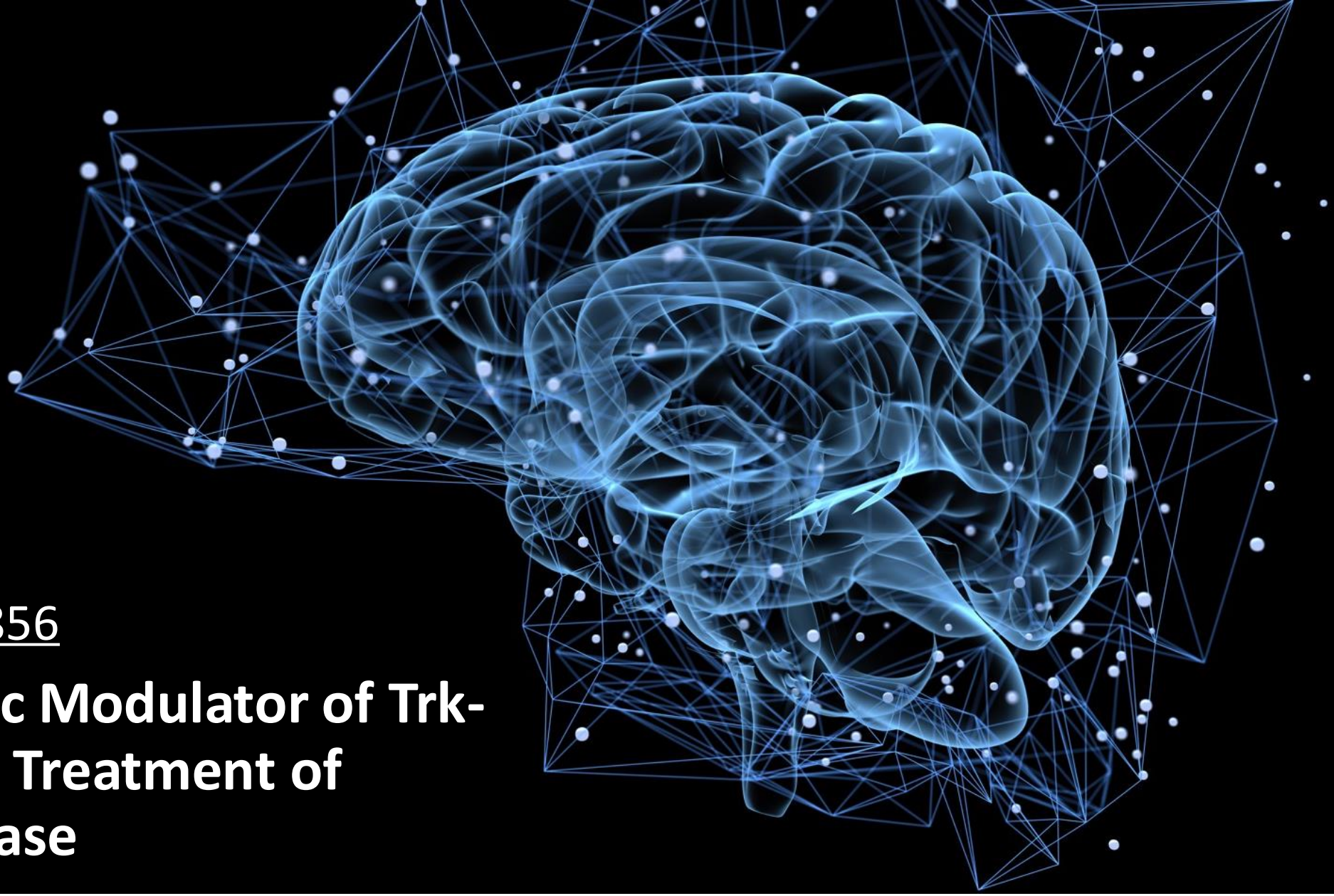
Article summary
December 2024



NeuroRestore ACD856

Positive Allosteric Modulator of Trk-receptors for the Treatment of Alzheimer's Disease

