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ON A MISSION TO DEVELOP TREATMENTS THAT RESTORE COGNITIVE FUNCTION

JEFFERIES VIRTUAL HEALTHCARE CONFERENCE

JUNE 1, 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.

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 2020 Form 10-K filed on February 25, 2021, and our subsequent SEC filings including the Form 10-Q filed on April 30, 2021. 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.

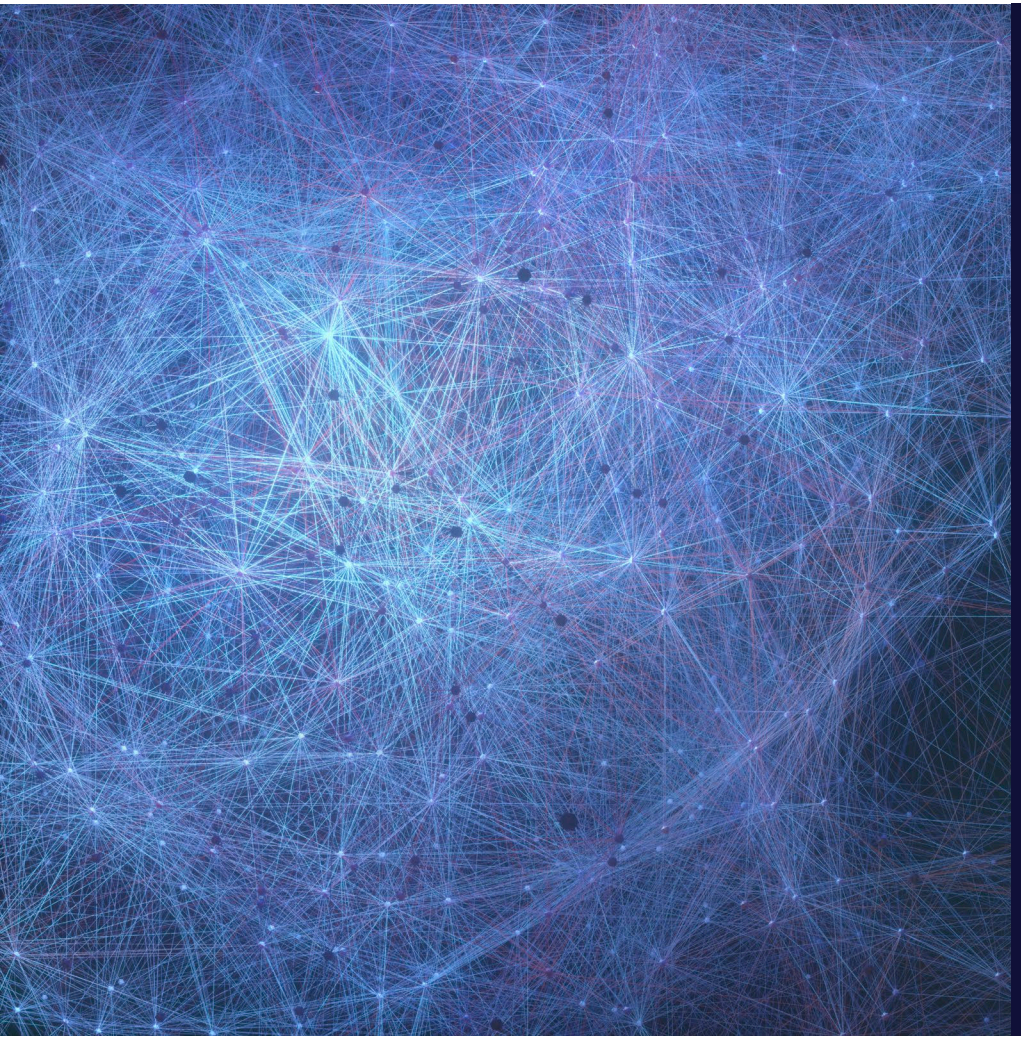
On a mission to develop treatments that restore cognitive function

Tapping into a fundamental CNS signaling pathway with CY6463, a first-in-class, CNS-penetrant sGC stimulator

Executing biomarker-guided development strategy in well-defined populations with cognitive impairment

Tackling the enormous burden and breadth of cognitive impairment through an innovative portfolio of indications and molecules

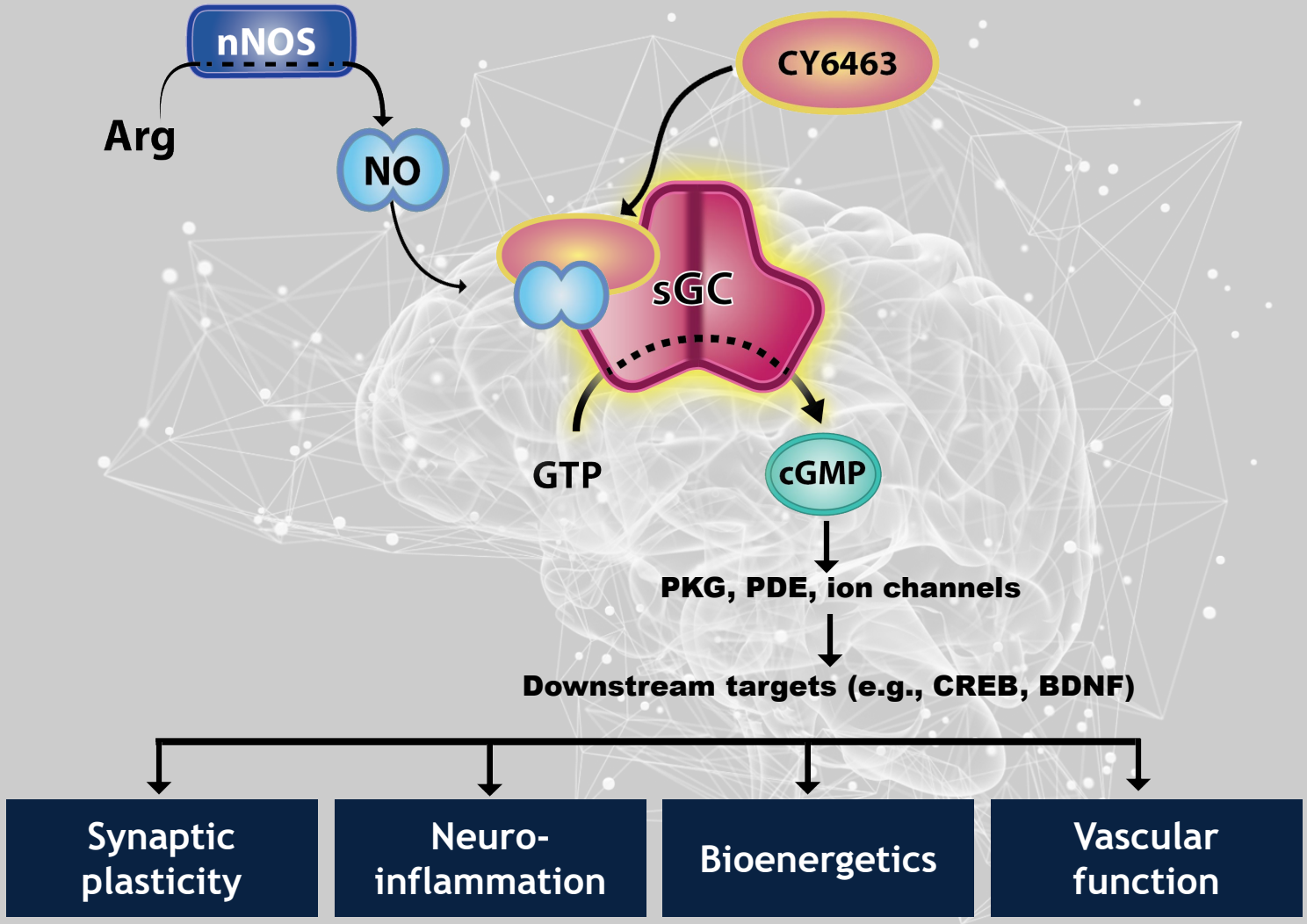
Agenda



- NO-sGC-cGMP is a fundamental CNS signaling pathway
- CY6463 translational pharmacology study results
- Pipeline centered around improving cognitive function
- ADv rationale and development strategy
- Executing on our priorities

