cyclerion

January 13, 2020

Creating breakthrough treatments for patients with serious and orphan diseases by harnessing the power of soluble guanylate cyclase (sGC)

Safe Harbor Statement

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Harnessing the power of Cyclerion's sGC stimulator platform

0

Introduction to Cyclerion:

clinical stage startup developing sGC therapeutics for serious diseases

1

DN praliciguat partnering:

out-license discussions based on promising phase 2

2

SCD olinciguat phase 2 completion:

potential for raising standard of care across four therapeutic domains

3

CNS IW-6463 advancement:

advancement from successful phase 1 in healthy volunteers to ongoing study in elderly subjects

Cyclerion

2020 catalysts across programs

- partnering
- clinical trials

~$102M cash[1] and reduced burn support our priorities into Q2 2021

Team, talent and intensity to deliver

1. Preliminary, unaudited unrestricted cash, cash equivalents and restricted cash balance as of Dec 31, 2019

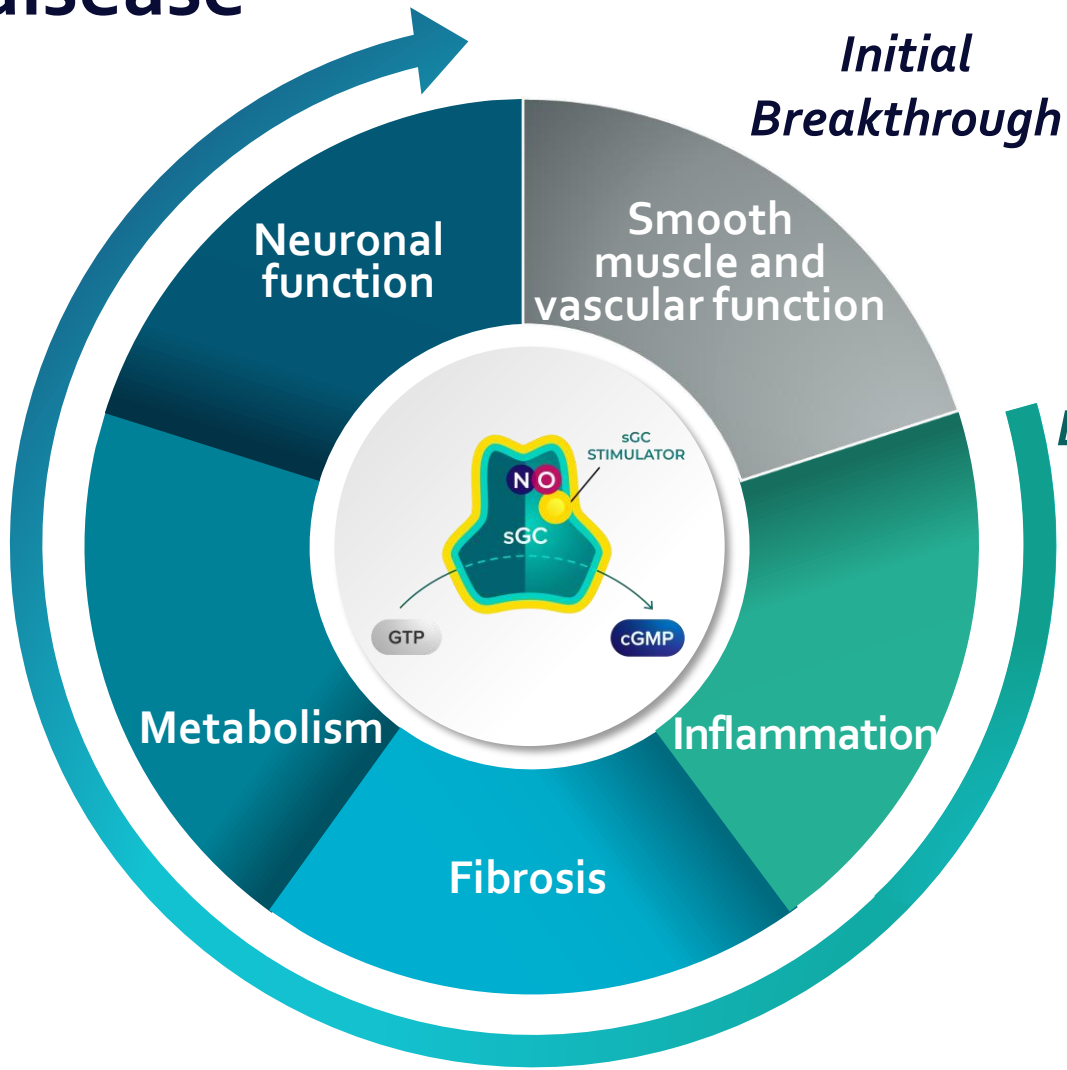
Cyclerion: clinical stage startup developing sGC therapeutics for serious diseases

