UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): January 13, 2021

CYCLERION THERAPEUTICS, INC.
(Exact name of registrant as specified in its charter)

Massachusetts	**001-38787**	**83-1895370**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification Number)**

245 First Street, 18th Floor
Cambridge, Massachusetts 02142
(Address of principal executive offices, including Zip Code)

Registrant's telephone number, including area code: **(857) 327-8778**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock, no par value	**CYCN**	**The Nasdaq Stock Market LLC (Nasdaq Global Select Market)**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter). Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 2.02 Results of Operations and Financial Condition.

On January 13, 2021, Cyclerion Therapeutics, Inc. (the "Company") released an updated corporate presentation ("the Corporate Presentation") as described in Item 7.01 below. The presentation includes information that the Company's preliminary unaudited cash, cash equivalents and restricted cash balance as of December 31, 2021 was approximately $58 million.

The foregoing information constitutes unaudited and preliminary estimates that (i) represent the most current information available to management as of the date of the presentation, (ii) are subject to completion of financial closing and procedures that could result in significant changes to the estimated amounts, and (iii) do not present all information necessary for an understanding of the Company's financial condition as of, and its results of operations for the year ended, December 31, 2020. Accordingly, undue reliance should not be placed on such estimates.

The information set forth in this Item 2.02 is being furnished pursuant to Item 2.02 of Form 8-K and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, and it shall not be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended (the "Securities Act"), or under the Exchange Act, whether made before or after the date hereof, except as expressly provided by specific reference in such a filing.

Item 7.01. Regulation FD Disclosure.

Beginning on January 13, 2021, the Company intends to use the Corporate Presentation, or portions thereof, which provides updates on its business activities, in one or more meetings with investors. The Corporate Presentation is attached as Exhibit 99.1 to this Current Report on Form 8-K, is incorporated by reference and is posted on the Company's website, www.cyclerion.com.

The information set forth in and incorporated by reference into this Item 7.01 is being furnished pursuant to Item 7.01 of Form 8-K and shall not be deemed "filed" for purposes of Section 18 of the Exchange Act or otherwise subject to the liabilities of that section, and it shall not be deemed incorporated by reference in any filing under the Securities Act or under the Exchange Act, whether made before or after the date hereof, except as expressly provided by specific reference in such a filing. By filing this Current Report on Form 8-K and furnishing the information in and incorporated by reference into this Item 7.01, the Company makes no admission as to the materiality of Item 7.01 in this report or the presentations available on the Company's website. The information contained in the presentations is summary information that is intended to be considered in the context of the Company's filings with the Securities and Exchange Commission (the "SEC") and other public announcements that the Company makes, by press release or otherwise, from time to time. The Company undertakes no duty or obligation to publicly update or revise the information contained in this report, or incorporated by reference herein, although it may do so from time to time as its management believes is appropriate or as required by applicable law. Any such updating may be made through the filing of other reports or documents with the SEC, through press releases, by updating its website or through other public disclosure.

Forward-Looking Statements

This report and the presentations may contain forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act. Our forward-looking statements are based on current beliefs and expectations of our management team that involve risks, potential changes in circumstances, assumptions, and uncertainties, including statements about the anticipated timing of release of topline results of our clinical trials; the progression of our discovery programs into clinical development; and the business and operations of the Company. We may, in some cases use terms such as "predicts," "believes," "potential," "continue," "anticipates," "estimates," "expects," "plans," "intends," "may," "could," "might," "likely," "will," "should" or other words that convey uncertainty of the future events or outcomes to identify these forward-looking statements. Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement. Applicable risks and uncertainties include those related to the possibility that any results of operations and financial condition of the Company reported are preliminary and subject to final audit and the risks listed under the heading "Risk Factors" and elsewhere in our 2019 Form 10-K filed on March 12, 2020, and our subsequent SEC filings, including the Form 10-Qs filed on May 4, 2020, August 3, 2020 and November 5, 2020. Investors are cautioned not to place undue

reliance on these forward-looking statements. These forward-looking statements (except as otherwise noted) speak only as of the date of this report, and the Company undertakes no obligation to update these forward-looking statements, except as required by law.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	Description
99.1	Corporate Update Presentation dated January 13, 2021

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Cyclerion Therapeutics, Inc.

Dated: January 13, 2021

By: /s/ Anjeza Gjino
Name: Anjeza Gjino
Title: Chief Financial Officer

Exhibit 99.

cyclerion

On a mission to develop treatments that restore cognitive function

January 2021

Safe Harbor Statement

This document contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended.

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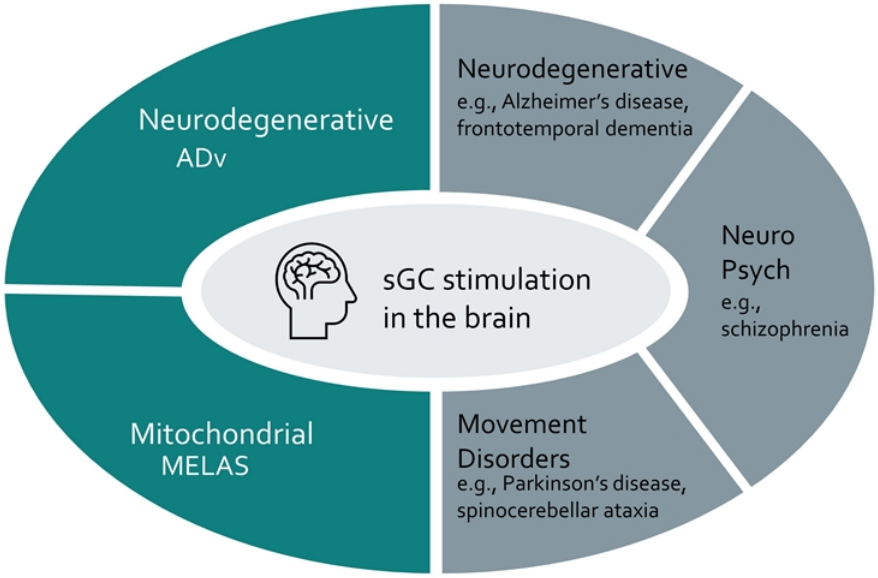
On a mission to develop treatments that restore cognitive function

- **first-in-class:** CY6463 crosses the blood-brain barrier to modulate a key node in a fundamental CNS signaling network
- **broad potential:** multidimensional pharmacology to impact a wide range of CNS diseases
- **promising clinical profile:** rapid improvement in biomarkers associated with cognitive impairment
- **biomarker-guided development strategy:** targeted patient populations ADv and MELAS to start