NO-sGC-cGMP IS A FUNDAMENTAL CNS SIGNALING PATHWAY

CY6463 amplifies the fundamental NO-sGC-cGMP signaling pathway



CY6463

- First-in-class BBB-permeable, positive allosteric modulator of sGC
- Amplifies endogenous NO-sGC-CGMP signaling to address central aspects of disease pathophysiology

Preclinical data and extensive academic work validate the crucial role of the NO-sGC-cGMP pathway in brain physiology

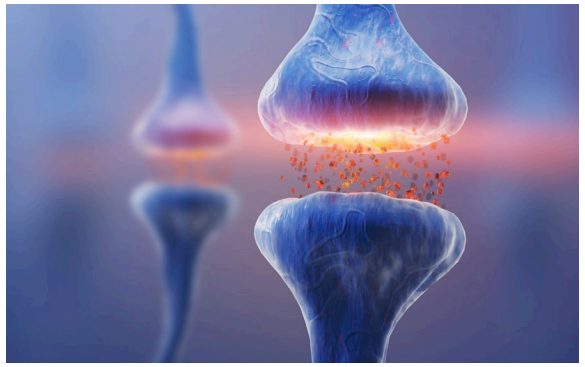
Important role in learning and memory

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

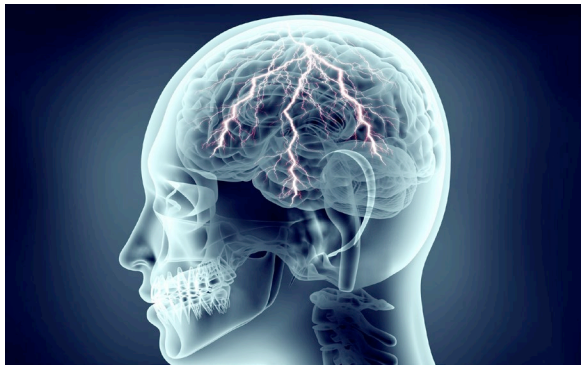
Neuro-inflammation

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

ENHANCED

Cellular Bioenergetics

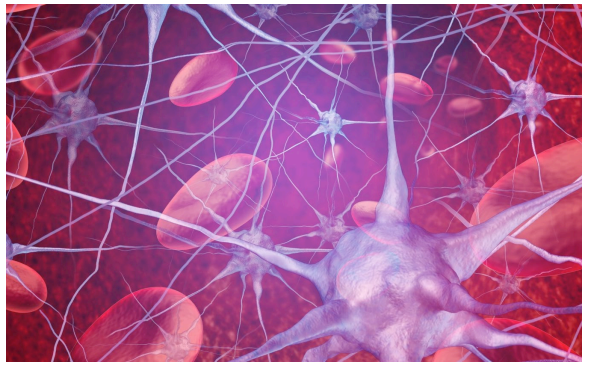
Increased ATP and restored gene expression in cells from patients with mitochondrial diseases



IMPROVED

Vascular Function

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



CY6463 improved neuronal function

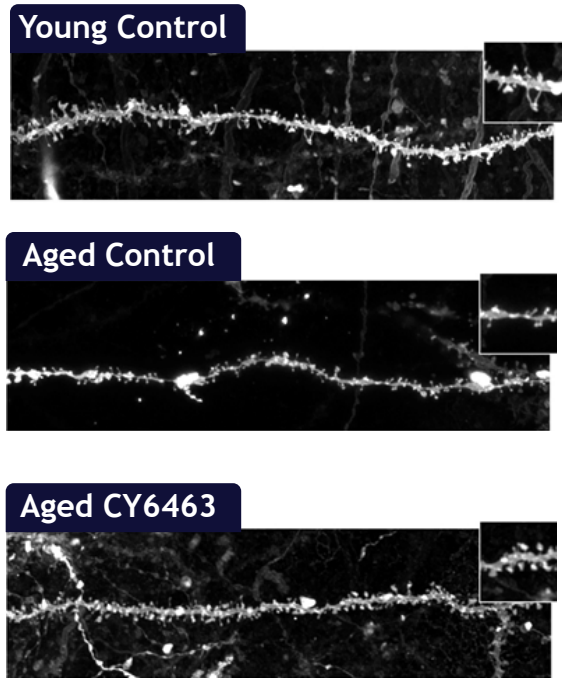
Enhanced hippocampal spine density in aged animals treated with CY6463

