Leveraging Biomarker Data & Preclinical Models to Guide the Design of Clinical Studies

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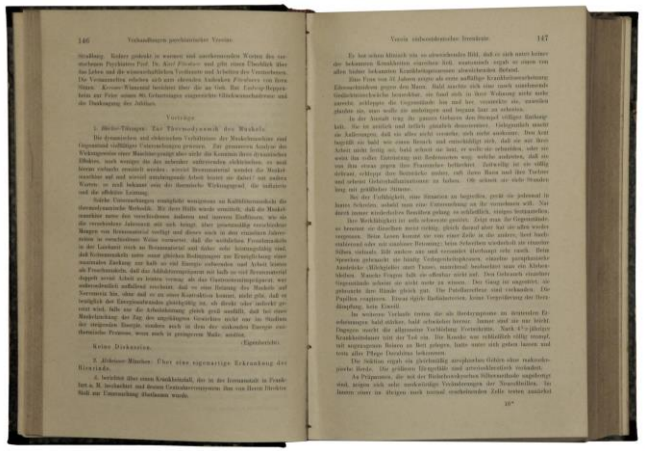
AD Biomarkers - integrating preclinical data to guide clinical strategies

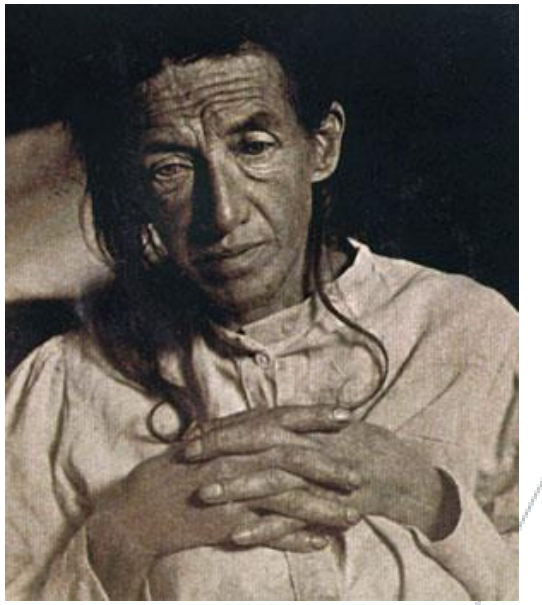
- Range of opportunities for applying biomarkers in AD studies including:
  - Target engagement
  - Pharmacodynamics
  - Disease progression
- Modalities can include plasma, CSF and imaging biomarkers
- Recent clinical failures question the relevance of specific biomarkers and concepts of underlying disease pathophysiology (e.g., amyloid, vascular pathology…)
- AD may be best addressed through targeting multiple aspects of disease
- NO-sGC-cGMP pathway disrupted in AD. sGC stimulation provides multi-faceted approach.
- Translation - employ relevant preclinical markers that can be evaluated clinically
- Build biomarker evaluations early in Phase 1 to inform subsequent clinical strategies in patients

Early recognition of cerebrovascular and endothelial dysfunction in AD

Alois Alzheimer (www.commons.wikimedia.org)



Über eine eigenartige Erkrankung der Hirnrinde
(About a peculiar disease of the cerebral cortex)
- Alois Alzheimer, 1907