Leadership position in sGC → **Patient impact and value creation**

- sGC: a clinically validated fundamental mechanism
- portfolio of 5 wholly-owned assets
- Starting 2020 with ~$102M cash[1] supports our priorities into Q2 2021
- experienced and successful leadership team

1. Preliminary, unaudited unrestricted cash, cash equivalents and restricted cash balance as of Dec 31, 2019

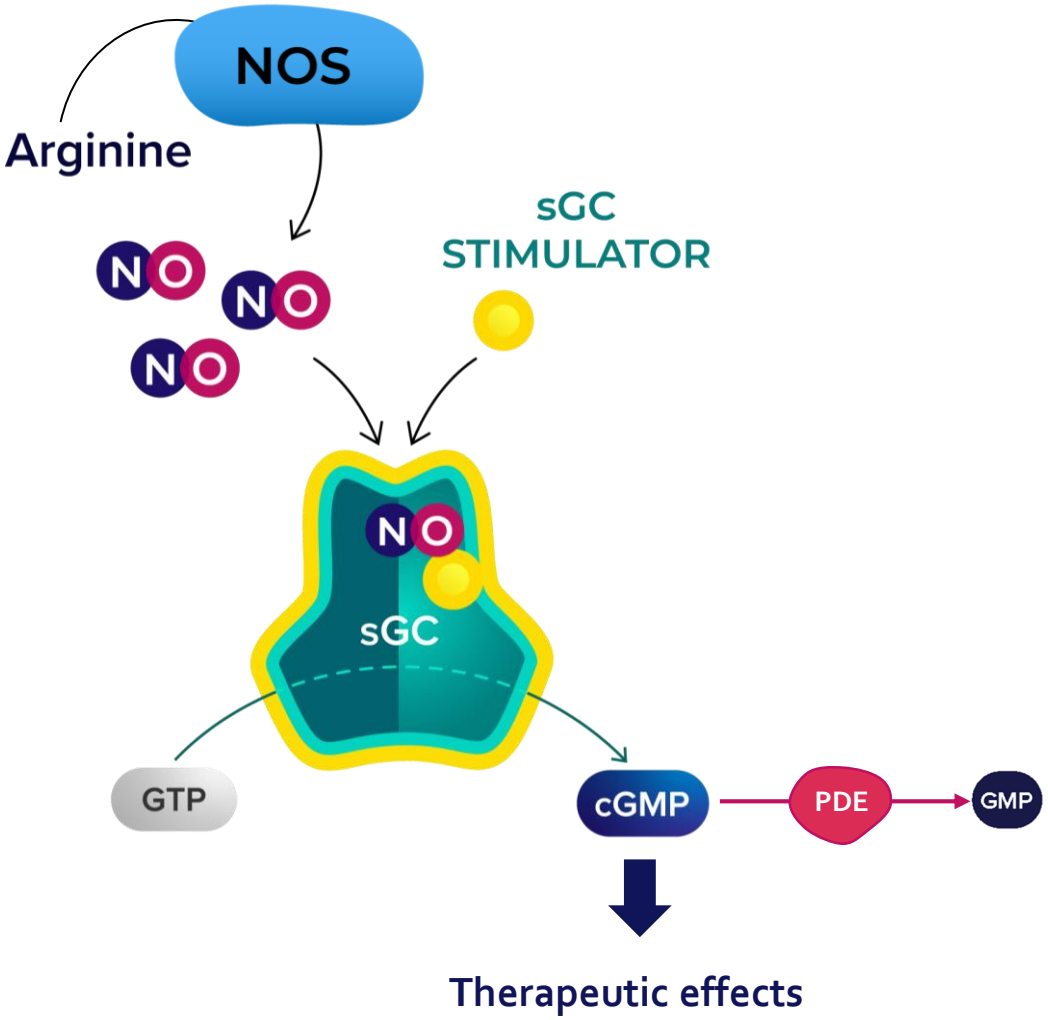
sGC: single target with potential to address multiple aspects of disease



Differentiated sGC stimulators designed to **modulate signaling in tissues most relevant to targeted diseases**

Graphic adapted from Buys et al. 2018. Discovery and development of next generation sGC stimulators with diverse multidimensional pharmacology and broad therapeutic potential. Nitric Oxide 78:72-80

Nitric oxide (NO) signaling: clinically validated pathway



- **Multiple drugs created by targeting different steps in pathway**
  - **NO donors** for angina (eg, Nitropress®, Imdur®, Corvasal®, Corvaton®)
  - **PDE5 inhibitors** for erectile dysfunction and pulmonary arterial hypertension (eg, Viagra®, Cialis®, Revatio®, Adcirca®)
  - **sGC stimulator** indicated for multiple forms of pulmonary arterial hypertension: Adempas®
- **sGC stimulator mechanism has the potential to fully leverage the NO-sGC-cGMP pathway**
  - target is **broadly expressed** in the body (unlike PDEs)
  - **synergizes** with endogenous NO (unlike NO donors)
  - **drives cGMP levels at the source** (unlike PDE inhibitors)
  - has a **durable response** (unlike NO donors)

A wholly owned pipeline of differentiated molecules

Completed Clinical POC

Praliciguat

Results in DN study support out-license for further development

Ongoing Clinical Programs

Olinciguat

Phase 2 proof-of-concept study in sickle cell disease ongoing (SCD)

Topline data expected mid-2020

IW-6463

Phase 1 in young healthy volunteers completed, with good CNS exposure, once-daily oral PK, and good safety/tolerability.