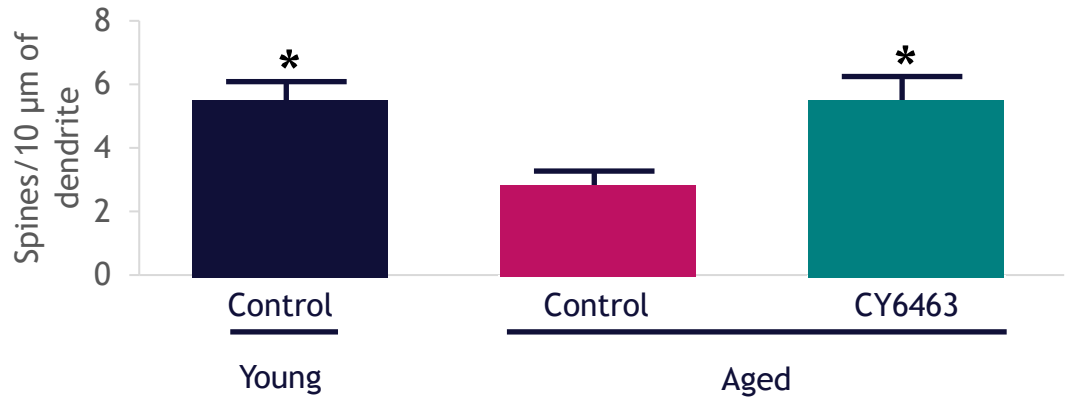
Improve Neuronal Function

Reduce Neuroinflammation

Enhance Cellular Bioenergetics

Improve Cerebral Blood Flow





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

**p<0.05 vs. Aged*

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

CY6463 improved learning and memory in aged rats

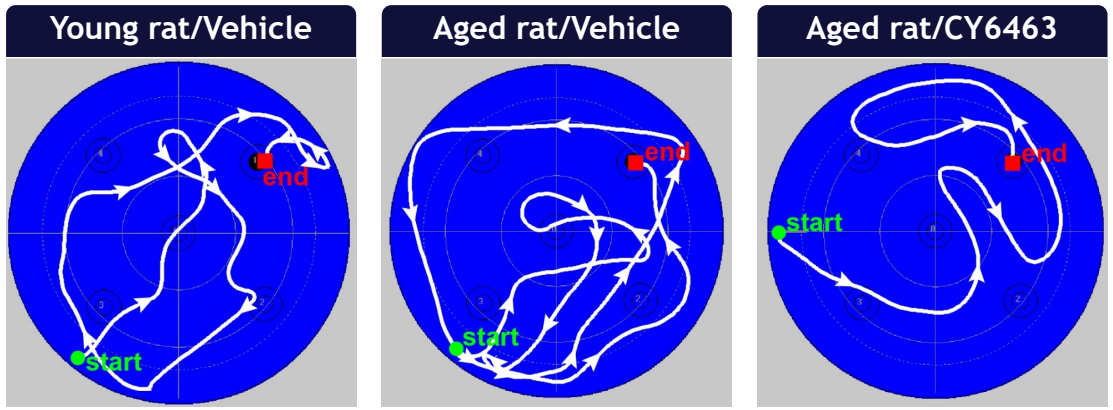
Increased rate of learning in aged rats treated with CY6463 in Morris Water Maze

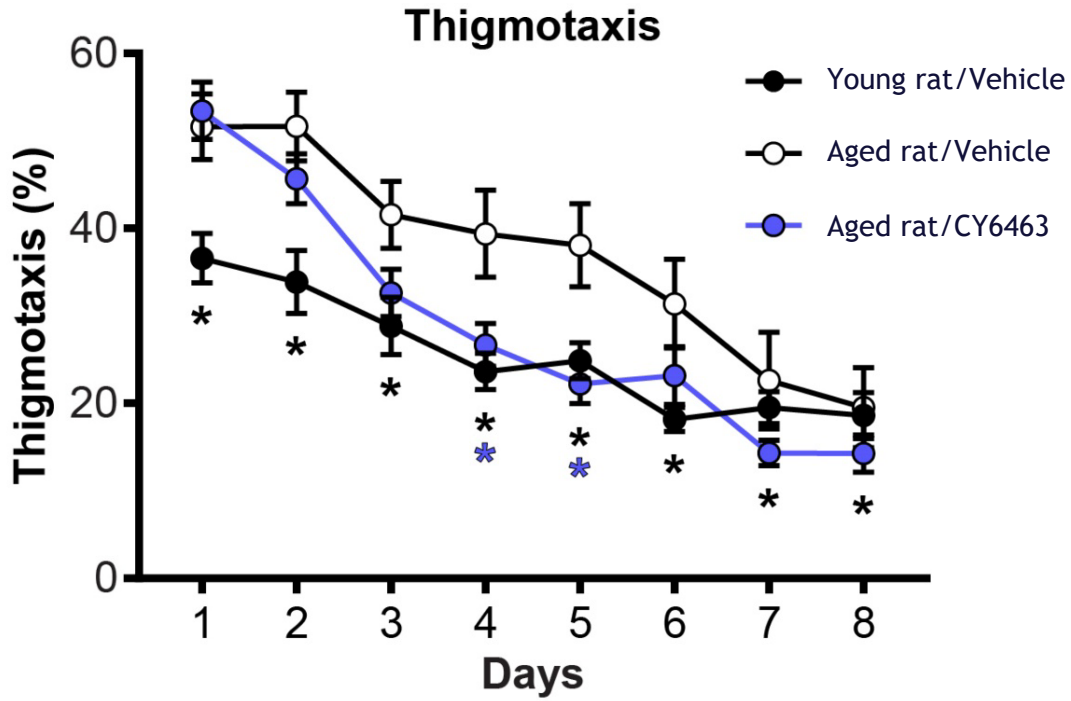
Improve Neuronal Function

Reduce Neuroinflammation

Enhance Cellular Bioenergetics

Improve Cerebral Blood Flow





*p<0.05 vs. Aged vehicle-treated

CY6463 and donepezil act independently to enhance qEEG signal

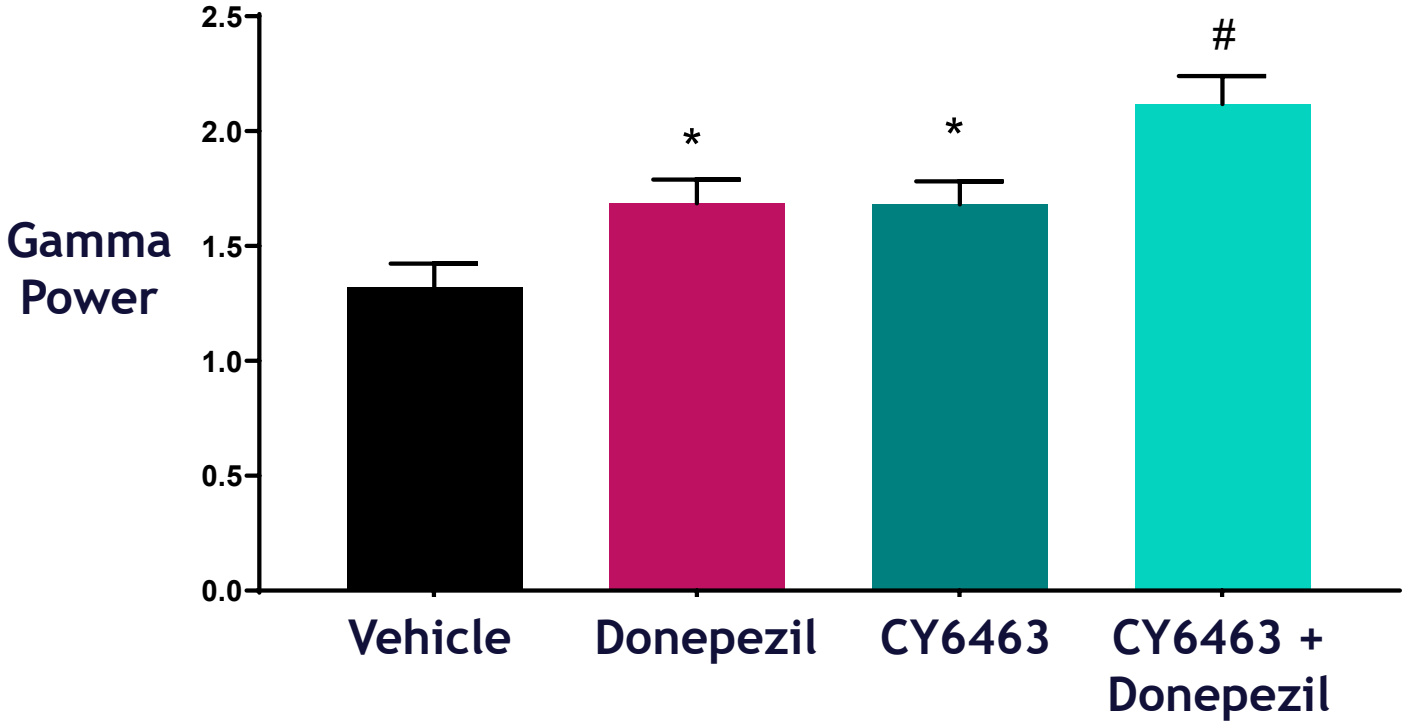
Combination elicited additive increase in gamma band power in healthy rats