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Summary of a scientific article published in Pharmaceuticals in 2024

pharmaceuticals

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Review

Positive allosteric modulators of Trk-receptors for the treatment of Alzheimer's disease

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Link to article: https://www.mdpi.com/1424-8247/17/8/997

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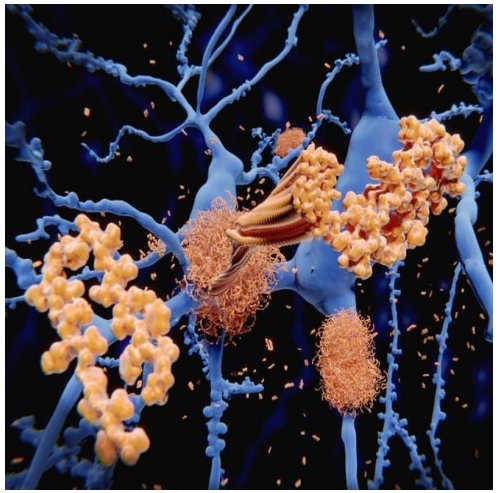
Neurotrophins and their signaling

- The neurotrophins Brain-Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF) are **key for brain health and cognition**
- BDNF & NGF signaling are implicated in several key neuronal functions, including **cholinergic function**, hippocampal neurogenesis and **synaptic plasticity**
- **Loss of NGF-dependent cholinergic neurons** in the basal forebrain and hippocampal atrophy are early hallmarks of Alzheimer's disease and **correlates with cognitive decline**
- **Certain genetics** in man, like the BDNF-Val66Met polymorphism, leads to **lower levels of BDNF**, and is associated with **more rapid cognitive impairment** and **increased disease progression** in Alzheimer's
- Several lines of evidence point to the involvement of BDNF also in **depression**, e.g, depressed patients show a lower expression of BDNF and that **antidepressants regulate BDNF/TrkB expression**



Reduced BDNF and/or NGF-levels could limit the brain's ability to withstand pathological conditions

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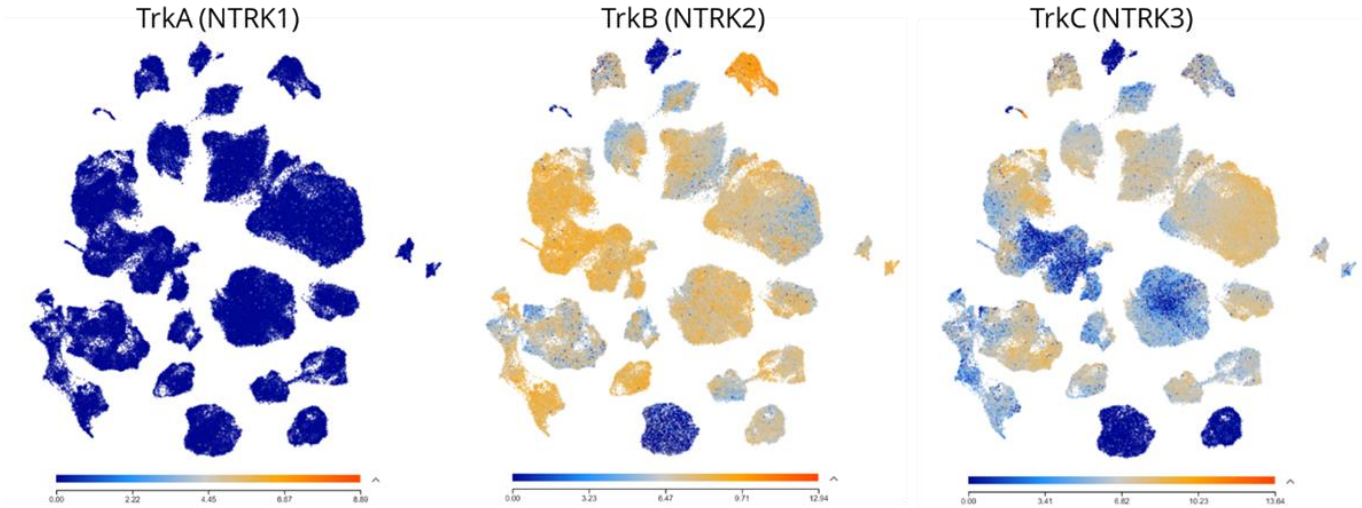
Expression of Trk-receptors in the human brain