*previously known as IW-6463

Potential to impact a wide range of CNS diseases

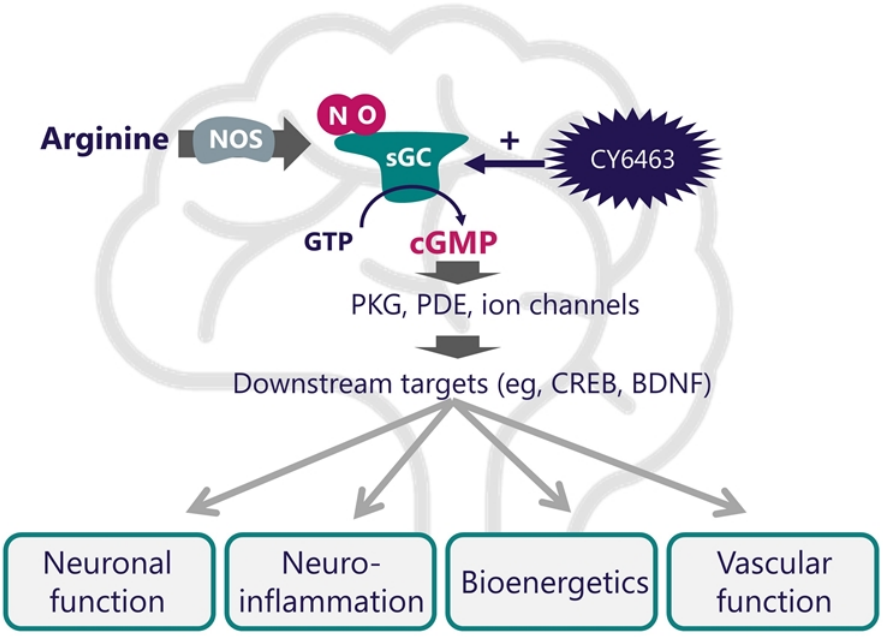
Current Focus



Future Opportunities

sGC = soluble guanylate cyclase

CY6463 modulates a key node in a fundamental CNS signaling network

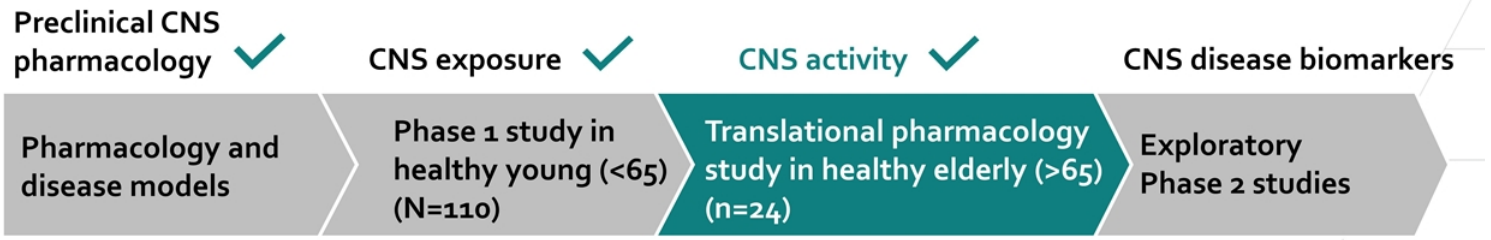


CY6463:

- first in class BBB-permeable, positive allosteric modulator of sGC
- amplifies endogenous NO-sGC-cGMP signaling

Preclinical data and extensive academic work validate the central role of the pathway in brain physiology

CY6463 biomarker-driven development strategy



ongoing	*completed Jan 2020*	*completed Oct 2020*	*ongoing*
✓ CNS-exposure ✓ drug-like properties ✓ pharmacological profile consistent with known role of pathway in CNS	✓ safety ✓ once-daily ✓ target engagement ✓ dose selection	✓ safety ✓ pharmacodynamic biomarkers ✓ neurodegenerative biomarkers	• focused patient subsets • predictive biomarker data • early impacts on disease

CY6463 showed rapid and persistent improvements in multiple independent biomarkers associated with cognitive impairment

In a 15-day study in 24 healthy elderly subjects CY6463 demonstrated:

increased alpha and gamma power

improved mismatch negativity (MMN) latency

faster saccadic eye movement (SEM) reaction time

reduction in neuroinflammatory biomarkers

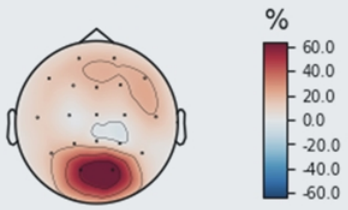
- rapid onset (<15 days)
- effect increased with age
- biomarkers linked to AD and aging

CY6463 improved qEEG measures

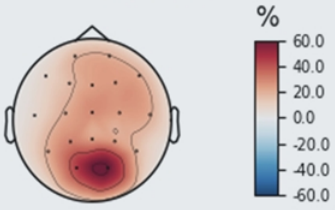
Significant increase in EEG alpha power; trend improvements in gamma power

Significant increase in EEG alpha power

CY6463 vs. baseline

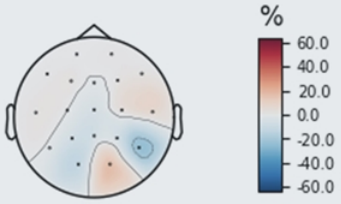


CY6463 vs. placebo



No effect of placebo

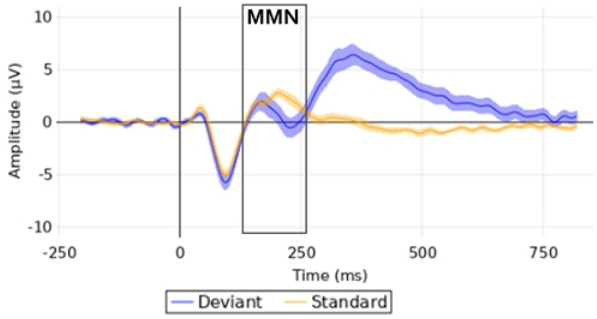
Placebo vs. baseline



change (%) in alpha power on day 15

CY6463 improved mismatch negativity (MMN) latency

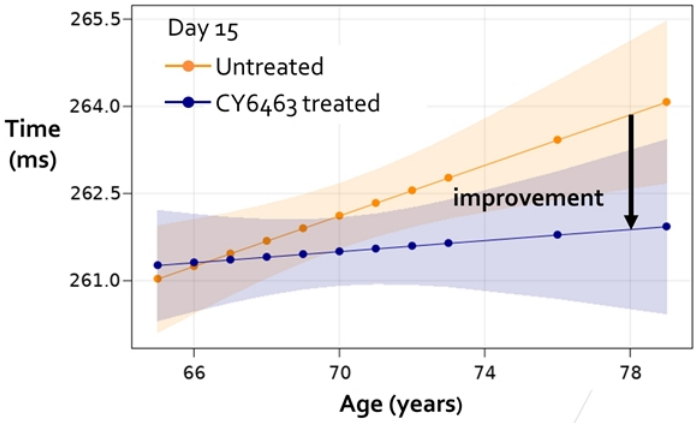
MMN measures reactions between a standard and deviant tone