Improve Neuronal Function

Reduce Neuroinflammation

Enhance Cellular Bioenergetics

Improve Cerebral Blood Flow



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

*p<0.05 vs Veh

# p<0.05 CY6463 vs CY6463 +Donepezil

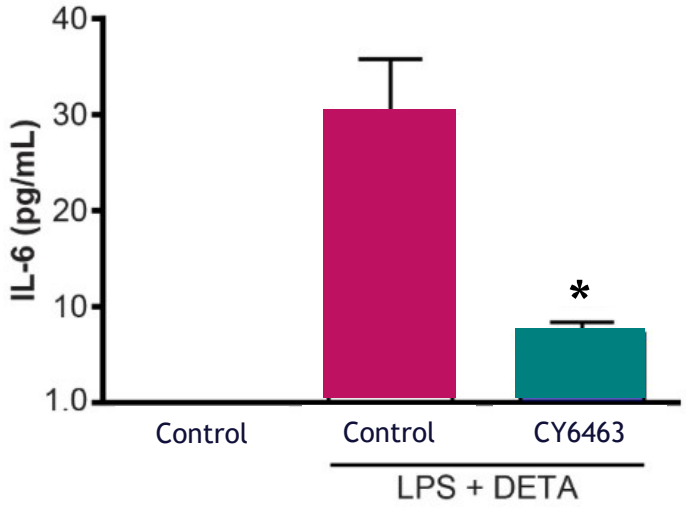
Healthy rats orally administered CY6463 (10mg/kg), Donepezil (1mg/kg), or a combination. Graph displays 1-2h post-dose, mean ± SEM

CY6463 reduced neuroinflammation

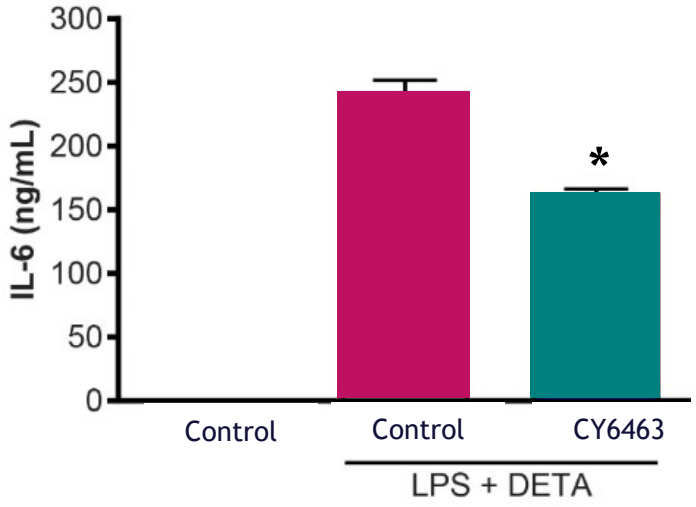
Inhibited in vitro LPS-induction of biomarkers of neuroinflammation

Improve Neuronal Function | **Reduce Neuroinflammation** | Enhance Cellular Bioenergetics | Improve Cerebral Blood Flow

Neuroinflammation in rat brain 3D microtissues



Neuroinflammation in mouse microglial cells

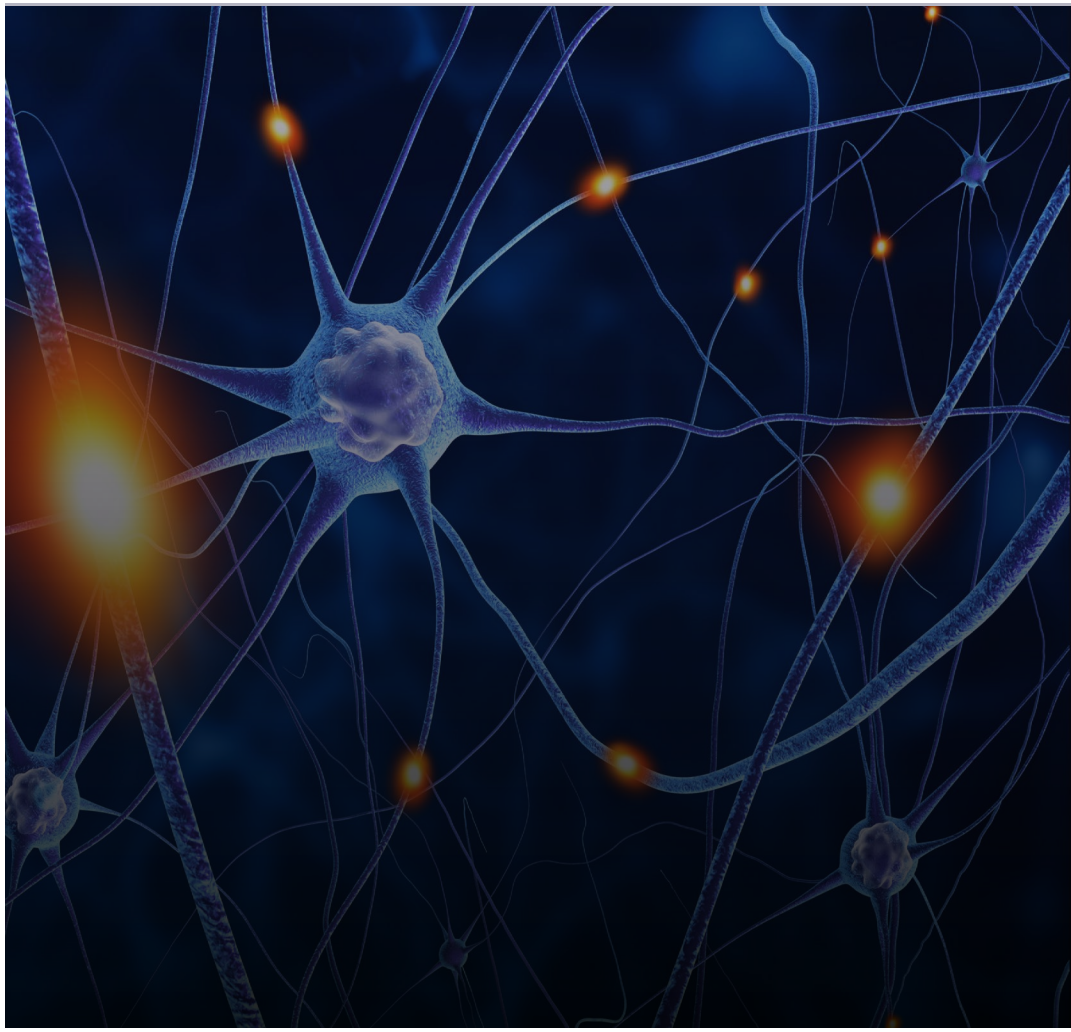


*p<0.05 vs. control LPS-treated wells

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

CY6463 amplifies a fundamental CNS signaling pathway

- NO-sGC-cGMP pathway plays a critical role in brain function
- sGC stimulation with CY6463 amplifies NO-sGC-cGMP signaling
- Morphological, *ex vivo* and *in vivo* data demonstrate important role of sGC in synaptic plasticity, learning and memory, and 6463's ability to restore deficits in these endpoints