TrkA (NTRK1)
High
Basal forebrain
Nucleus basalis
Medial septum
Striatum
Brainstem
Cerebral cortex
Cingulate cortex
Hippocampus
Lower

TrkB (NTRK2)
High
Hippocampus
Cerebral cortex
Striatum
Cerebellum
Amygdala
Midbrain
Hypothalamus
Spinal cord
Choroid plexus
Lower

TrkC (NTRK3)
High
Hippocampus
Cerebral cortex
Cerebellum
Amygdala
Midbrain
Hypothalamus
Choroid plexus
Striatum
Spinal cord
Lower



Trk-receptors are expressed in discrete regions of the human brain

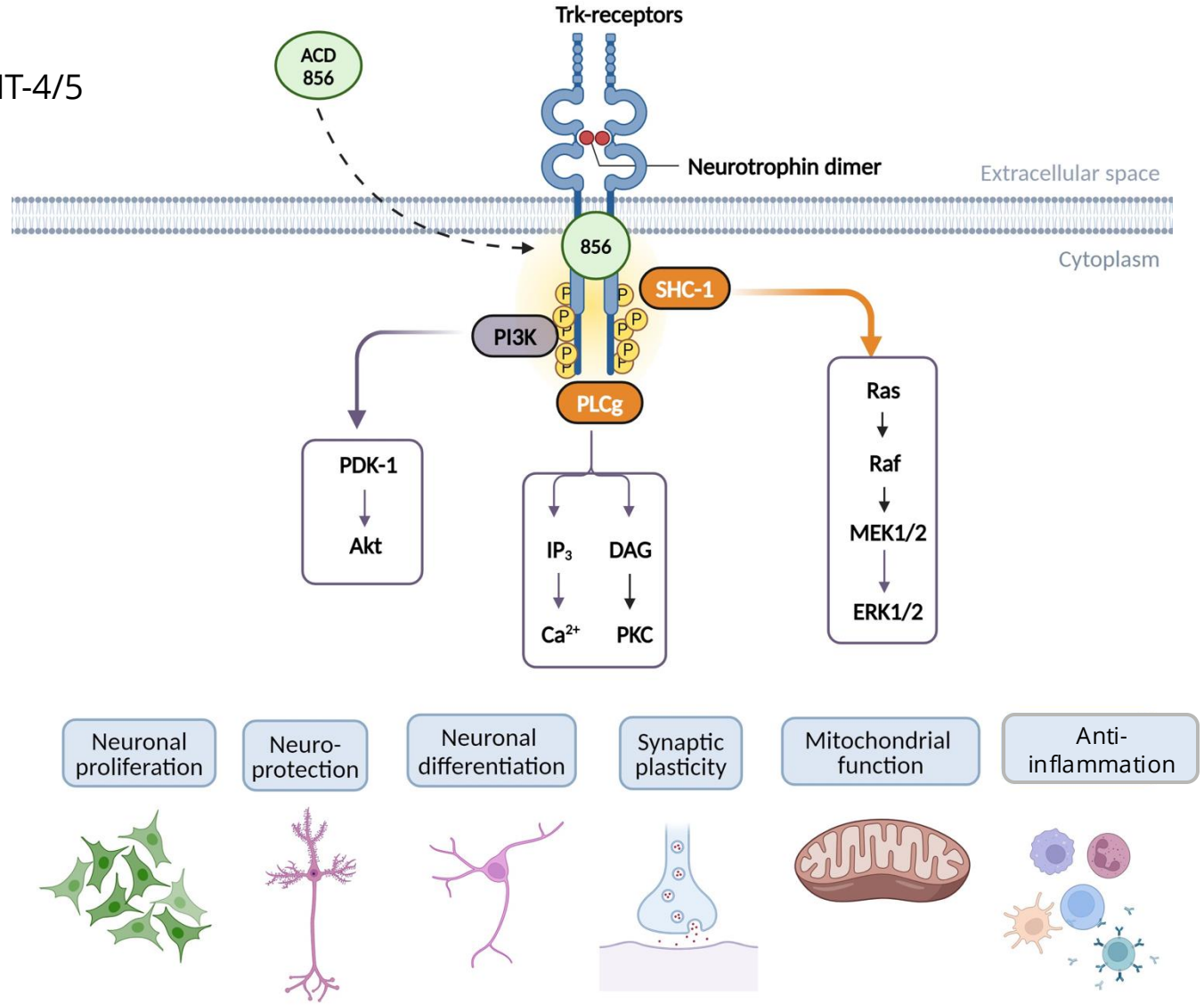
ACD856 – Symptomatic Effects with Potential for Disease Modification