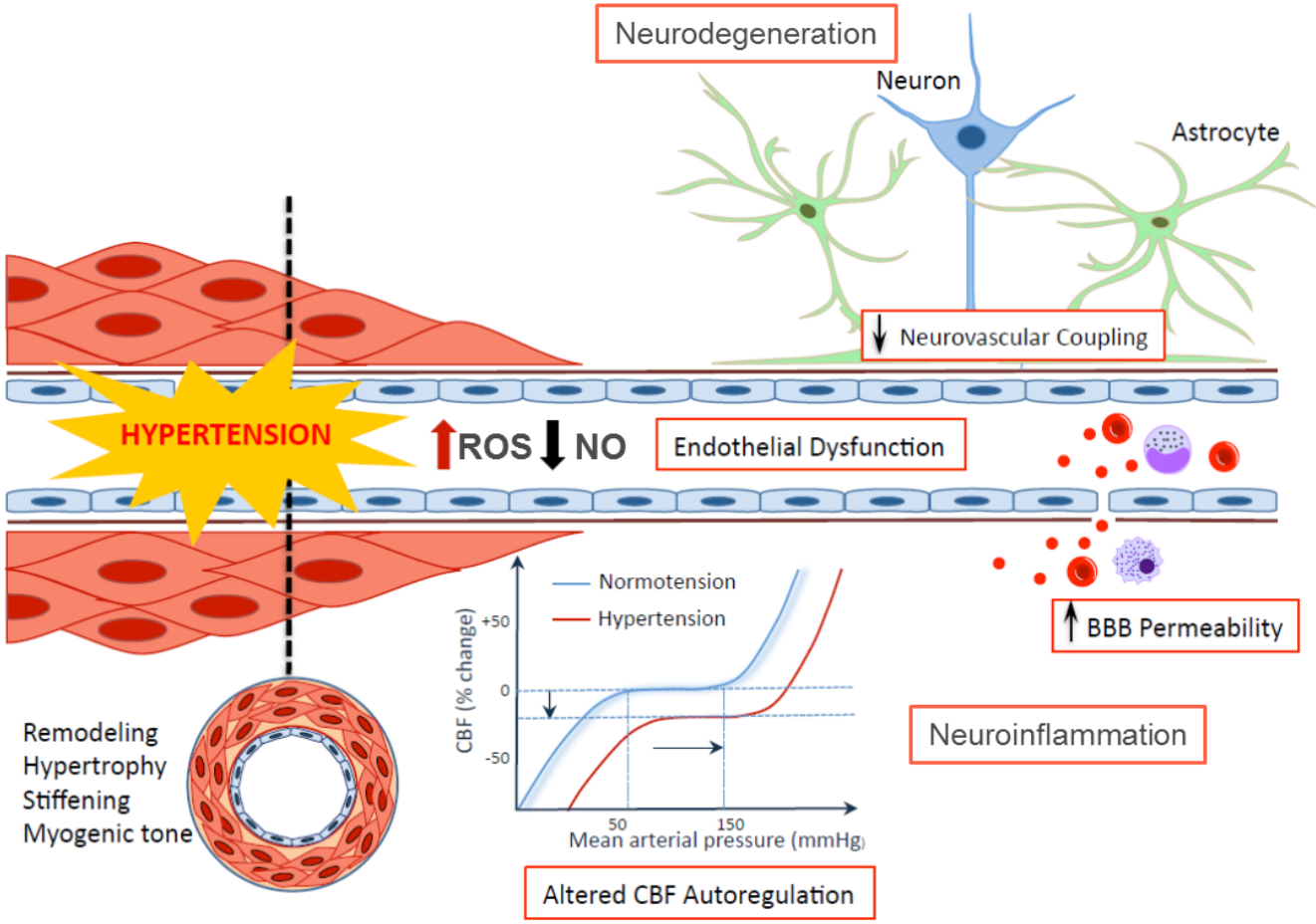


Auguste D. (www.commons.wikimedia.org)

The post-mortem showed an evenly atrophic brain without macroscopic focal degeneration. The larger vascular tissues show arteriosclerotic change.

The glia have developed numerous fibers, moreover, many glial cells show adipose saccules. There is no infiltration of the vessels, however, a growth appears on the endothelia, in some places also a proliferation of vessels.

Vascular pathology in dementia and dysregulation of NO signaling

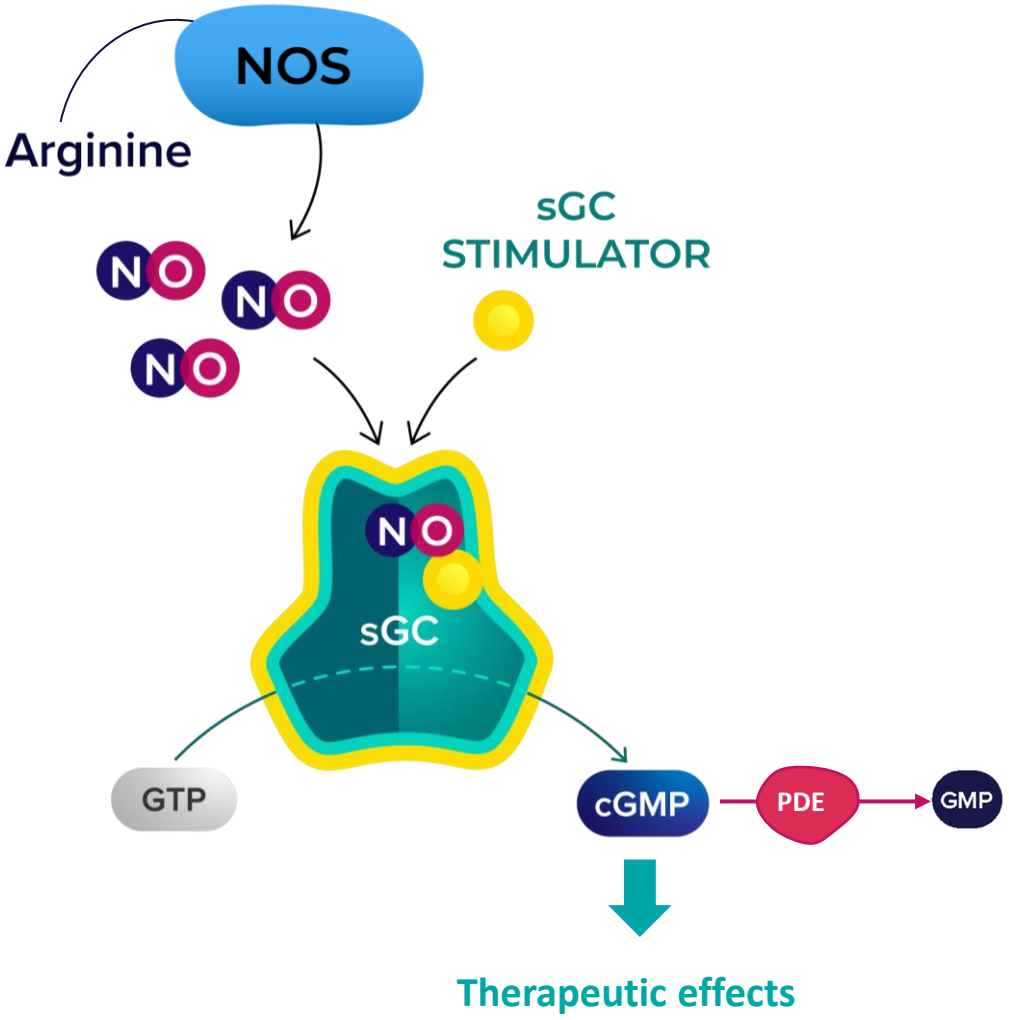


SUPPORTIVE EVIDENCE

- Risk factors and common comorbidities: DM, HTN, HL, Smoking, CAD
- ApoE risk partly mediated by endothelial dysfunction and BBB breakdown
- Brain ischemic changes present in dementia, including AD; possibly independent disease progression risk factor
- Vasculature implicated in a-beta brain clearance, a process that fails in AD