Latency is affected in aging and neurodegenerative diseases with cognitive impairment

Significant decrease in MMN latencies for CY6463 vs untreated on day 15 ($p<0.02$)

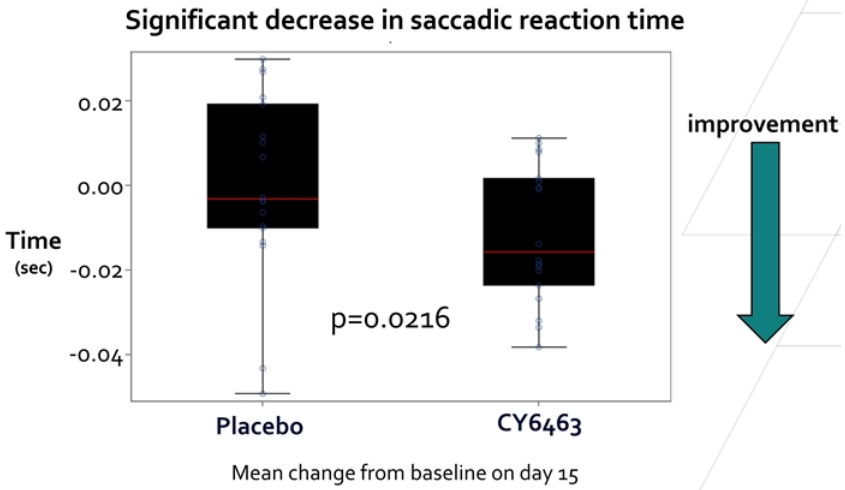
effect more pronounced in older subjects



CY6463 improved saccadic reaction time

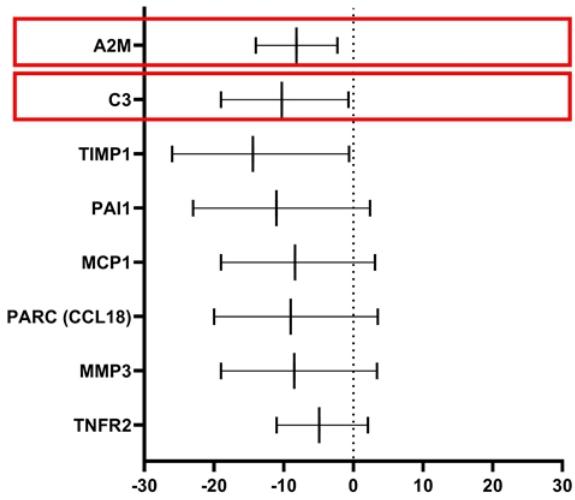
Saccadic eye movement is an objective, functional measure associated with cognition

- short, fast, simultaneous tracking of both eyes in the same direction
- reflective of attention/arousal
- aging associated with longer reaction times and slower velocities



* average of the post dose values on Day 15

CY6463 improved neuroinflammatory biomarkers



LS % Mean Difference from placebo at Day (95% CI)

Alpha-2-macroglobulin (A2M) levels predict cognitive decline and development of AD; may lead to tau hyperphosphorylation

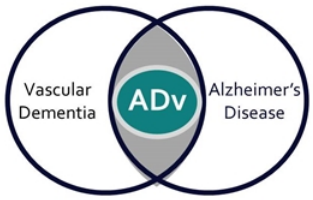
Complement C3 (C3) colocalizes with Aβ plaques and tau tangles; involved in synaptic remodeling and degeneration

A2M and C3 are associated with pathological aging and Alzheimer's Disease

CY6463 biomarker-driven development strategy

Preclinical CNS pharmacology ✓	CNS exposure ✓	CNS activity ✓	CNS disease biomarkers
Pharmacology and disease models	**Phase 1 study in healthy young (<65) (N=110)**	**Translational pharmacology study in healthy elderly (>65) (n=24)**	**Exploratory Phase 2 studies**
ongoing	*completed Jan 2020*	*completed Oct 2020*	*ongoing*
✓ CNS-exposure ✓ drug-like properties ✓ pharmacological profile consistent with known role of pathway in CNS	✓ safety ✓ once-daily ✓ target engagement ✓ dose selection	✓ safety ✓ pharmacodynamic biomarkers ✓ neurodegenerative biomarkers	• focused patient subsets • predictive biomarker data • early impacts on disease

Biomarker-guided development strategy: ADv



growing patient population, devastating impact, limited treatments

Today

Exploratory Phase 2 near-term impact on disease-specific biomarkers and cognition

Tomorrow

Larger, longer symptomatic trials focused on cognition

Initial approval expected on surrogate, symptomatic or functional endpoints

Future

Standard of care for patients with ADv

Potential for disease modification and expansion into broader AD

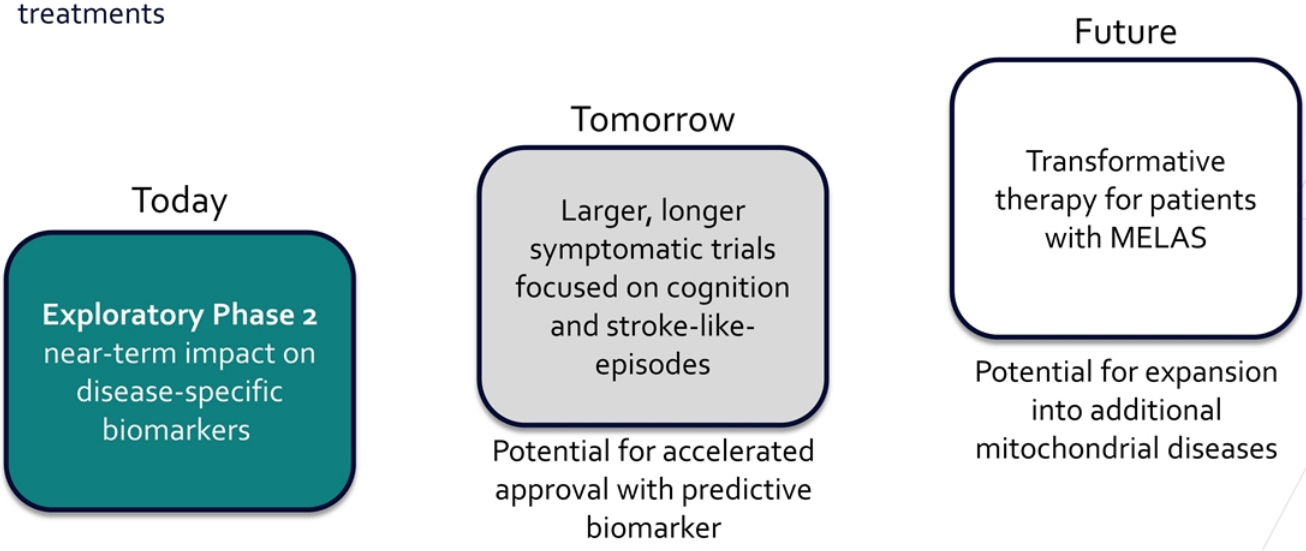
ADv study expected to initiate in mid-2021