Neurotrophins:
NGF, BDNF, NT-3 and NT-4/5

Receptors:
TrkA, TrkB and TrkC

Short term effects:
- Phosphorylation
- Gene transcription

Long term effects:
- Proliferation
- Neuroprotection
- Neurite outgrowth
- Synaptic plasticity
- Cognition



ACD856:

A pan-Trk **positive allosteric modulator** leading to:
- Increased receptor activity
- Increased synaptic function
- Improved memory

The mechanism of action implies **several indications**, including:
- Alzheimer's disease
- Parkinson's disease
- Traumatic Brain injury
- Disorders relating to neuroinflammation
- Depression

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Two examples of successful discovery and development of PAMs are the TrkA-PAM E2511 and the pan-Trk PAM ACD856.

	Eisai E2511	AlzeCure ACD856
Mechanism of Action	Positive allosteric modulator	Positive allosteric modulator
Target	TrkA	TrkA, TrkB and TrkC
Type	Novel small molecule (<400 Da)	Novel small molecule (<400 Da)
Stage of dev.	Phase I: SAD/MAD, half-life = 3.2 h	**Phase I: SAD/MAD, half-life = 20 h**
Effect on neurite outgrowth	No, not reported	**Yes, *in two different in vitro models***
Neuroprotective	Yes, in two in vivo models	Yes, in two in vitro models
Anti-inflammatory effects	Not reported	**Yes, *both in vivo & in vitro***
Effect on neuro-transmitters	Yes ACh	Yes Serotonin, noradrenaline and dopamine
Effect on cognition	Not reported	**Yes, *cognitive enhancement in several models***
Effect on depression	Not reported	**Yes, *and long-term effects + additive to SSRI***

AlzeCure: Cells. 2021; Drug Discov Today 2022; Psychopharmacology, 2023, International J. Mol. Sciences 2023
Eisai: AAIC, P51985, 2021; ADPD, P186, 2022; AAIC, P62590 and P66208, 2022