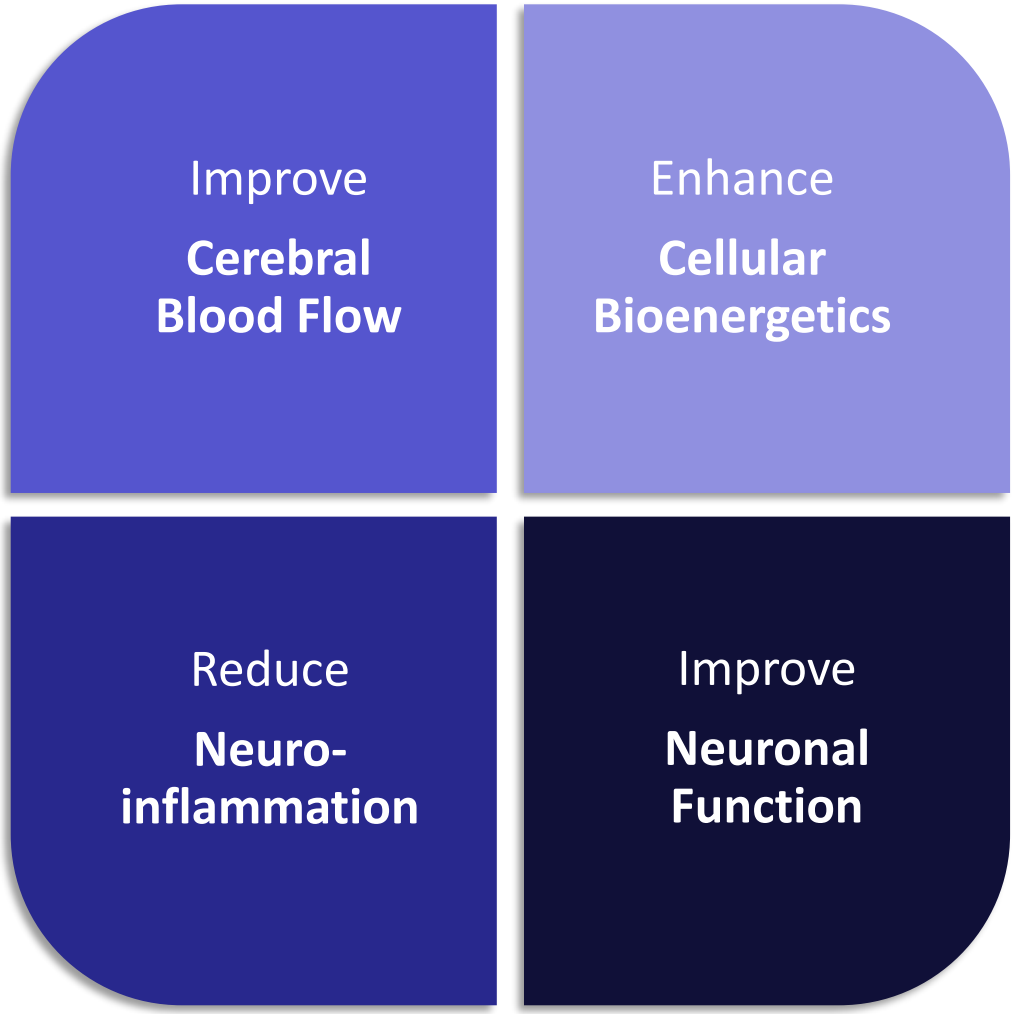
Adapted from Faraco and Iadecola (2013) Hypertension 62:810

sGC stimulators: intervening at the ideal place to address underlying pathophysiologies in AD



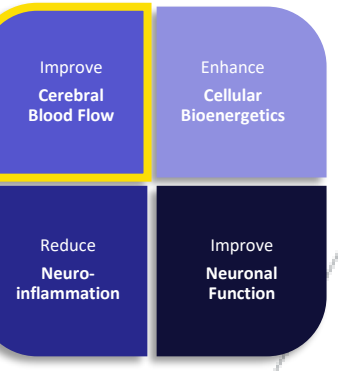
- **Multiple successful drugs target the NO-sGC-cGMP pathway for the treatment of CV diseases**
  NO donors, PDE5 inhibitors, sGC stimulators
- **NO-sGC-cGMP represents an untapped neurotransmitter system and plays a central role in CNS diseases**
  NO-sGC-cGMP signaling dysregulated with aging and in AD
- **sGC: optimal target for pathway intervention**
  Broadly expressed in CNS, amplifies endogenous signaling, increases cGMP levels at the source with no attenuation of response
- **IW-6463 is a CNS-penetrant, small molecule sGC stimulator**
  Completed Phase 1 SAD/MAD/FI studies. Identified safe and well-tolerated dose levels with steady-state CNS exposure in therapeutic target range with QD PK.