POM study TLD and POC start to mid-2020

Preclinical

Liver-targeted

Lung-targeted

Experienced team and successful leadership

- Distinctive track record of innovative drug discovery/development (e.g.--CELEBREX®, KALYDECO®, LINZESS®, LUNESTA®, OPDIVO®, ORKAMBI®, YERVOY ®)
- Successful sGC/cGMP drug hunters; deep knowledge of nitric oxide (NO)-cGMP pathway
- Broad experience in creating strong organizations and commercializing products

1 Praliciguat in diabetic nephropathy (DN): out-license discussions based on promising phase 2

Data support further development → **Out-license discussions underway**

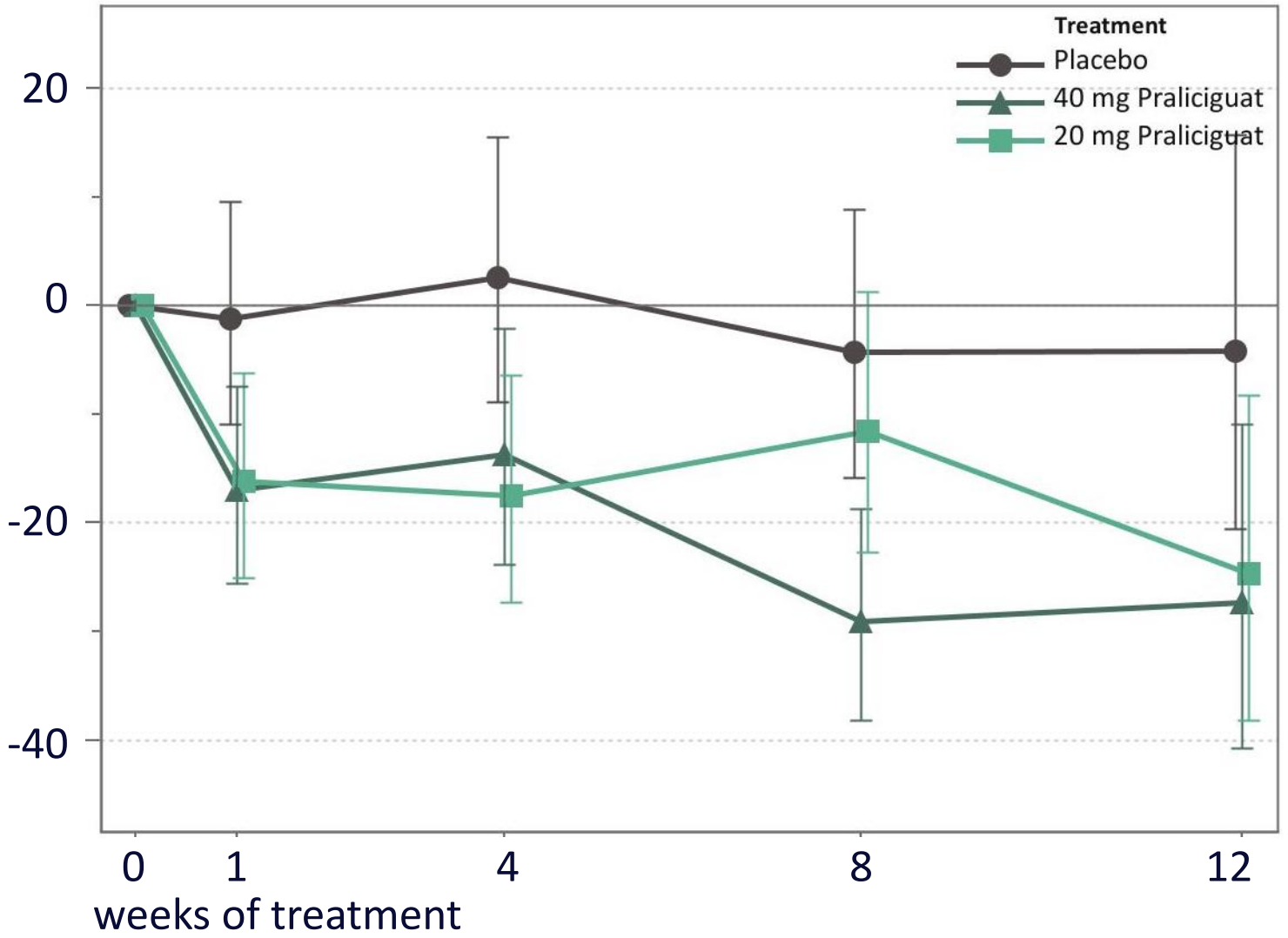
- UACR reductions on top of standard of care
  - 20%[1] placebo-adjusted (p=0.0303[2])
  - 24%[1] absolute change from baseline
- reductions in blood pressure, HbA1c, total and LDL cholesterol
- favorable safety profile, consistent with previous studies
- attractive dosing and PK relative to others in class