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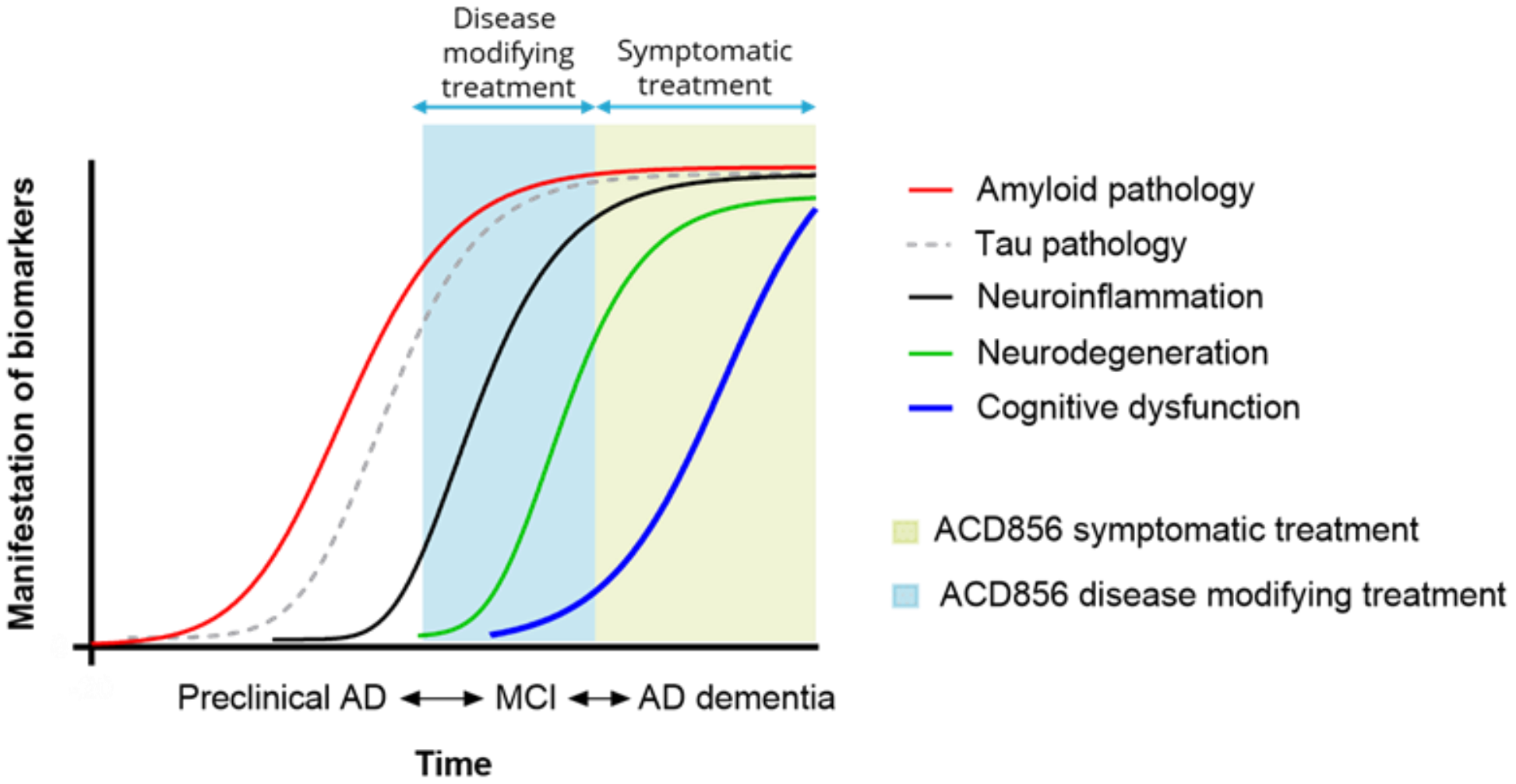