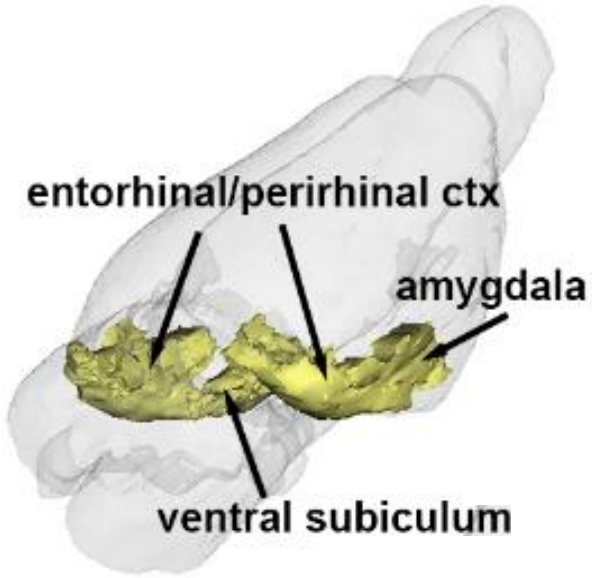
CNS-penetrant sGC stimulator IW-6463 demonstrates beneficial effects across four key domains of neurodegenerative diseases in preclinical studies



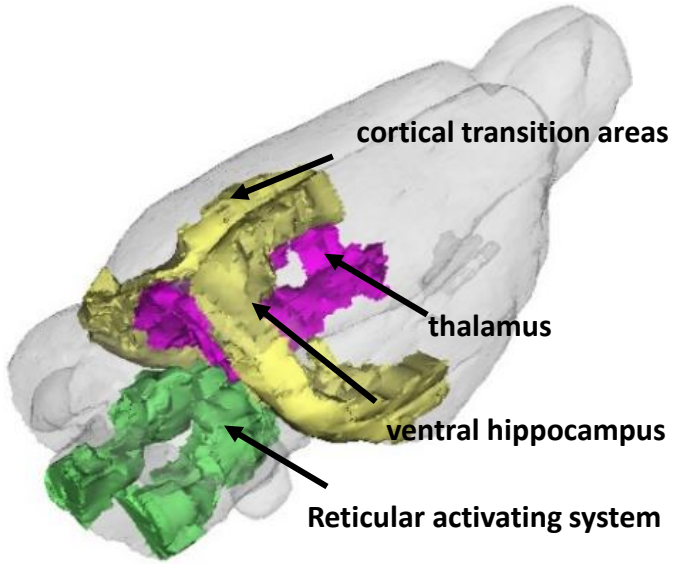
IW-6463 increased cerebral blood flow in rats

Increases observed in areas associated with memory and arousal by fMRI BOLD imaging





Peripherally restricted sGC stimulator



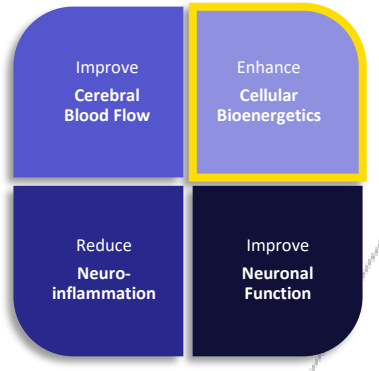
CNS-penetrant sGC stimulator (IW-6463)

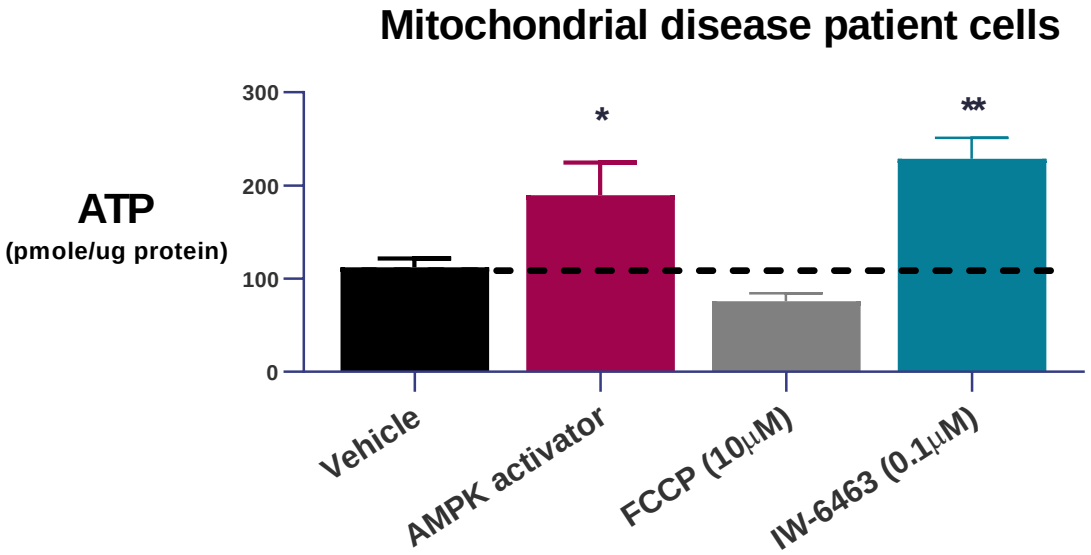
Clinical assessment can be conducted using fMRI and associated imaging of cerebral blood flow.