1. Modified intent-to-treat population, pooled praliciguat 20 and 40mg dose, placebo-adjusted average of weeks 8 and 12 (primary endpoint)
2. Nominal p-value; not adjusted for multiplicity

Phase 2 showed promising improvement in UACR

% UACR change from baseline

LS mean (90% CI) change UACR in (mg/g) (mITT)[1]



(90 % CIs by dose & timepoint)

1. mITT: modified intent-to-treat population n=133 excludes data from site 00A where data inconsistencies were observed in both the treatment and control groups

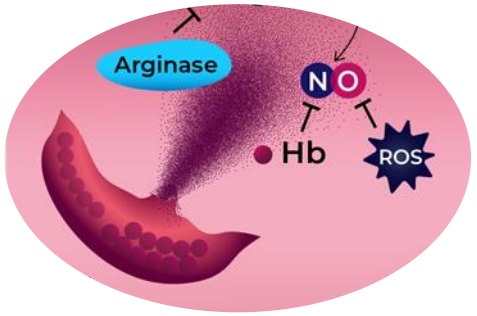
2 Olinciguat in sickle cell disease (SCD): potential for raising standard of care across four therapeutic domains

Dynamic mechanism - alone or complementing approved treatments → **Topline phase 2 results mid-2020**

- upstream + downstream pharmacological intervention
- impact potential in four clinical domains: anemia, daily symptoms, VOC, and organ protection--not fully addressed by approved therapies
- oral, QD drug for use in a broad range of SCD patients
- STRONG SCD trial designed to assess safety and pharmacodynamic effects across full dose range

Olinciguat: upstream and downstream intervention in SCD

Increased hemolysis leads to reduced nitric oxide state



sGC restores deficient nitric oxide signaling

Upstream

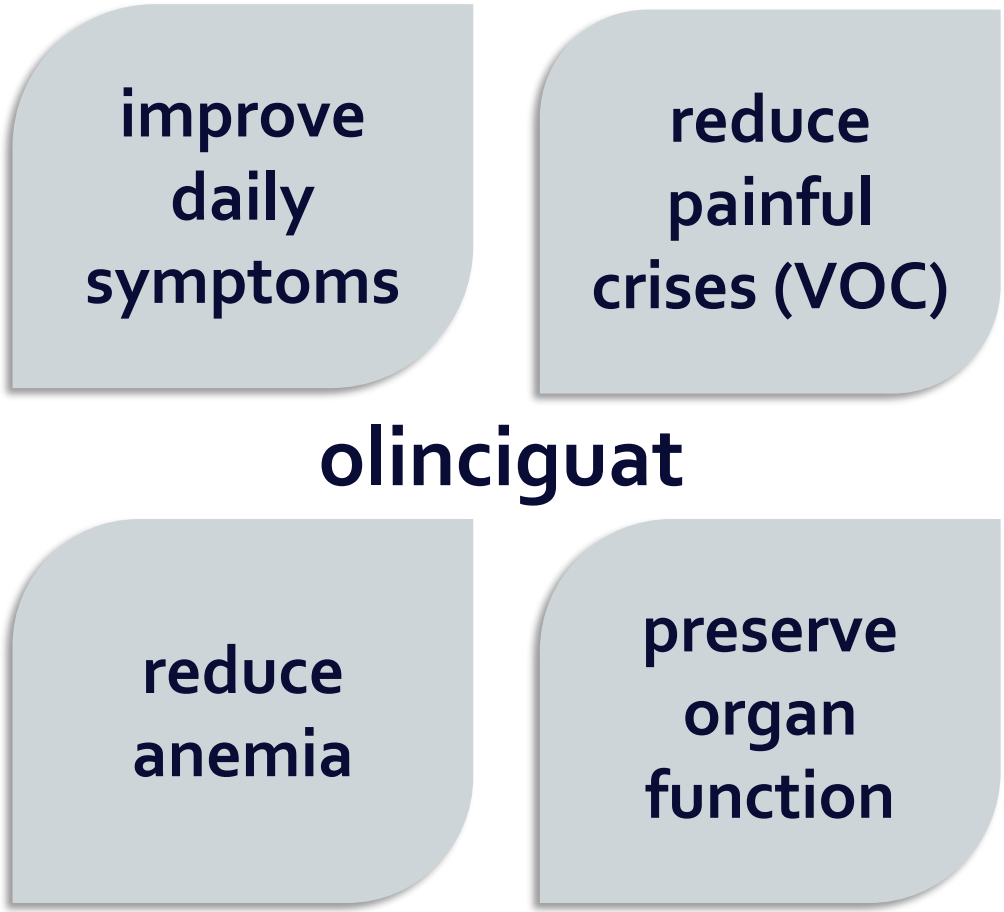
- increased HbF leads to reduced proportion of sickled RBCs1