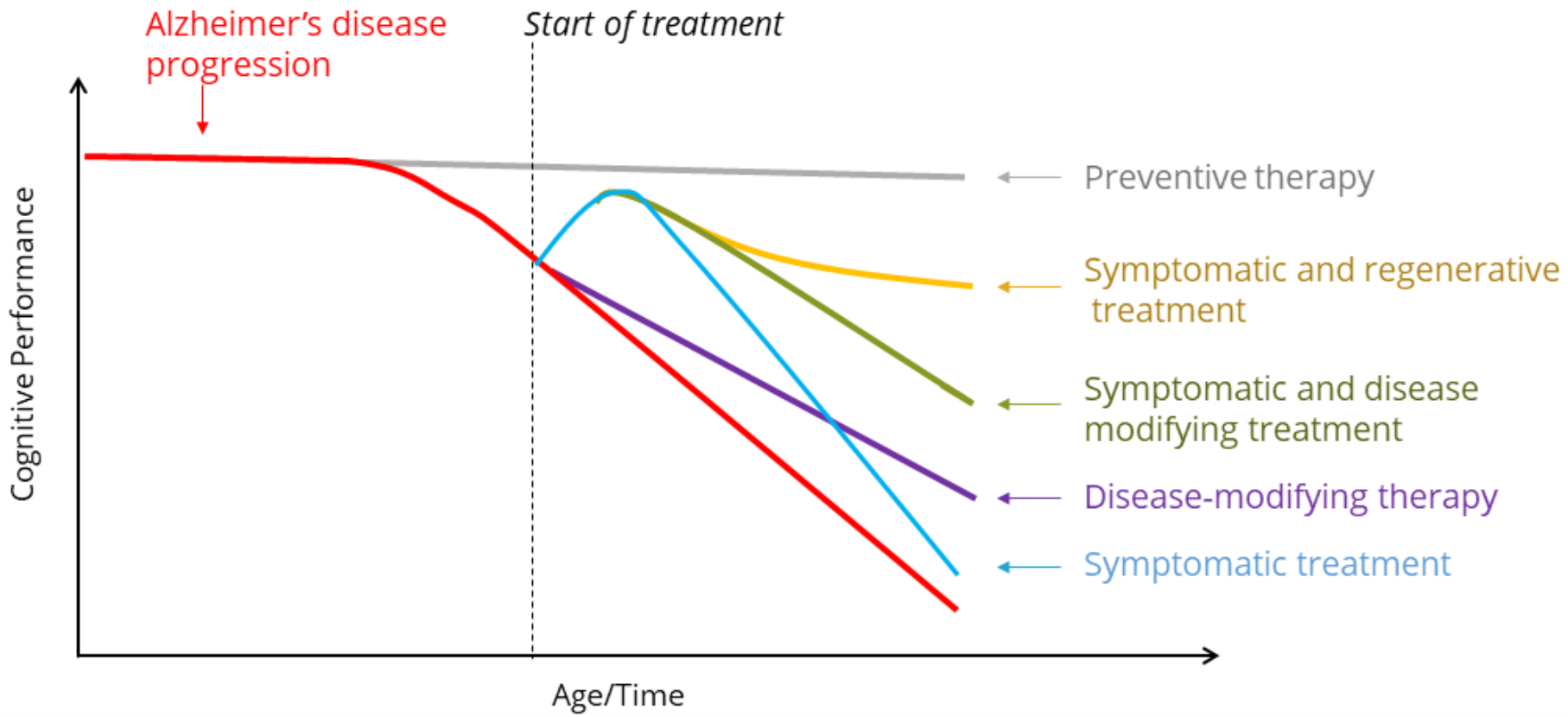
A schematic representation of biomarkers and clinical course of Alzheimer's disease