Objectives	• evaluate safety, tolerability, and pharmacodynamic effects (EEG, MRI, neuroinflammatory biomarkers, cognition)
Treatment	• once-daily CY6463 vs. placebo • 12 weeks
Enrichment strategy	• confirmed AD pathology (PET, CSF) • 2+ cardiovascular risk factors • mild-moderate subcortical small-vessel disease on MRI • Mini Mental State Exam score (20-26)

With the Alzheimer's Association's Part the Cloud-Gates

Biomarker-guided development strategy: MELAS

MELAS is a serious orphan disease, significant CNS impact, no approved treatments

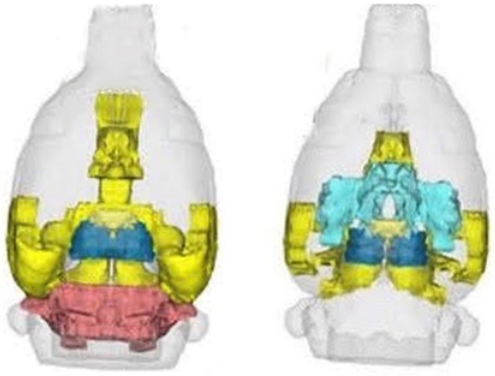


MELAS study underway; topline data expected mid-2021

Objectives	• evaluate safety, tolerability, and pharmacodynamic effects (MRI, EEG, biomarkers)
Treatment	• 29-day open label • once-daily CY6463 • up to 20 adults (targeting 12 completers)
Enrichment strategy	• genetically confirmed mitochondrial disease with neurological features of MELAS • elevated plasma lactate (disease biomarker)
Sites	• centers of excellence for mitochondrial medicine: CHOP, MGH, Children's National Hospital, Columbia, Johns Hopkins

Broadening clinical potential: NextGen sGC program

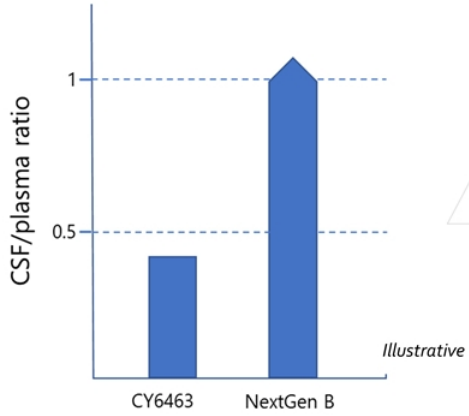
Eliciting different patterns of CNS engagement*



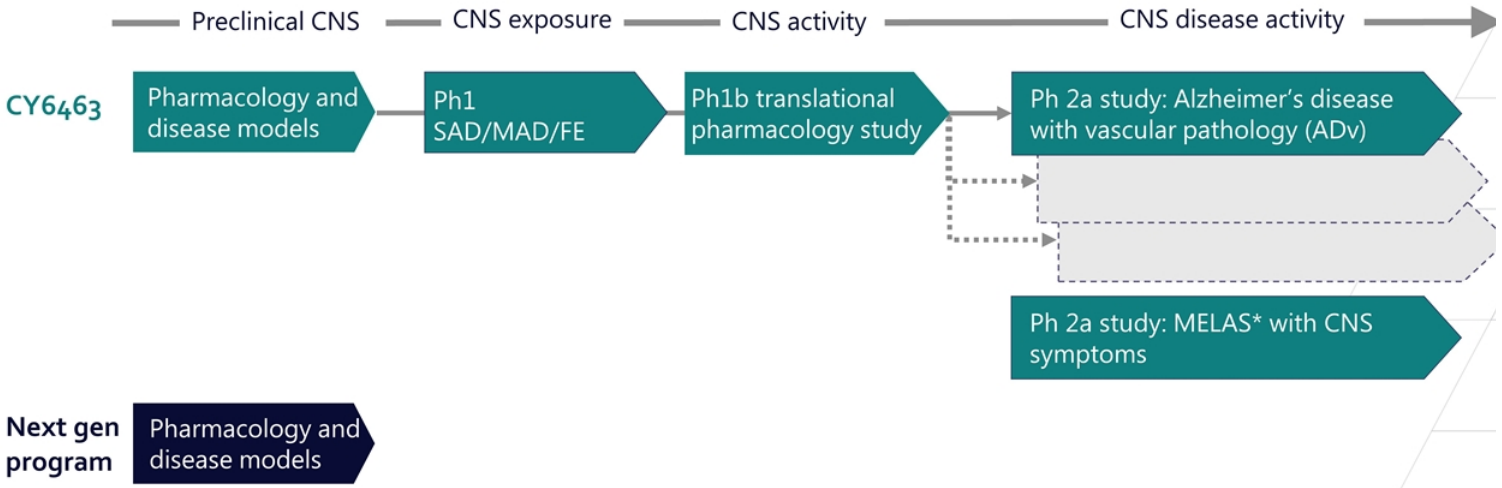
CY6463 NextGen A

Yellow = hippocampal complex and cortical areas associated with memory
Red = anterior cerebellum
Dark blue = midbrain dopaminergic system
Light blue = amygdala/hypothalamus

Increasing CNS/plasma exposure



Advancing a growing pipeline for targeted patient populations



2021: executing on our priorities

Clinical	• ADv Ph2 study start mid-2021 • MELAS Ph2 study topline data mid-2021
Pipeline	• additional indication investigation • NextGen development candidate
Partnerships, capabilities and capital	• praliciguat out-license; explore CNS partnerships • grow external CNS network to augment core team • Q4 2020 ending cash balance of ~$58M* funds current priorities

* Preliminary, unaudited unrestricted cash, cash equivalents and restricted cash balance as of December 31, 2020