Downstream

- improved blood flow
- decreased vascular inflammation & cell adhesion
- improved endothelial integrity

1. Conran, N., & Torres, L. (2019). cGMP modulation therapeutics for sickle cell disease. *Experimental Biology and Medicine*, 244(2), 132–146.

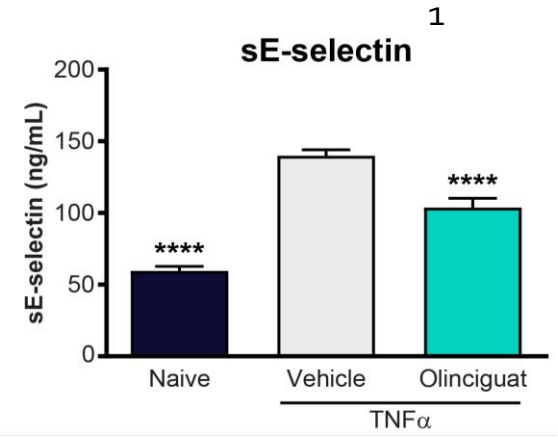
Potential to raise standard of care across four therapeutic domains



- newly approved therapies each target a single clinical domain…
- …olinciguat has the potential to improve four
- daily symptoms and end-organ protection remain unaddressed, decreasing QoL and increasing mortality
- further improvement in anemia and/or VOC possible with olinciguat alone or as add-on therapy serving broad SCD patient population

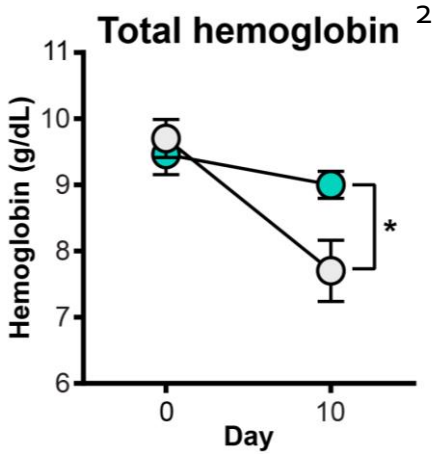
Preclinical data support clinical investigation

Inflammation



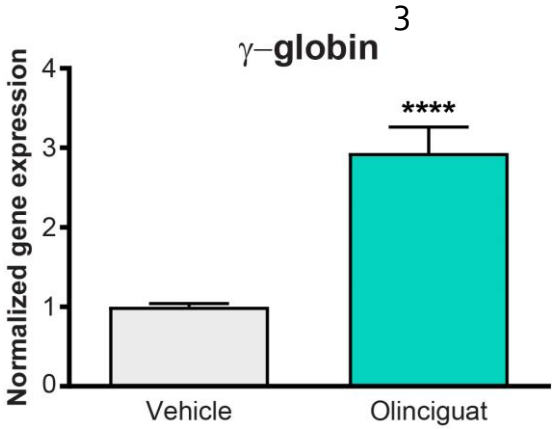
Lower levels of vascular inflammatory markers and improved vascular function in mouse models of inflammation†

Anemia



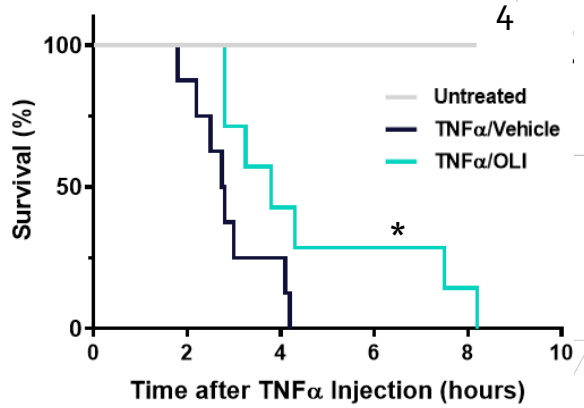
Decrease in progression of hemolytic anemia in Townes SCD mouse model

Fetal Hemoglobin



Higher mRNA expression of the γ-globin subunit of fetal hemoglobin in cultured cells

Survival



Olinciguat extended survival in TNFα challenge Berkeley SCD mouse model

† Adhesion can occlude microcirculation and lead to painful VOC and other serious complications; 1. **** p<0.0001 vs TNFα-vehicle, 1h predose olinciguat followed by treatment with TNFα in normal mice; 2.*p<0.05; 3. **** p<0.0001 vs vehicle Treatment of K562 cells with vehicle or olinciguat for 7 days in cell culture, 4 * p<0.05 vs TNFα-vehicle, work done collaboratively with the laboratory of Paul Frenette (Albert Einstein), HU did not show benefit to survival