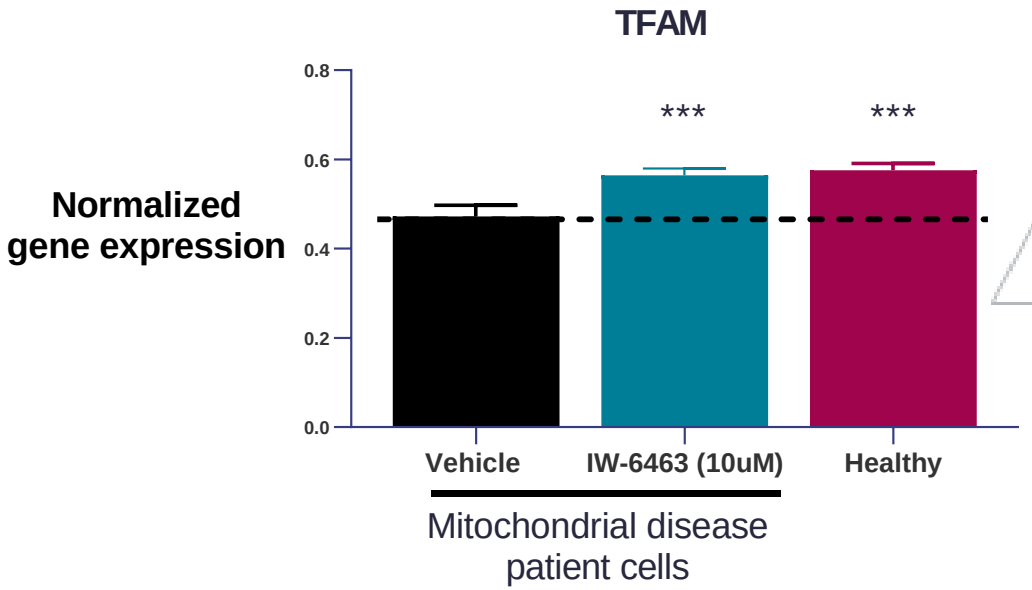
Healthy awake male rats treated with 0.3 mg/kg iv; image quantification 20-30 minutes post-dose

IW-6463 enhanced markers of cellular bioenergetics

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







Clinical evaluation of neurometabolites attainable by magnetic resonance spectroscopy.

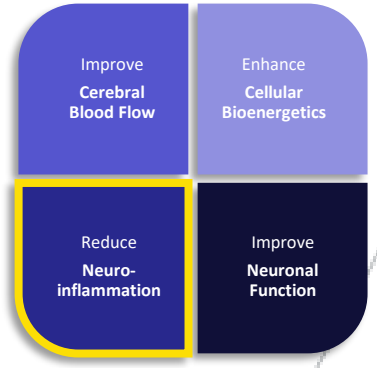
Mitochondrial disease patient cells obtained from the Coriell Institute were treated for 24h before ATP quantification

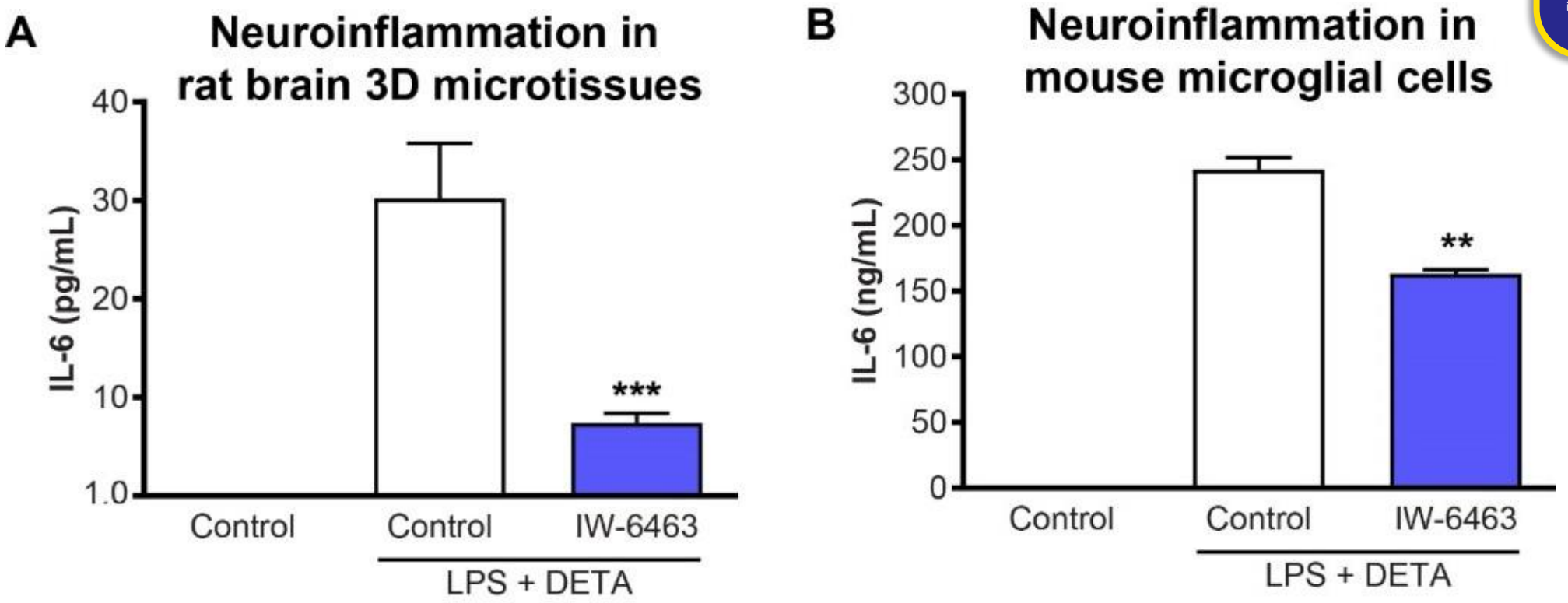
TFAM: mitochondrial transcriptional factor A, a key activator of mitochondrial transcription as well as a participant in mitochondrial genome replication.

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

IW-6463 reduced markers of neuroinflammation

Decreased markers of LPS-induced neuroinflammation in vitro



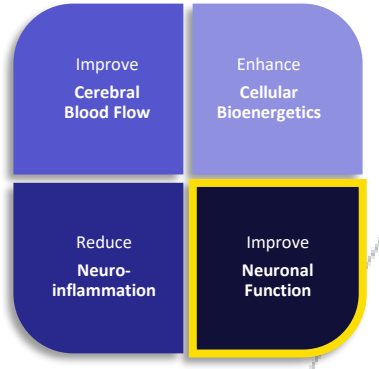


Clinical evaluation can include plasma and CSF markers of inflammation.

