#3140

Characterization of mechanisms-of-action of NeuroRestore ACD856, a positive allosteric modulator of Trk-receptors under clinical development for Alzheimer's disease

Cristina Parrado-Fernández[1,2], Azita Rasti[1], Maria Backlund[1], Veronica Lidell[1], Nather Madjid[1], Gunnar Nordvall[1,2], Johan Sandin[1,2], Pontus Forsell[1,2]

1. AlzeCure Pharma AB, Hälsovägen 7, Huddinge, Sweden; 2. Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden.

Background

The neurotrophins BDNF and NGF support neuronal survival and cognition via Trk receptor activation. In disorders like Alzheimer's, this signaling is perturbed. NeuroRestore ACD856, a positive allosteric modulator of Trk receptors, has demonstrated safety and efficacy in clinical phase-I trials. It enhances BDNF activity, promotes cognition, and induces long-term antidepressant effects in vivo, while also promoting neurite outgrowth and exhibiting neuroprotective and anti-inflammatory properties.

Aim

Given the broad symptomatic and disease-modifying effects of ACD856, the aim was to further elucidate its mechanism-of-action in vitro and in vivo.

Methods

ACD856's effects on Trk signaling were evaluated in SH-SY5Y cells overexpressing TrKA and TrkB receptors using phospho-kinase arrays and western blot. Antidepressant-like effects were evaluated in mice using FST and phospho-kinase arrays to link efficacy with neurotrophin pathway activation.

Results

ACD856 induces dose-dependent phosphorylation of TrkB and time- and dose-dependent phosphorylation of downstream targets of TrkB in SHSY5Y-TrkB cells with the highest activation at 10-30 minutes. Trk inhibition confirms that PLC-γ, and GSK-3 phosphorylation is Trk-dependent. In mice, 5 days of ACD856 treatment enhances the phosphorylation of ERK1/2, GSK-3, and PLC-γ in the brain and exhibits an exposure-dependent anti-depressant effect in the FST.