On a mission to develop treatments that restore cognitive function

- **first-in-class:** CY6463 crosses the blood-brain barrier to modulate a key node in a fundamental CNS signaling network
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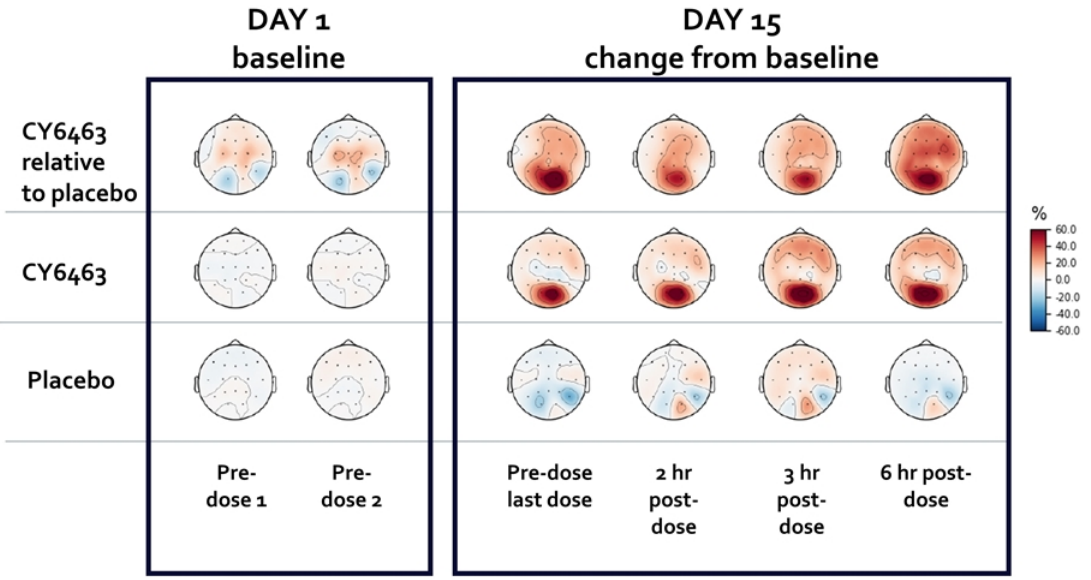
Appendix

CY6463's consistent alpha power effects across repeat sessions indicate stable and robust signal

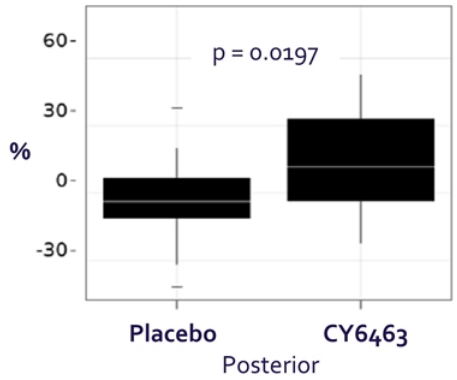


Magnitude of improvement represents decline after 2 years aging

CY6463 increased alpha power with high responder rate (>70%)

Increase in alpha power

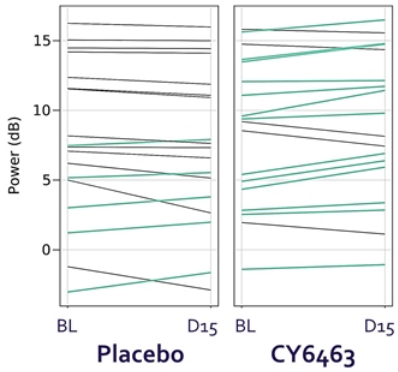
Day 15 change from baseline in mean closed-eye alpha (8-12 Hz) Power



- 17% treatment effect over placebo
- Similar increase in anterior alpha power observed (p=0.0752)

Consistent individual treatment responses

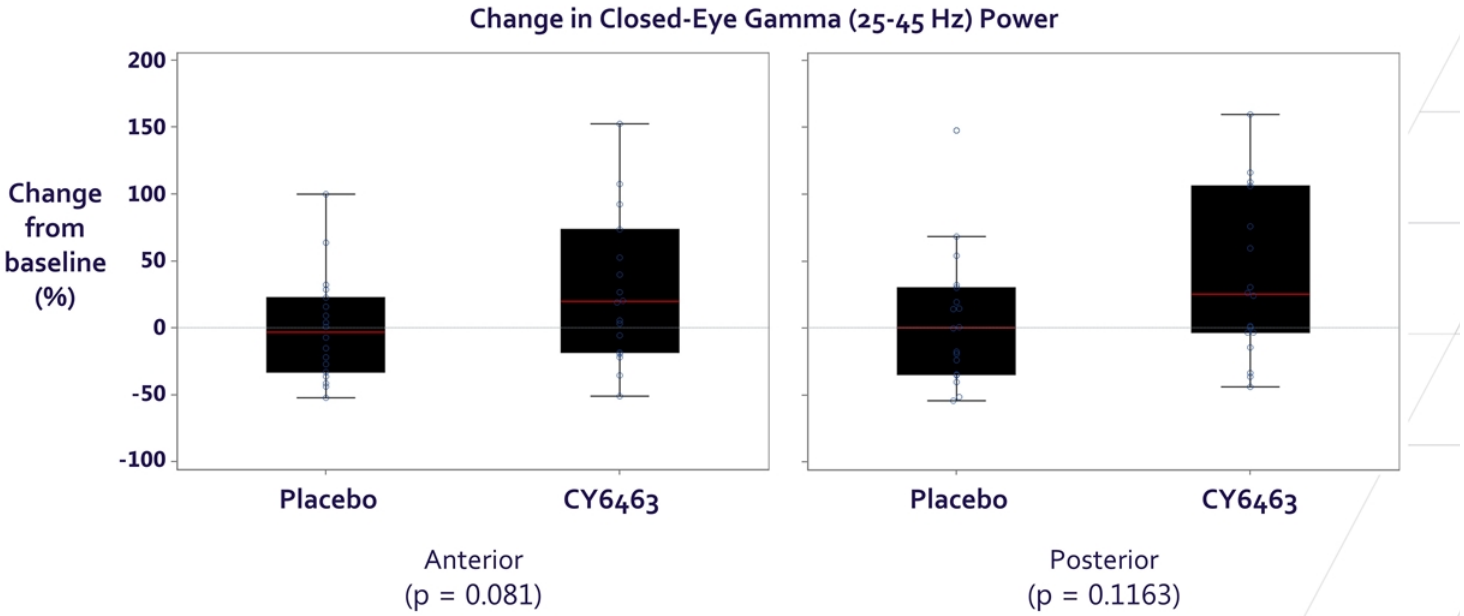
Posterior Closed-Eye Alpha (8-12 Hz) Power



- 13/18 participants increase with CY6463, vs 5/18 with placebo[1]
- Overall effect not driven by outliers

1. Includes all subjects. For CY6463 and pbo each: n=12 for period 1, n=6 for period 2

Improvement trend in gamma power associated with CY6463 treatment

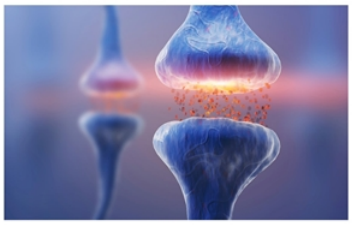


CY6463 demonstrated beneficial effects in preclinical studies across multiple domains associated with cognitive disease

IMPROVED

Neuronal Function

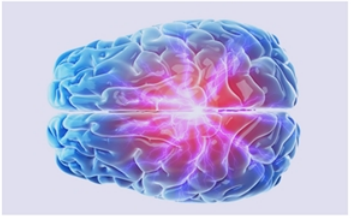
Enhanced memory & spine density in aged animals; increased LTP in neurodegenerative models; affected qEEG spectra