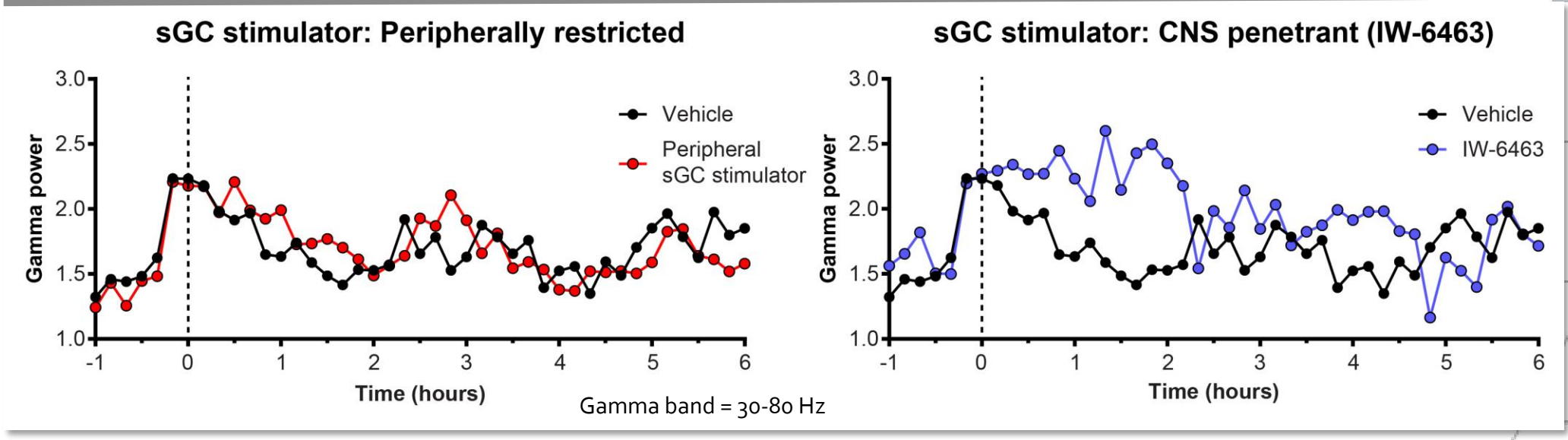
IW-6463 (10 µM) and DETA (30 µM) were incubated with SIM-A9 cells or rat brain 3D microtissues for 30 min before LPS (100 ng/ml) incubation and further incubated for 18-20h at 37°C before IL-6 quantification

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

IW-6463 increased gamma band intensity in quantitative EEG studies



IW-6463 elicited an increase in gamma band intensity, which has been associated with cognitive processing, while a peripheral sGC stimulator did not

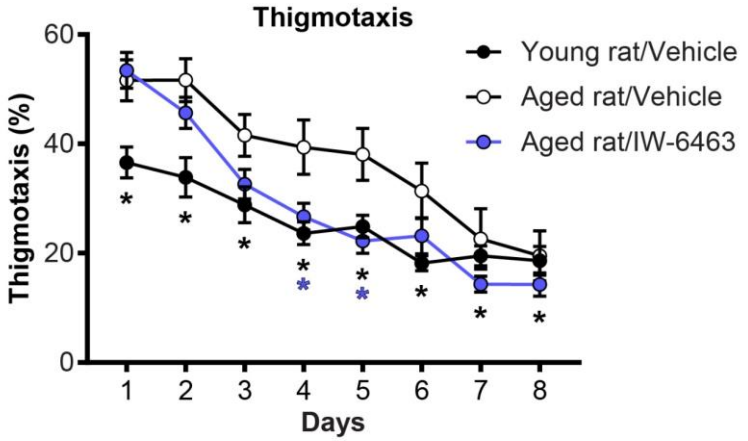


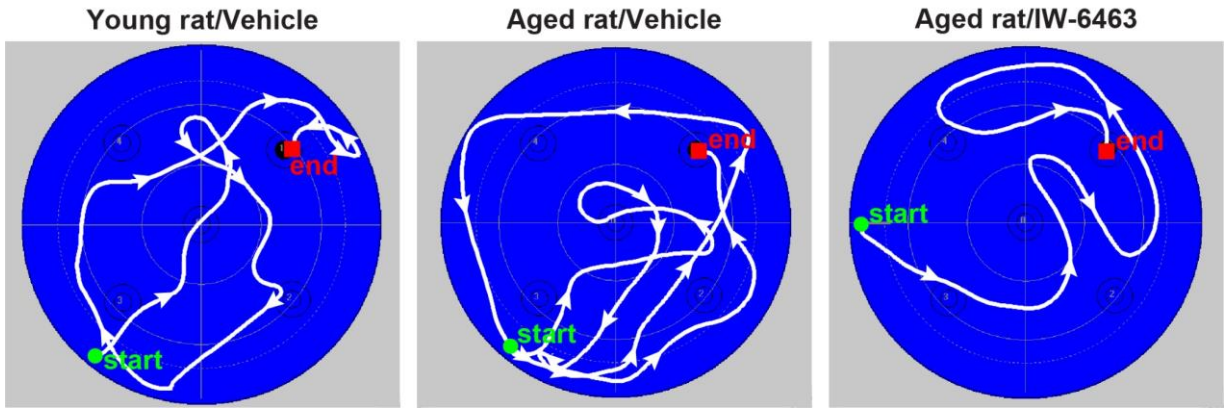
EEG provides a sensitive and translational measure of cortical brain activity that can be captured clinically to evaluate PD effects.