Figure 1. Trk-dependent phosphorylation of ACD856 in vitro

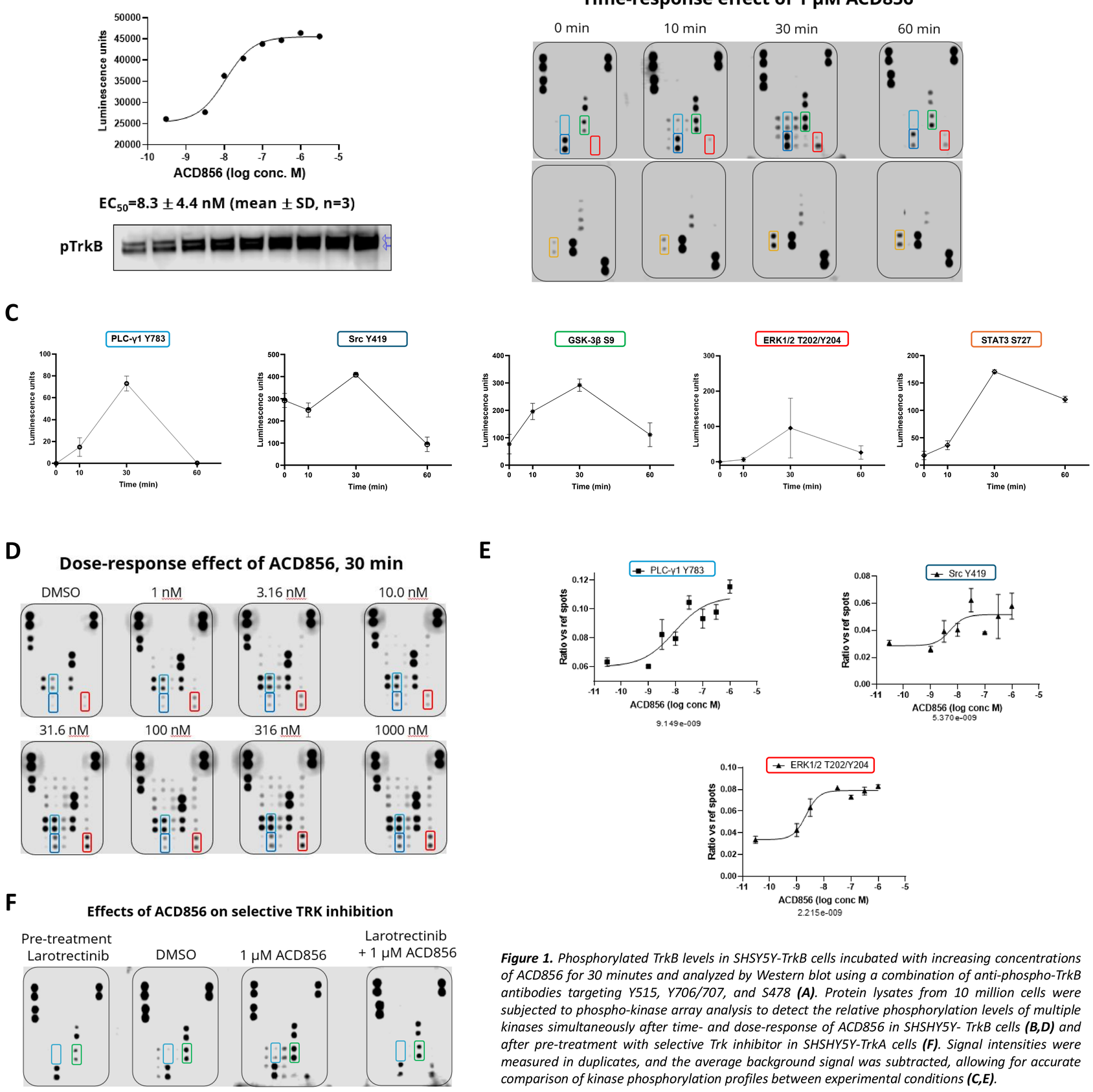

Figure 1. *Phosphorylated TrkB levels in SHSY5Y-TrkB cells incubated with increasing concentrations of ACD856 for 30 minutes and analyzed by Western blot using a combination of anti-phospho-TrkB antibodies targeting Y515, Y706/707, and S478* ***(A)****. Protein lysates from 10 million cells were subjected to phospho-kinase array analysis to detect the relative phosphorylation levels of multiple kinases simultaneously after time- and dose-response of ACD856 in SHSHY5Y- TrkB cells* ***(B,D)*** *and after pre-treatment with selective Trk inhibitor in SHSHY5Y-TrkA cells* ***(F)****. Signal intensities were measured in duplicates, and the average background signal was subtracted, allowing for accurate comparison of kinase phosphorylation profiles between experimental conditions* ***(C,E)****.*

Figure 2. Dose-dependent antidepressant-like effect and exposure effect in vivo and downstream signaling in vivo

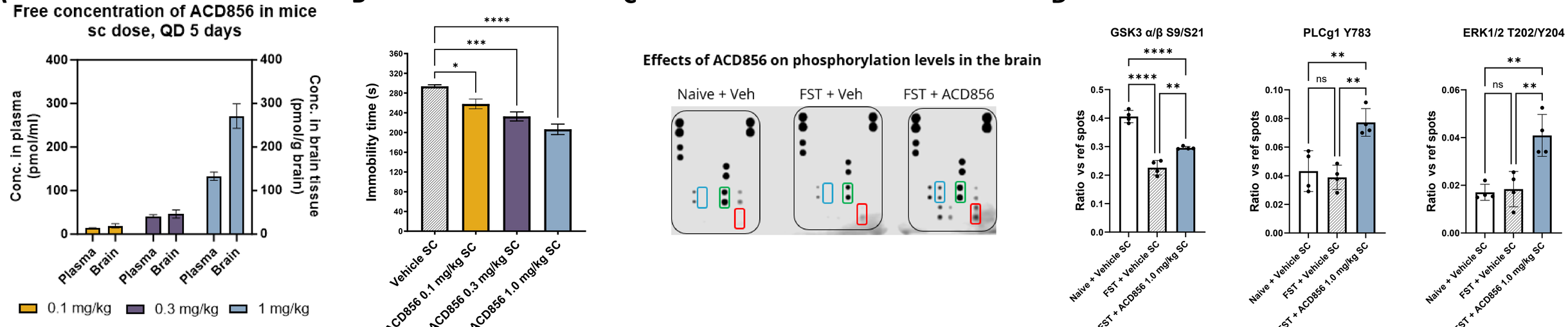

Figure 2. *Dose-dependent brain and plasma concentrations of ACD856* ***(A)*** *and exposure –dependent efficacy in the force swim test* ***(B)*** *in mice following repeat subcutaneous (SC) administration of ACD856. Animals were treated once daily with a dose of 0.1, 0.3, and 1 mg/kg for 5 days (n=8). Midbrain protein lysates (4.5 mg per group), obtained from pools of equal protein amounts from each individual within a group, were subjected to phospho-kinase array analysis to detect the relative phosphorylation levels* ***(C, D).***

Conclusion

ACD856, a novel Trk-PAM in clinical development for Alzheimer's disease, induces Trk-dependent phosphorylation and exerts dose-, time-, and exposure-dependent effects on downstream signaling and in vivo efficacy in a preclinical model of depression. The antidepressant effects complements the procognitive effects of ACD856 and are of relevance as a large number of Alzheimer's patients are on antidepressant treatment.

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martin.jonsson@alzecurepharma.com

Hälsovägen 7, 141 57, Huddinge, Sweden
www.alzecurepharma.com