STRONG SCD

Olinciguat phase 2 trial designed to support rapid advancement

Topline results expected mid-2020

DESIGN

- double blind
- global sites
- 4 dose levels
- up to 88 patients aged 16 – 70
- 12-week treatment in all SCD genotypes

OBJECTIVES

- assess safety and tolerability
- confirm PK profile in SCD patients
- development of the CYCN fit-for-purpose patient-reported outcomes (ePRO) instrument
- signs of pharmacodynamic effect: biomarkers (Hb, HbF, inflammation, adhesion) and daily symptom effects

INSIGHTS FOR PHASE 3 DESIGN

- endpoint selection based on results (biomarkers and ePRO)
- determine study sample size and dose(s)

3 IW-6463 in CNS: advancing development for treatment of serious neurodegenerative diseases

Ph 1 showed safety, target engagement, CNS exposure

Additional clinical studies in 2020 to accelerate and de-risk program

Preclinical evidence: stimulation of nitric oxide-cGMP pathway improves determinants of brain health

Impaired brain function associated with low nitric oxide-cGMP

Enhanced NO-cGMP in the CNS leads to:

- enhanced neuronal function
- increased cerebral vascular function
- decreased microglial activity
- improved mitochondrial output

Potential for improved brain health

1. Cyclerion's pre-clinical work www.cyclerion.com

IW-6463 potential to restore nitric oxide-cGMP signaling

Nitric oxide insufficiency leads to

- neuroinflammation and neurodegeneration
- impaired neurovascular blood flow

Improved brain health

- decreased inflammation
- increase blood flow
- neuroprotection and enhanced cognition

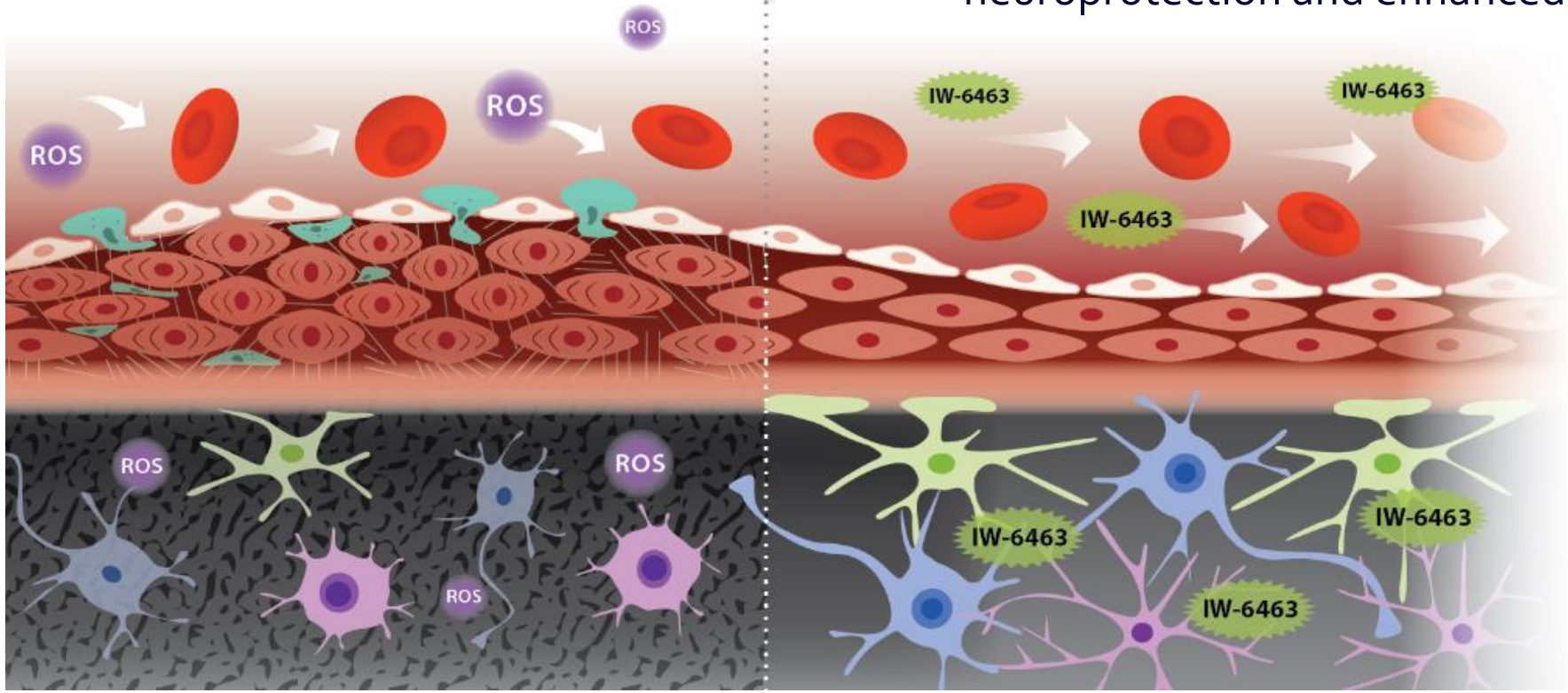
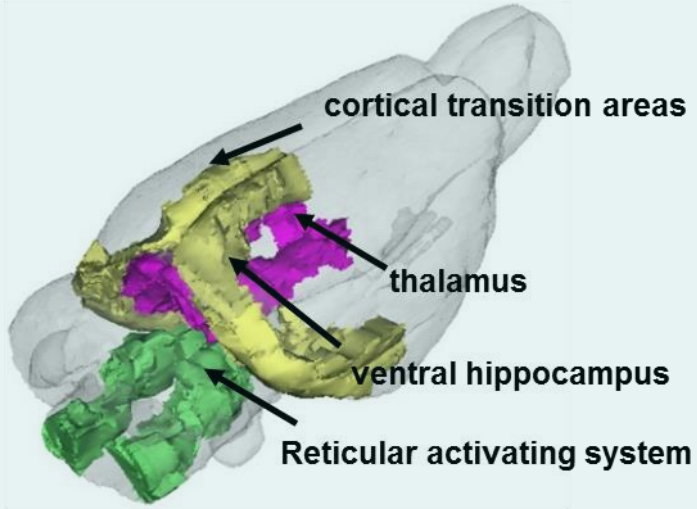