REDUCED

Neuro-inflammation

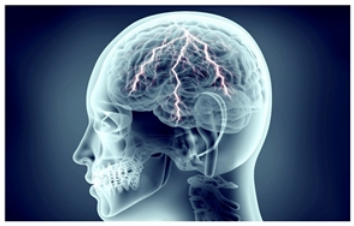
Decreased markers of LPS-induced neuroinflammation (ICAM1, VCAM1, IL6) *in vitro*



ENHANCED

Cellular Bioenergetics

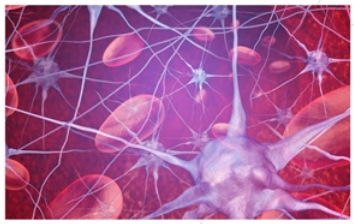
Increased ATP and restored gene expression in cells from patients with mitochondrial diseases



IMPROVED

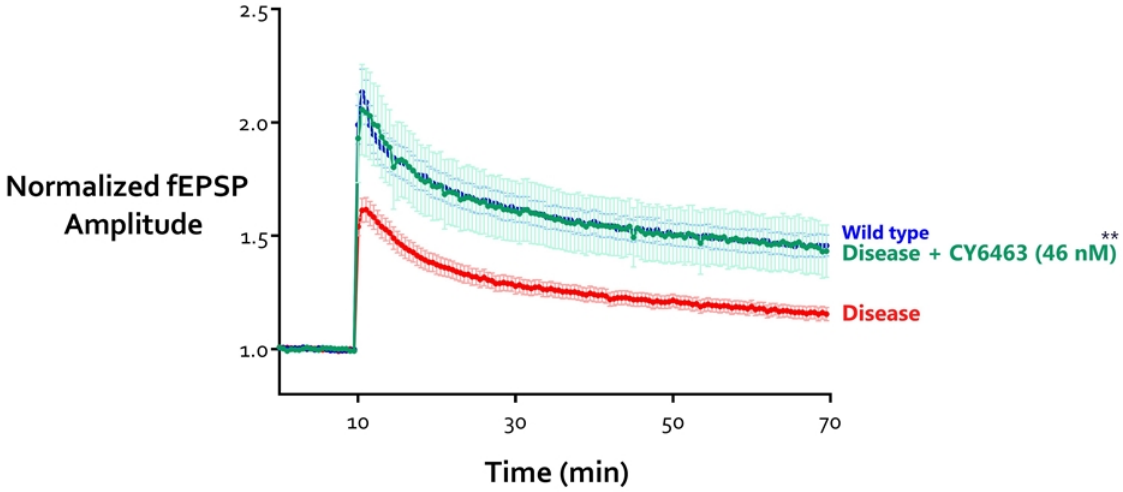
Cerebral Blood Flow

Increased blood flow in areas associated with memory and arousal by fMRI BOLD imaging



CY6463 improved neuronal function

Restored hippocampal long-term potentiation to wild-type levels in a mouse neurodegenerative model



By acting directly on the neurons, CY6463 could restore impaired neurotransmission

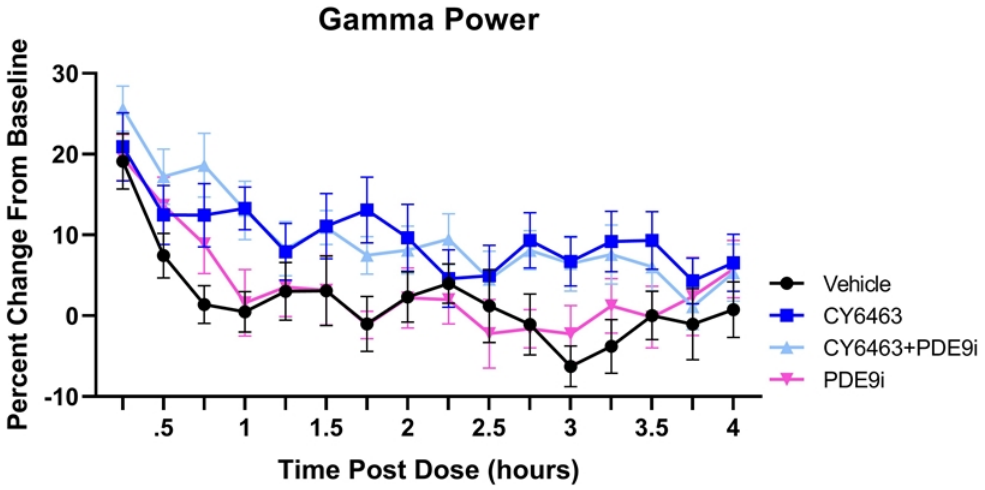
Hippocampal slices from symptomatic Huntington's Disease (R6/2) mice incubated with CY6463 for 25-30 minutes before LTP induction

Extracellular field potentials recordings performed using Multi-Electrode Array; **p<0.01 vs. Disease

CY6463 increased qEEG gamma power

No effect seen with PDE9 inhibitor

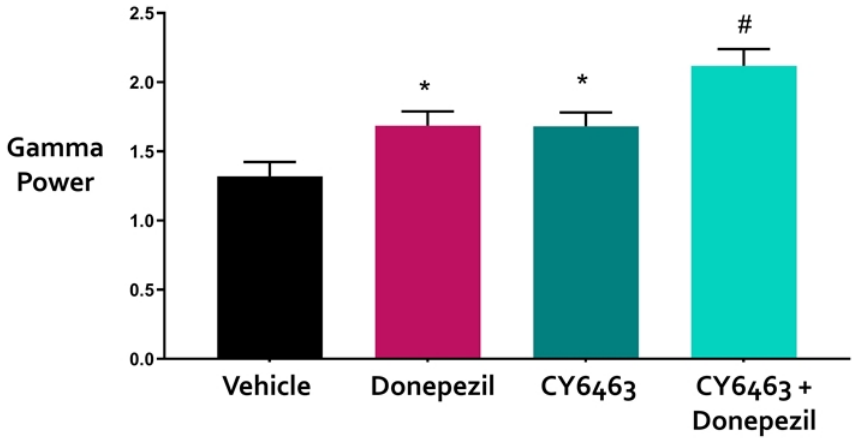
Improve Neuronal Function | Reduce Neuro-inflammation | Enhance Cellular Bioenergetics | Improve Cerebral Blood Flow



Healthy awake rats were treated with clinically relevant doses of CY6463 (3 mg/kg) or PDE9 inhibitor (10 mg/kg)

CY6463 and donepezil act independently to enhance qEEG signal

Combination elicited additive increase in gamma band power in healthy rats



CY6463 may offer opportunity to enhance attention and cognitive performance alone and on top of standard of care