Male rats administered IW-6463 (1 mg/kg) or a peripheral sGC stimulator (3 mg/kg) with telemetry EEG monitoring

IW-6463 improved learning and memory in aged rats

Effects observed in aged rats treated with IW-6463 in Morris Water Maze





A range of objective behavioral and cognition measures can readily be assessed in the clinic.

Healthy aged male rats were administered IW-6463 (10 mg/kg, p.o.) daily during Morris Water Maze training

*p<0.05 vs. Aged vehicle-treated

Biomarker-driven early clinical development strategy

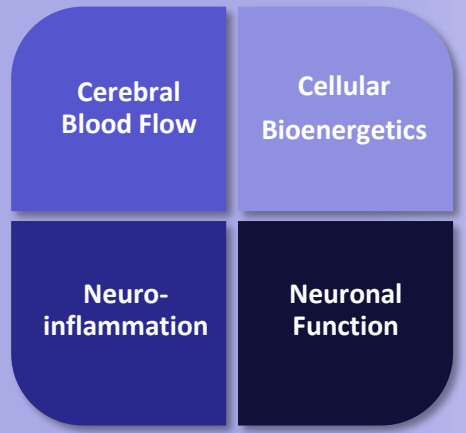
Incorporating a translational pharmacology study in elderly volunteers

Phase 1

Safety
Pharmacokinetics
CNS exposure
Pharmacodynamics
Dose selection for next study

Translational pharmacology study in elderly participants

Safety
Pharmacokinetics
Central target engagement
Pharmacodynamic biomarkers



Parallel exploratory Phase 2 studies

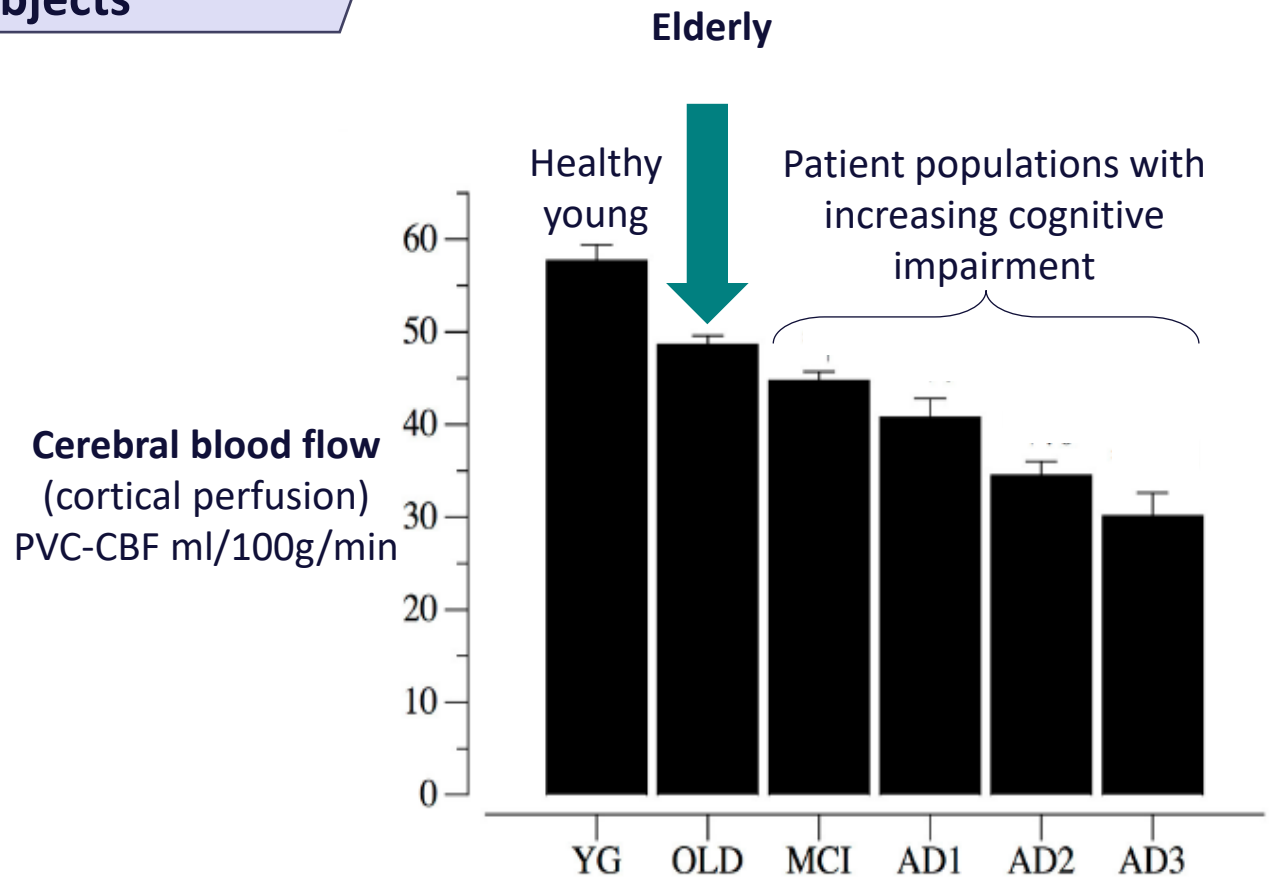
Focused patient population subsets supported by translational biomarker and preclinical data

Safety/PK
Pharmacodynamics
Target engagement
PD biomarkers
Early impact on disease