CY6463 TRANSLATIONAL PHARMACOLOGY STUDY RESULTS

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 N200 latency

Faster saccadic eye movement (SEM) reaction time

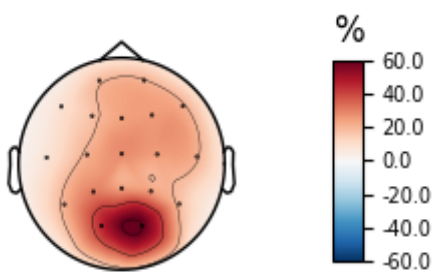
Reduced neuroinflammatory biomarkers

- Rapid onset (<15 days)
- Effect increased with age
- Biomarkers linked to AD and aging

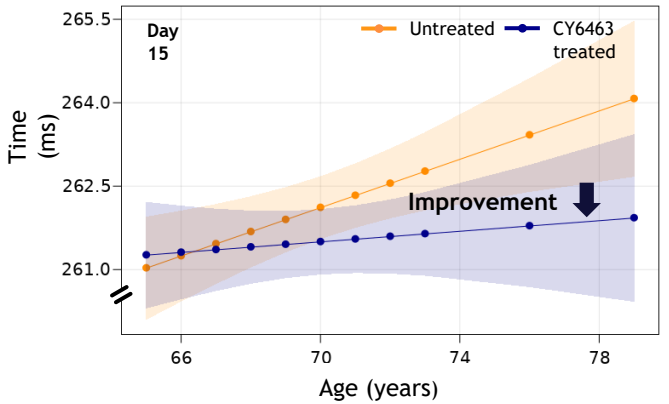
CY6463 showed rapid improvement in biomarkers of cognition

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

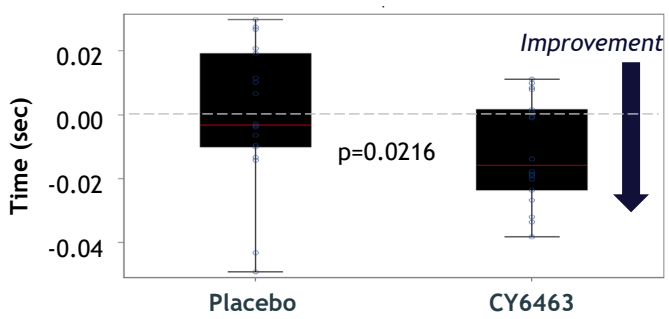
Increased alpha and gamma power



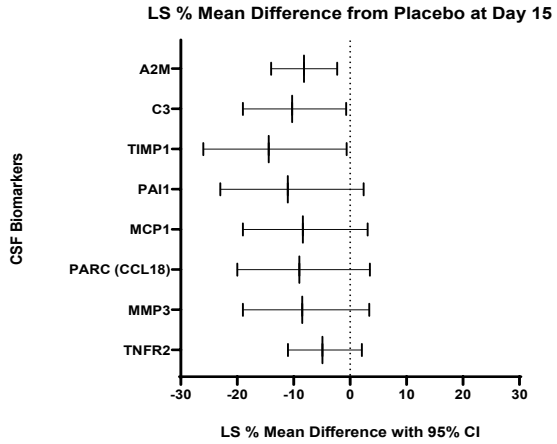
Improved N200 latency



Faster saccadic eye movement reaction time



Reduced neuroinflammatory biomarkers



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PIPELINE CENTERED AROUND IMPROVING COGNITIVE FUNCTION

CY6463 data point to potential in cognition

Preclinical CNS pharmacology

- Neuronal function
- Neuro-inflammation
- Bioenergetics
- Vascular function

+

Clinical CNS pharmacology*

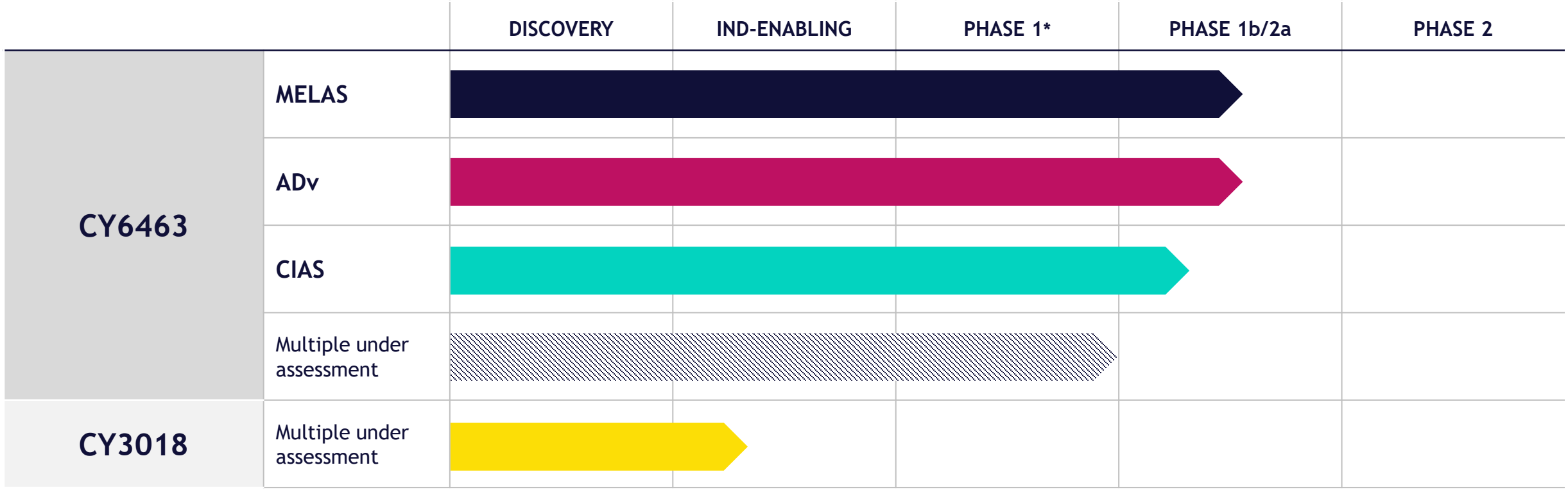
- Increased posterior alpha and gamma power
- Improved N200 latency
- Faster saccadic eye movement (SEM) and reaction time
- Reduced neuroinflammatory biomarkers in CSF

=

Potential to improve cognitive function

**In a 15-day study in 24 healthy elderly subjects*

Advancing parallel, signal-seeking, exploratory studies in priority patient populations



**Two phase 1 studies were completed in healthy young and old (>65 years of age) volunteers confirming targeted CNS exposure and activity*