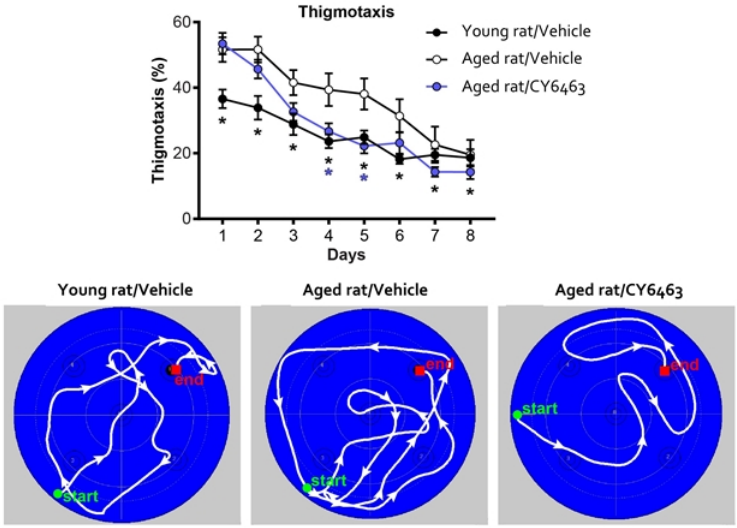
Improve Neuronal Function | Reduce Neuro-inflammation | Enhance Cellular Bioenergetics | Improve Cerebral Blood Flow

Healthy rats orally administered CY6463 (10mg/kg), Donepezil (1mg/kg), or a combination.
Graph displays 1-2h post-dose, mean ± SEM

*p<0.05 vs Veh
# p<0.05 CY6463 vs CY6463 +Donepezil

CY6463 improved learning and memory in aged rats

Increased rate of learning in aged rats treated with CY6463 in Morris Water Maze

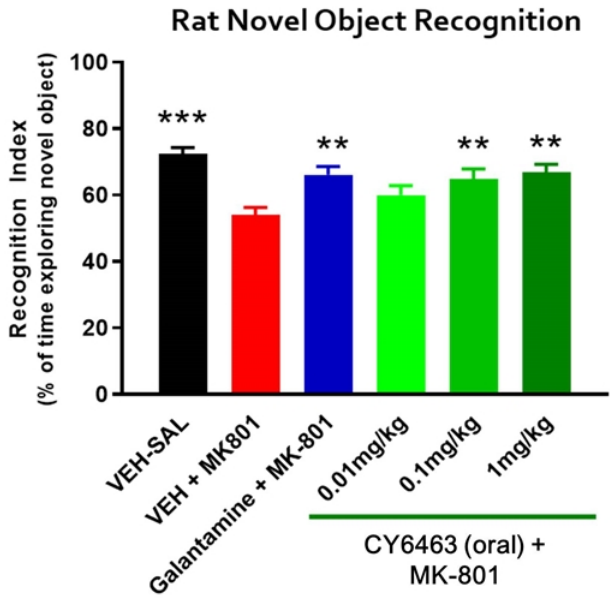


Healthy aged male rats were administered CY6463 (10 mg/kg, p.o.) daily during Morris Water Maze training

*p<0.05 vs. Aged vehicle-treated

CY6463 improved cognitive function in pharmacologically impaired rats

Improve Neuronal Function | Reduce Neuro-inflammation | Enhance Cellular Bioenergetics | Improve Cerebral Blood Flow

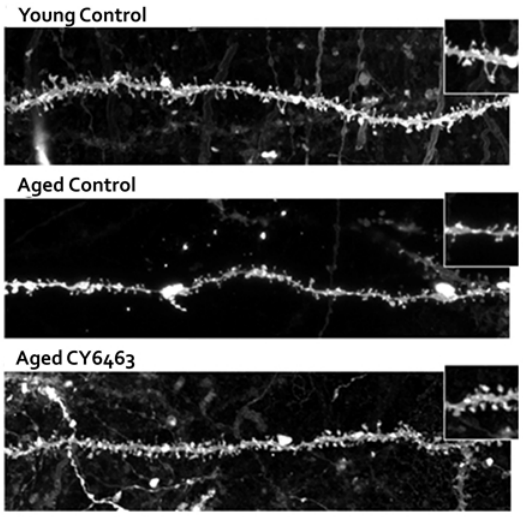


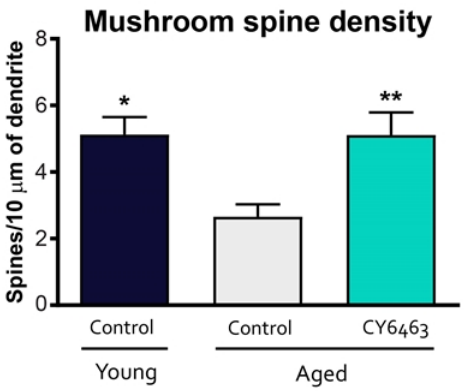
Male rats administered vehicle, galantamine (positive control) or CY6463, followed by MK-801 or vehicle

**p<0.01 vs. VEH + MK801 rats
***p<0.001 vs. VEH + MK801 rats

CY6463 improved neuronal function

Enhanced hippocampal spine density in aged animals treated with CY6463





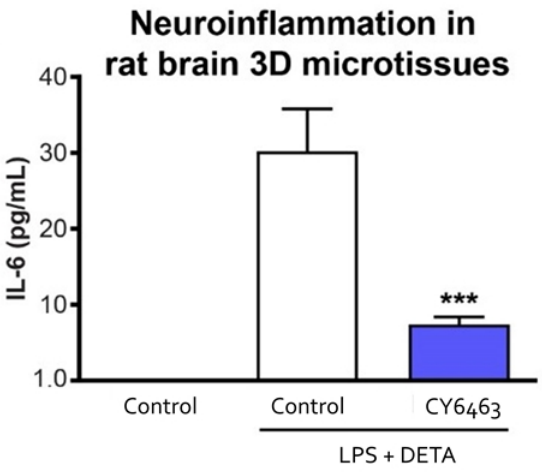
Restoration of spine density has potential to provide neuroprotective effects and improve synaptic function in neurodegenerative diseases

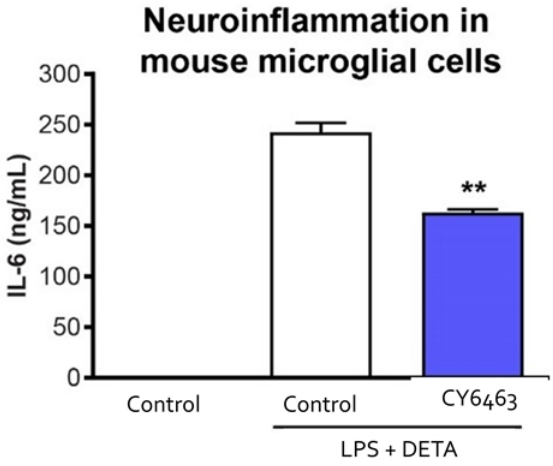
3-month old (young) or 16-month old (aged) healthy mice at study initiation
Aged mice treated for 4 months with 1 mg/kg CY6463