Figure adapted from Tobin, Zimmer et al. J Pharmacol Exp Ther 2018;365:664-675. Copyright © 2018 The Author(s).

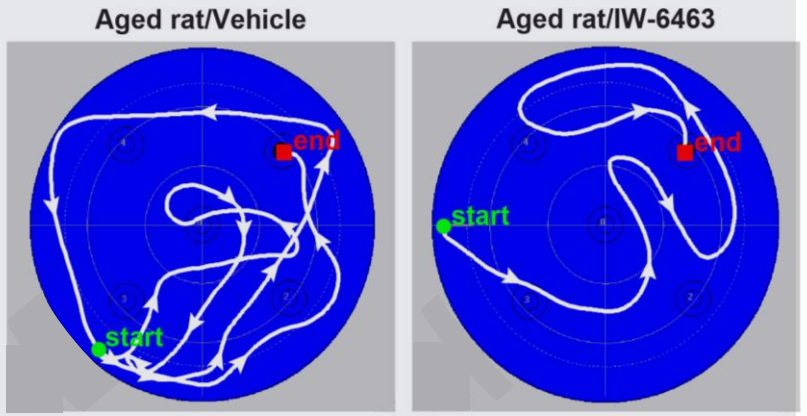
IW-6463 preclinical results support potential broad utility in CNS disease

Cerebral blood flow

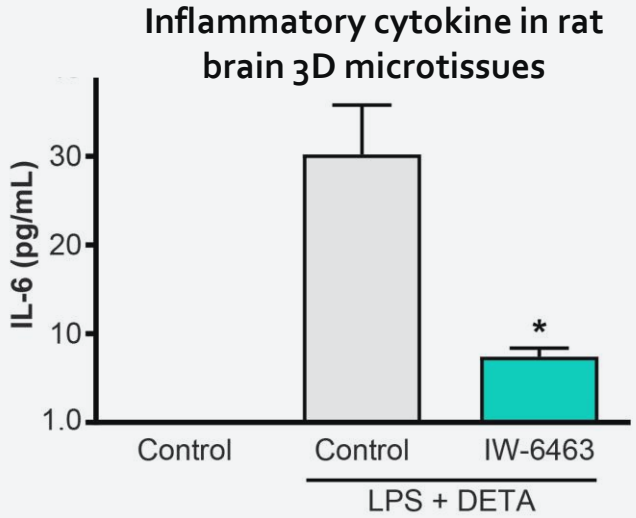


Cognitive function

Maze performance in aged rats



Neuro-inflammation



Note: data provided in this slide is based on preclinical models, *p<0.05 vs LPS + DETA Control