ADv RATIONALE AND DEVELOPMENT STRATEGY

AD with vascular pathology (ADv) – focused mixed dementia subset

Defined population well suited for treatment with CY6463

DISEASE RATIONALE FOR PATIENT SELECTION

Pathophysiology

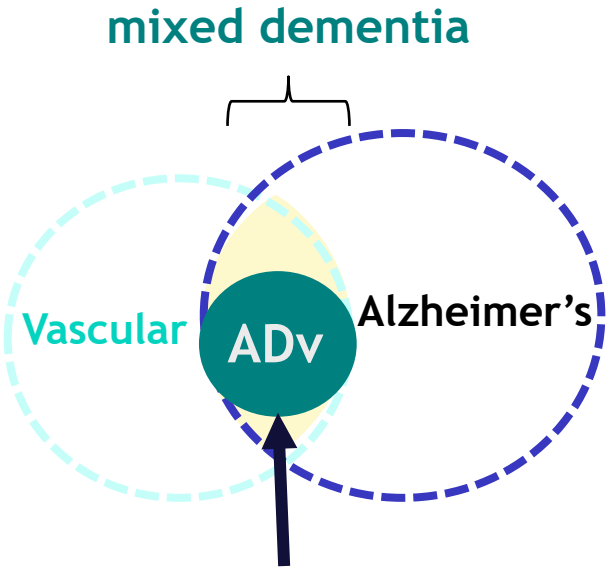
NO dysregulation, endothelial cell loss, impaired blood flow, vascular leakage, inflammation, neuronal dysfunction, and neuronal loss are major contributing factors to rapid disease progression

Standard of care

No approved therapies to treat vascular dementia.
AD therapies offer limited benefits

Pharmacology

Our pharmacology data suggest CY6463 has potential to improve cerebral blood flow, endothelial health, neuroinflammation, and cellular energetics as well as prevent neurodegeneration



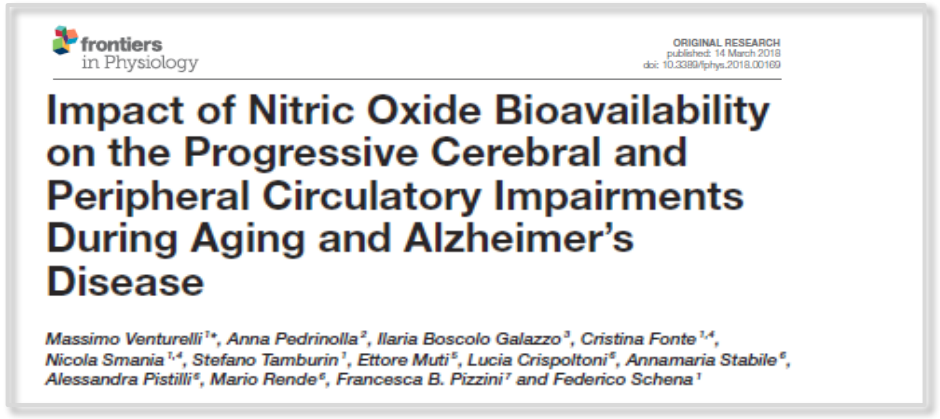
Target population

ADv: an identifiable subset of mixed dementia patients with:

- AD pathology **AND**
- sub-cortical vascular disease **AND**
- CV risk factors

Alzheimer's Association, Rizzi et al., NCI Analysis

Targeting NO-sGC-cGMP pathway to directly impact ADv

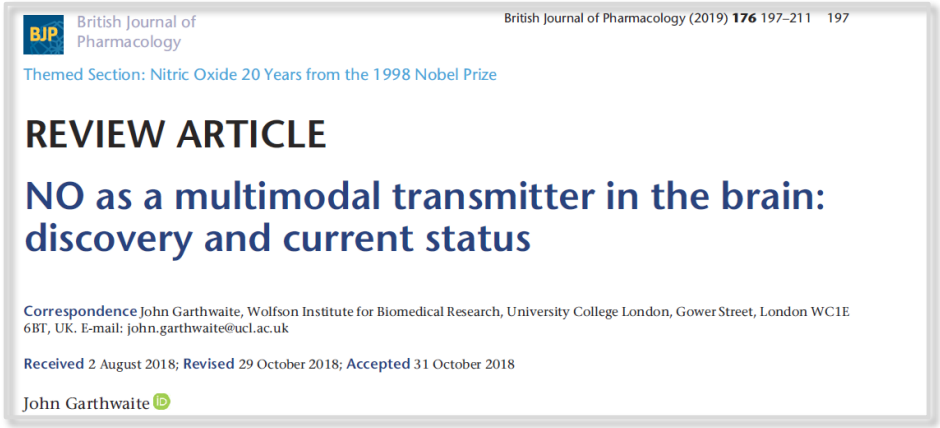


frontiers in Physiology

ORIGINAL RESEARCH
published: 14 March 2018
doi: 10.3389/fphys.2018.00169

Impact of Nitric Oxide Bioavailability on the Progressive Cerebral and Peripheral Circulatory Impairments During Aging and Alzheimer's Disease

Massimo Venturelli[1], Anna Pedrinolla[2], Ilaria Boscolo Galazzo[3], Cristina Fonte[1,4], Nicola Smania[1,4], Stefano Tamburin[1], Ettore Muti[5], Lucia Crispoltoni[5], Annamaria Stabile[6], Alessandra Pistilli[6], Mario Rende[6], Francesca B. Pizzini[7] and Federico Schena[1]*



BJP British Journal of Pharmacology

British Journal of Pharmacology (2019) **176** 197–211 197

Themed Section: Nitric Oxide 20 Years from the 1998 Nobel Prize

REVIEW ARTICLE

NO as a multimodal transmitter in the brain: discovery and current status

Correspondence John Garthwaite, Wolfson Institute for Biomedical Research, University College London, Gower Street, London WC1E 6BT, UK. E-mail: john.garthwaite@ucl.ac.uk

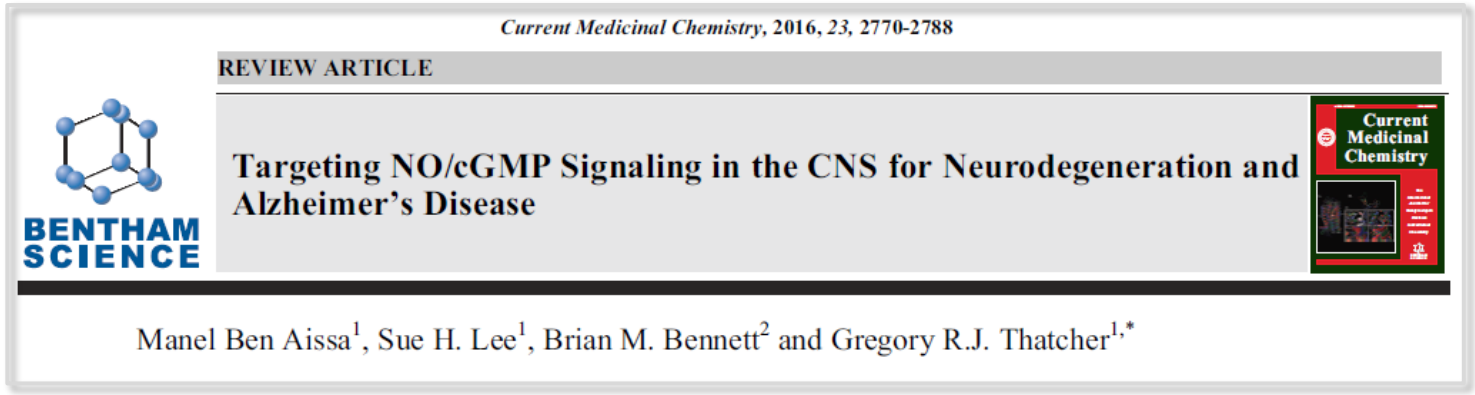
Received 2 August 2018; **Revised** 29 October 2018; **Accepted** 31 October 2018

John Garthwaite

Neuron. 2013 November 20; 80(4): . doi:10.1016/j.neuron.2013.10.008.