*p<0.05, **p<0.01 vs. Aged

CY6463 reduced neuroinflammation

Decreased markers of LPS-induced neuroinflammation in vitro





CY6463 (10 µM) and DETA (30 µM) were incubated with SIM-A9 cells or rat brain 3D microtissues for 30 minutes before LPS (100 ng/ml) incubation and further incubated for 18-20h at 37°C before IL-6 quantification in the media

*p<0.05, **p<0.01, ***p<0.001 vs. control LPS-treated wells

CY6463 enhanced cellular bioenergetics

Increased ATP and restored decreased gene expression in cells from patients with mitochondrial diseases

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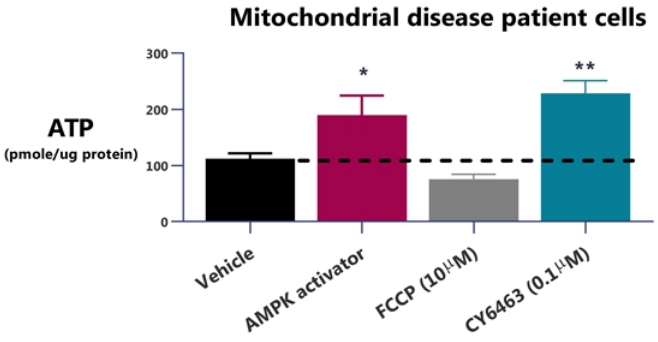

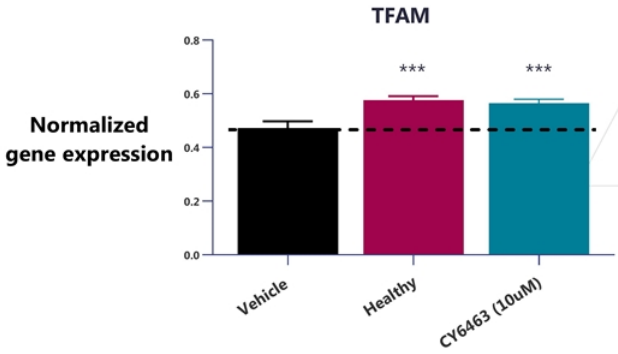

GM13740 Leigh Syndrome patient cells obtained from the Coriell Institute were treated for 24h before ATP quantification

TFAM: mitochondrial transcriptional factor A, a key activator of mitochondrial transcription as well as a participant in mitochondrial genome replication.

*p<0.05, **p<0.01, ***p<0.001 vs. vehicle-treated wells

CY6463 improved cerebral blood flow

Increased blood flow in areas associated with memory and arousal by fMRI BOLD imaging

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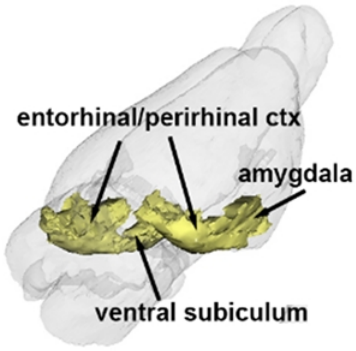
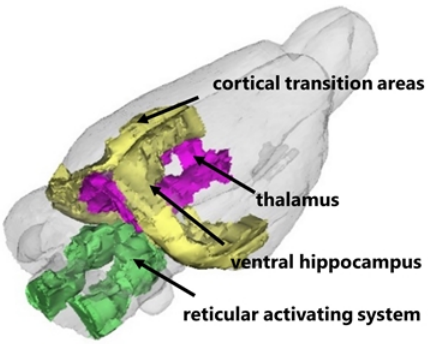


Peripherally restricted sGC stimulator



CNS-penetrant sGC stimulator (CY6463)

Healthy awake male rats treated with 0.3 mg/kg iv; image quantification 20-30 minutes post-dose

Relevant reference publications (1 of 2)

NO-sGC-cGMP signaling in the CNS

- Garthwaite, John. “Nitric oxide as a multimodal brain transmitter.” Brain and neuroscience advances vol. 2 2398212818810683. 4 Dec. 2018
- Kleppisch T, Feil R. cGMP signalling in the mammalian brain: role in synaptic plasticity and behaviour. Handb Exp Pharmacol. 2009;(191):549-79
- Ben Aissa M, Lee SH, Bennett BM, Thatcher GR. Targeting NO/cGMP Signaling in the CNS for Neurodegeneration and Alzheimer's Disease. Curr Med Chem. 2016;23(24):2770-2788
- Hollas MA, Ben Aissa M, Lee SH, Gordon-Blake JM, Thatcher GRJ. Pharmacological manipulation of cGMP and NO/cGMP in CNS drug discovery. Nitric Oxide. 2019 Jan 1;82:59-74

qEEG spectral frequency analysis

- Ishii et al. Healthy and Pathological Brain Aging: From the Perspective of Oscillations, Functional Connectivity, and Signal Complexity. Neuropsychobiology, 2018Kleppisch T, Feil R. cGMP signalling in the mammalian brain: role in synaptic plasticity and behaviour. Handb Exp Pharmacol. 2009;(191):549-79
- Babiloni, et al. Resting-state posterior alpha rhythms are abnormal in subjective memory complaint seniors with preclinical Alzheimer's neuropathology and high education level: the INSIGHT-preAD study. Neurobiol Aging. 2020;90:43-59

Relevant reference publications (2 of 2)

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- Bennys K, Portet F, Touchon J. Diagnostic value of event-related evoked potentials N200 and P300 subcomponents in early diagnosis of Alzheimer's disease and mild cognitive impairment. J Clin Neurophysiol 2007;24:405–12Kleppisch T, Feil R. cGMP signalling in the mammalian brain: role in synaptic plasticity and behaviour. Handb Exp Pharmacol. 2009;(191):549-79
- Fruehwirt et al. Associations of event-related brain potentials and Alzheimer's disease severity: A longitudinal study. Progress in Neuropsychopharmacology and Biological Psychiatry 92 (2019) 31-38

Saccadic eye movement (SEM)

- Wilcockson et al. Abnormalities of saccadic eye movements in dementia due to Alzheimer's disease and mild cognitive impairment. Aging 2019, Vol.11, No.15
- James A. Sharpe & David H. Zackon (1987) Senescent Saccades: Effects of Aging on Their Accuracy, Latency and Velocity, Acta Oto-Laryngologica, 104:5-6, 422-428

ADv

- Cortes-Canteli M, Iadecola C. Alzheimer's Disease and Vascular Aging: JACC Focus Seminar. J Am Coll Cardiol. 2020;75(8):942-951

MELAS

- El-Hattab AW, Adesina AM, Jones J, Scaglia F. MELAS syndrome: Clinical manifestations, pathogenesis, and treatment options. Mol Genet Metab. 2015;116(1-2):4-12


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On a mission to develop treatments
that restore cognitive function