Translational pharmacology population: elderly volunteer study

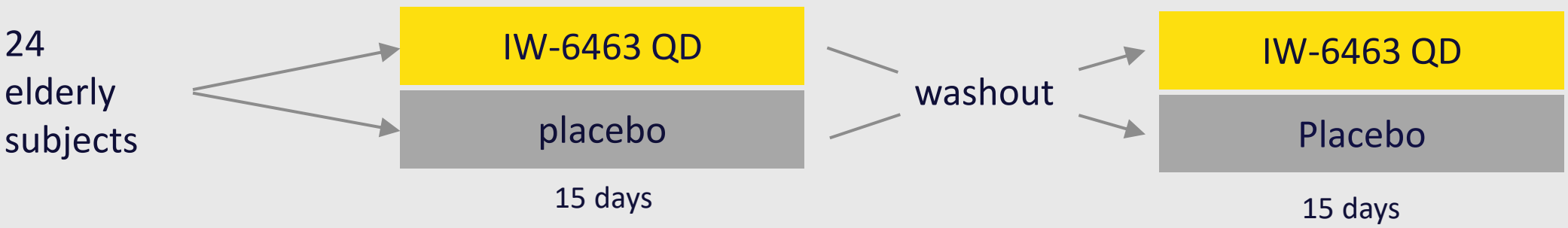
Phase 1 → **Translational pharmacology study in elderly subjects**

- Nitric oxide bioavailability and cerebral blood flow are known to decrease with age and with increasing severity of cognitive impairment
- Elderly Phase 1 subjects serve as a homogeneous population for evaluation of sGC stimulation in the CNS



Adapted from Venturelli, Pedrinolla, Boscolo Galazzo, Fonte, Smania, Tamburin, Muti, Crispoltoni, Stabile, Pistilli, Rende, Pizzini and Schena 2018, Front Physiol. 14;9:169.
N=5 to 10 per group,

Phase 1 translational pharmacology study design - ongoing



Assessing safety, PK, CNS exposure and target engagement in CNS (cGMP)

Cerebral Blood Flow

- MRI arterial spin labeling (ASL)

Cellular Bioenergetics

- brain metabolism via magnetic resonance spectroscopy (MRS)

Neuro-inflammation

- cytokines, adhesion molecules

Neuronal Function

- qEEG
- measures of cognition and behavior (NeuroCart®)

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

Defined population well suited for treatment

DISEASE RATIONALE FOR PATIENT SELECTION

Pathophysiology

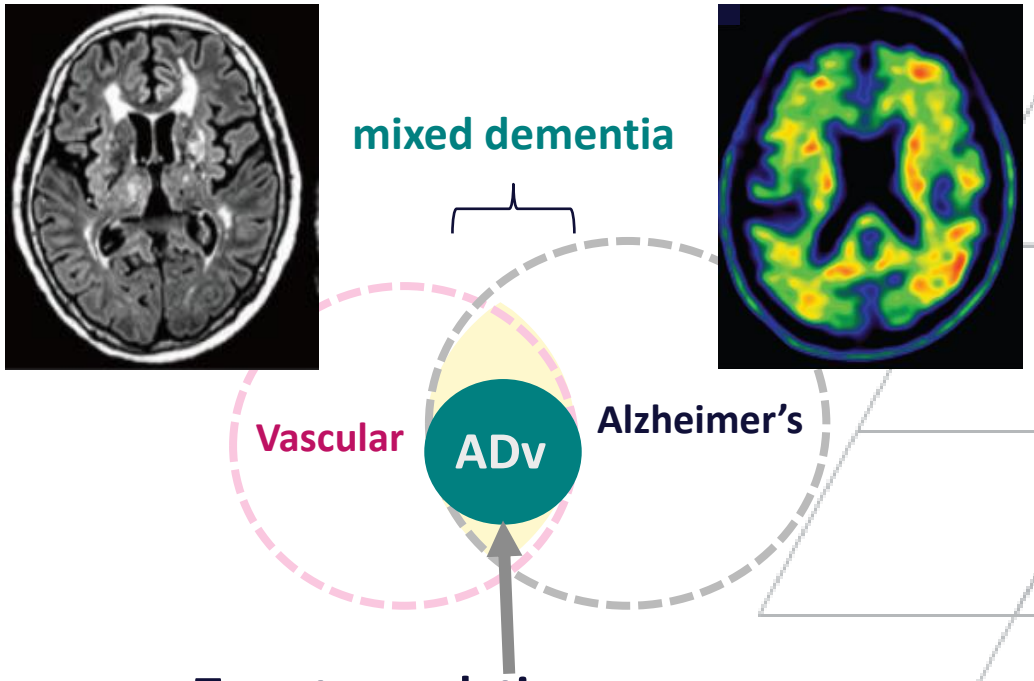
NO dysregulation, endothelial cell loss, impaired blood flow, vascular leakage, inflammation, neuronal dysfunction, and neuronal loss are major contributing factors to rapid disease progression

Standard of care

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

Pharmacology

Our preclinical data suggest IW-6463 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

Clinical strategy will be informed by the results of the translational pharmacology study

Rizzi et al. 2014 Biomed Res Int. 2014:908915; Roh and Lee 2014 J Stroke. 16(1): 18–26.; Alzheimer's Association; NCI Analysis

Summary and conclusions

- Accumulating clinical data point to new understanding of AD contributors (e.g., vascular pathologies) and considerations for designing next-generation trials
- A multi-faceted approach offers more opportunities to simultaneously treat a range of AD pathologies
- Focus on translatable preclinical measures can enable efficient bridging into Phase 1
- Selecting a discrete and well-defined patient population key for early POC studies
- Critical evaluation of biomarkers early in clinical development can serve to inform patient studies