The pathobiology of vascular dementia

Costantino Iadecola, M.D.
Brain and Mind Research Institute, Weill Cornell Medical College, New York, NY 10021



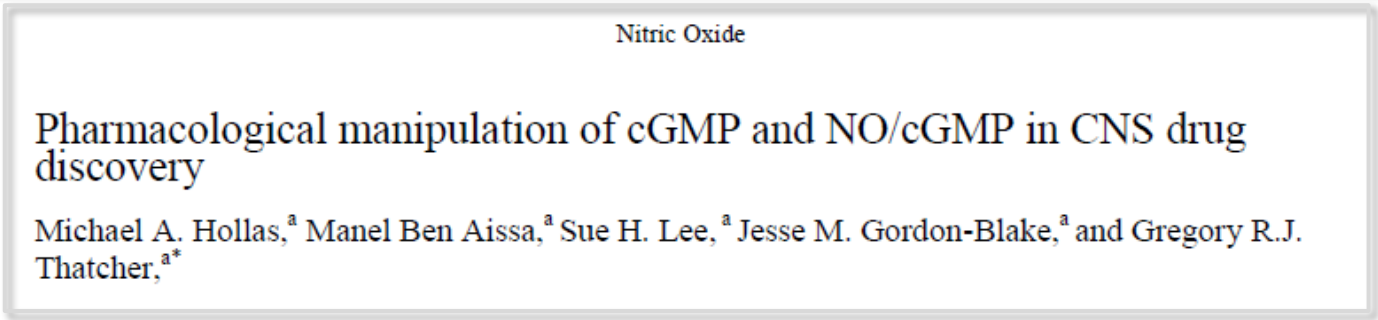
Current Medicinal Chemistry, 2016, *23*, 2770-2788

REVIEW ARTICLE

BENTHAM SCIENCE

Targeting NO/cGMP Signaling in the CNS for Neurodegeneration and Alzheimer's Disease

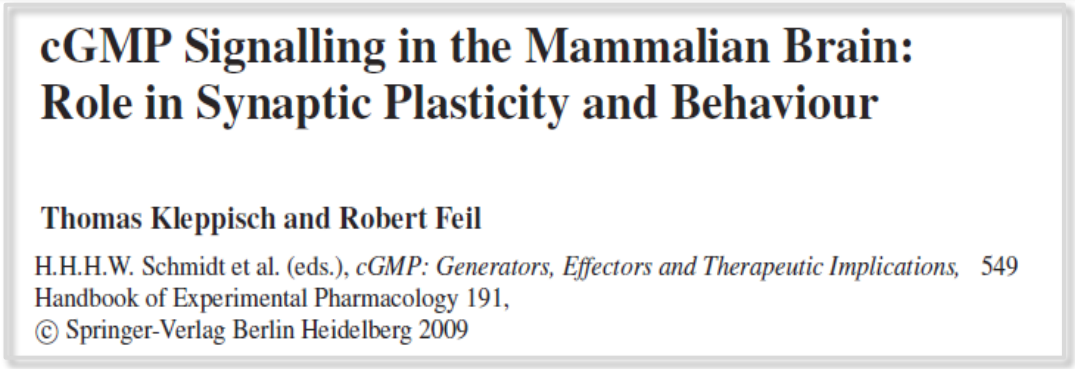
Manel Ben Aissa[1], Sue H. Lee[1], Brian M. Bennett[2] and Gregory R.J. Thatcher[1,*]



Nitric Oxide

Pharmacological manipulation of cGMP and NO/cGMP in CNS drug discovery

Michael A. Hollas,[a] Manel Ben Aissa,[a] Sue H. Lee,[a] Jesse M. Gordon-Blake,[a] and Gregory R.J. Thatcher,[a*]

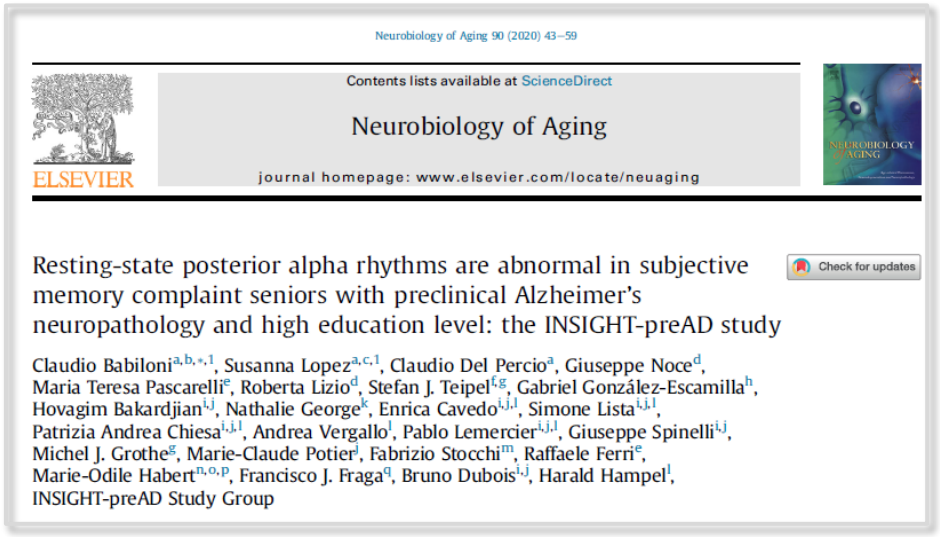


cGMP Signalling in the Mammalian Brain: Role in Synaptic Plasticity and Behaviour

Thomas Kleppisch and Robert Feil

H.H.H.W. Schmidt et al. (eds.), *cGMP: Generators, Effectors and Therapeutic Implications,* 549
Handbook of Experimental Pharmacology 191,

EEG and ERP are disrupted across dementias



Neurobiology of Aging 90 (2020) 43–59

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

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

Claudio Babiloni[a,b,*,1], Susanna Lopez[a,c,1], Claudio Del Percio[a], Giuseppe Noce[d], Maria Teresa Pascarelli[e], Roberta Lizio[d], Stefan J. Teipel[f,g], Gabriel González-Escamilla[h], Hovagim Bakardjian[i,j], Nathalie George[k], Enrica Cavedo[i,j,l], Simone Lista[i,j,l], Patrizia Andrea Chiesa[i,j,l], Andrea Vergallo[l], Pablo Lemercier[i,j,l], Giuseppe Spinelli[i,j], Michel J. Grothe[g], Marie-Claude Potier[j], Fabrizio Stocchi[m], Raffaele Ferri[e], Marie-Odile Habert[n,o,p], Francisco J. Fraga[q], Bruno Dubois[i,j], Harald Hampel[l], INSIGHT-preAD Study Group