ACD856 could potentially be used both as a symptomatic treatment but also as disease-modifying treatment earlier in the disease progression

Schematic view of different possible therapeutic modalities on Alzheimer's disease progression



A symptomatic treatment with disease-modifying properties could change the disease progression

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Summary

1. Neurotrophins and their receptors are important for both neuronal and non-neuronal function
2. Trk-receptors are expressed in different regions of the brain
3. Two different small molecule positive allosteric modulators of Trk-receptors are in clinical development, i.e. Eisai's E2511 and AlzeCure's ACD856
4. ACD856 could function as both a symptomatic as well as a disease-modifying therapy
5. A symptomatic treatment with disease-modifying properties could change the disease progression

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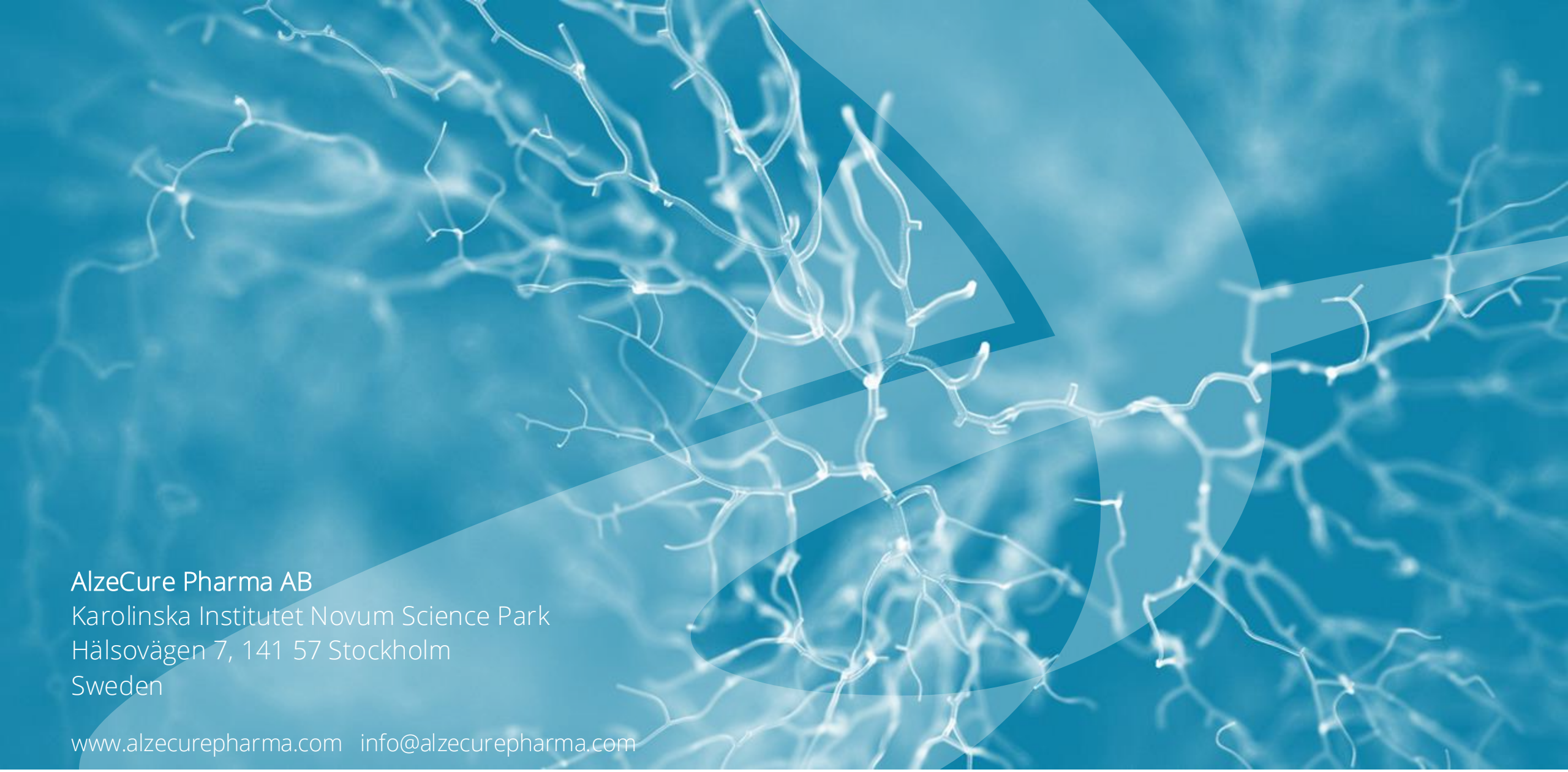

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