JAMA Network Open

Original Investigation | Neurology

Association of Sleep Electroencephalography-Based Brain Age Index With Dementia

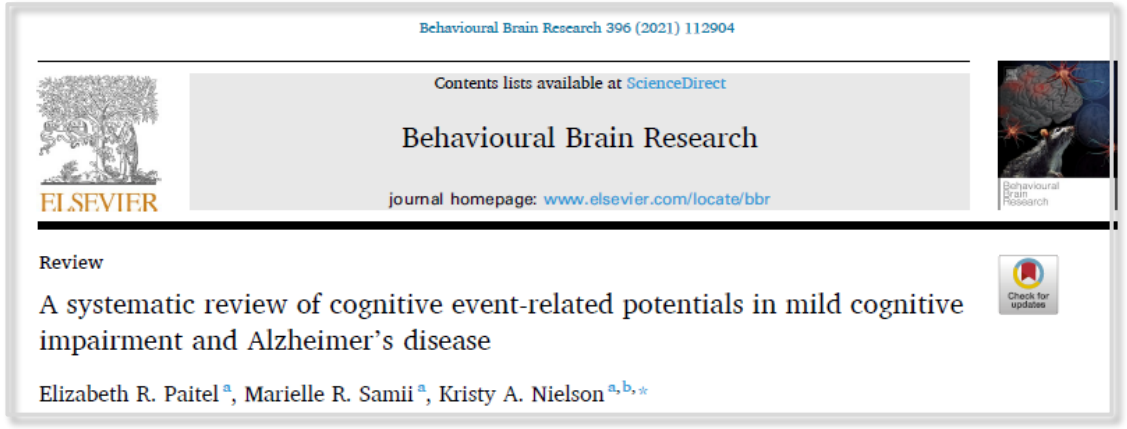
Elissa Ye, MSc; Haoqi Sun, PhD; Michael J. Leone, MSc; Luis Paixao, MD; Robert J. Thomas, MD; Alice D. Lam, MD, PhD; M. Brandon Westover, MD, PhD

JAMA Network Open. 2020;3(9):e2017357. doi:10.1001/jamanetworkopen.2020.17357 September 28, 2020 1/12

Journal of Alzheimer's Disease 80 (2021) 1413–1428
DOI 10.3233/JAD-201559
IOS Press

Event-Related Potentials, Inhibition, and Risk for Alzheimer's Disease Among Cognitively Intact Elders

Kathleen H. Elverman[a], Elizabeth R. Paitel[a], Christina M. Figueroa[a], Ryan J. McKindles[b] and Kristy A. Nielson[a,c,*]



Behavioural Brain Research 396 (2021) 112904

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Review

A systematic review of cognitive event-related potentials in mild cognitive impairment and Alzheimer's disease

Elizabeth R. Paitel[a], Marielle R. Samii[a], Kristy A. Nielson[a,b,*]

Neuroinflammatory markers are implicated in ADv

Original research

In vivo neuroinflammation and cerebral small vessel disease in mild cognitive impairment and Alzheimer's disease

Audrey Low ,[1] Elijah Mak,[1] Maura Malpetti ,[2] Luca Passam
Nicolas Nicastro ,[1,3] James D Stefaniak,[4,5] George Savulich,[1]
Li Su,[1] James B Rowe ,[2] Hugh S Markus,[2] John T O'Brien

Low A, *et al*. *J Neurol Neurosurg Psychiatry* 2021;**92**:45–52. doi:10.1136/jnnp-20

The American Journal of Pathology, Vol. 178, No. 4, April 2011

Complement 3 and Factor H in Human Cerebrospinal Fluid in Parkinson's Disease, Alzheimer's Disease, and Multiple-System Atrophy

Yu Wang,*† Aneeka M. Hancock,*
Joshua Bradner,* Kathryn A. Chung,‡
Joseph F. Quinn,‡ Elaine R. Peskind,§¶
Douglas Galasko,‖ Joseph Jankovic,**
Cyrus P. Zabetian,†††‡ Hojoong M. Kim,‡‡§§
James B. Leverenz,§¶‡‡‡ Thomas J. Montine,*
Carmen Ginghina,* Karen L. Edwards,¶¶
Katherine W. Snapinn,¶¶ David S. Goldstein,‖
Min Shi,* and Jing Zhang*

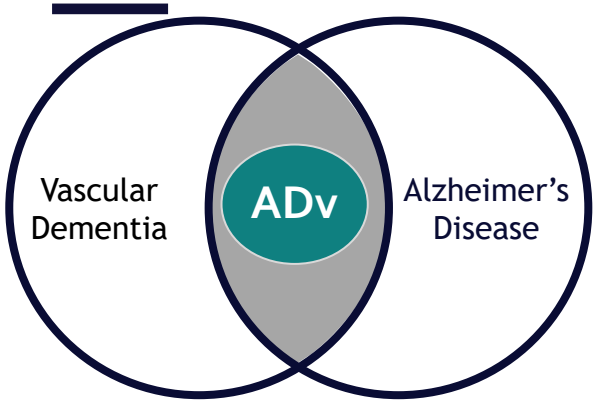
Biomarkers in Medicine

α2-macroglobulin in Alzheimer's disease: new roles for an old chaperone

Sahba Seddighi[1], Vijay Varma[1] & Madhav Thambisetty*,[1]

Biomark. Med. (2018) 12(4), 311–314 ISSN 1752-0363

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 studies 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	Exploratory, signal-seeking study to evaluate safety, tolerability, and pharmacodynamic effects (EEG, MRI, neuroinflammatory biomarkers, cognition)
Study design	• Once-daily CY6463 vs. placebo • 12 weeks • 30 participants
Patient targeting	• Confirmed AD pathology (PET, CSF) • 2+ cardiovascular risk factors • Mild-moderate subcortical small-vessel disease on MRI • Mini mental state exam score (20-26)
Collaborations	• Partially funded by the Alzheimer's Association's Part the Cloud-Gates Partnership • Collaborating with Dr. Andrew Budson at Boston University on a study to examine the relationship between ERP/EEG and cognitive measures in dementias

EXECUTING ON OUR PRIORITIES

2021: executing on our priorities

Clinical and pre-clinical	• ADv Ph2 study start mid-2021 • MELAS Ph2 study data by year end 2021 • CIAS Ph2b study start in 2H 2021 • Advancing CY3018, NextGen development candidate
Partnerships	• Explore CNS collaborations • Praliciguat out-license
Capabilities and capital	• Grow external CNS network and augment core team CNS expertise • Reduced monthly cash use to ~50% that of 2020 • Q1 2021 ending cash balance of ~$45M*

* Preliminary, unaudited unrestricted cash, cash equivalents and restricted cash balance as of March 31, 2021

On a mission to develop treatments that restore cognitive function

Tapping into a fundamental CNS signaling pathway with CY6463, a first-in-class, CNS-penetrant sGC stimulator

Executing biomarker-guided development strategy in well-defined populations with cognitive impairment

Tackling the enormous burden and breadth of cognitive impairment through an innovative portfolio of indications and molecules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Q&A