Positive phase 1 IW-6463 results support further development

Newly released—completed December 2019

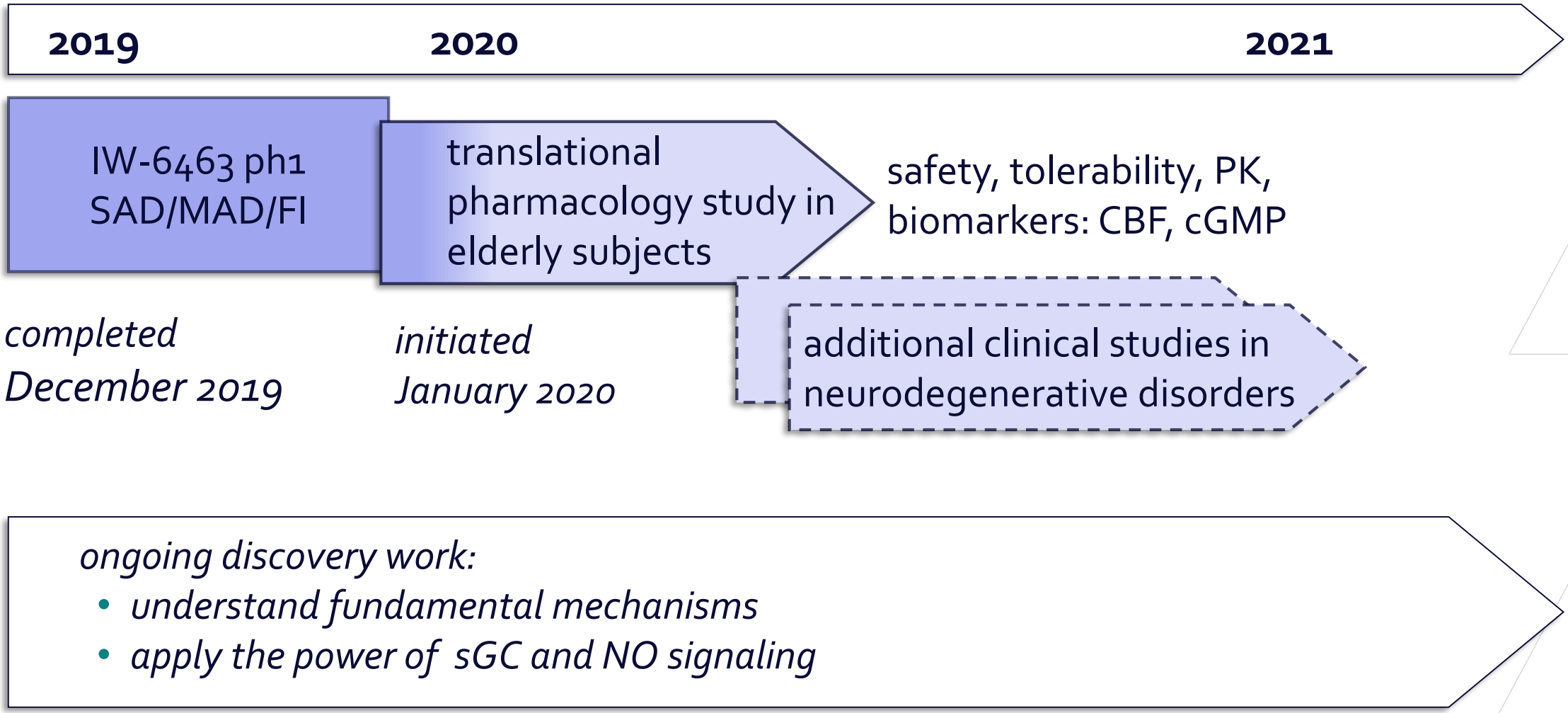
Phase 1 study design

- 3 stage: SAD, MAD and food interaction
- 110 healthy volunteers
- age range 18-63
- assessed safety, PK (blood & CSF)
- wide dose / exposure range tested

Insights

- CNS drug presence at levels expected to be pharmacologically active
- QD dosing, linear and predictable PK
- may be taken with or without food
- evidence of target engagement (blood pressure)
- well-tolerated at all dose levels
- all AEs mild in severity, no SAEs

Clinical direction: accelerate and de-risk into high value CNS indications



Translational pharmacology study to evaluate effect of IW-6463 on key CNS parameters

RATIONALE

- Obtain data on key CNS parameters relevant to a broad range of potential indications and further de-risk IW-6463's development

OBJECTIVES

- Evaluate the safety and tolerability of IW-6463 as well as IW-6463's impact on cerebral blood flow
- Additional exploratory endpoints include changes in plasma and CSF biomarkers, brain metabolites, brain activity/reactivity, and measures of cognitive and motor function

DESIGN

- Single-center, randomized, placebo-controlled two-way crossover in approximately 24 healthy elderly subjects, treated for 15 days
- Elderly individuals are likely to have reduced cerebral blood flow, impaired vascular reactivity, mitochondrial dysfunction, and dysregulated nitric oxide signaling

TOPLINE DATA

- Expected mid-2020

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clinical stage startup developing sGC therapeutics for serious diseases

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DN praliciguat partnering:

out-license discussions based on promising phase 2

2

SCD olinciguat phase 2 success:

potential for disease impact in 4 therapeutic domains that is complementary

3

CNS 6463 advancement into patients:

advancement from successful phase 1 in healthy volunteers
to exploratory work in serious CNS disorders

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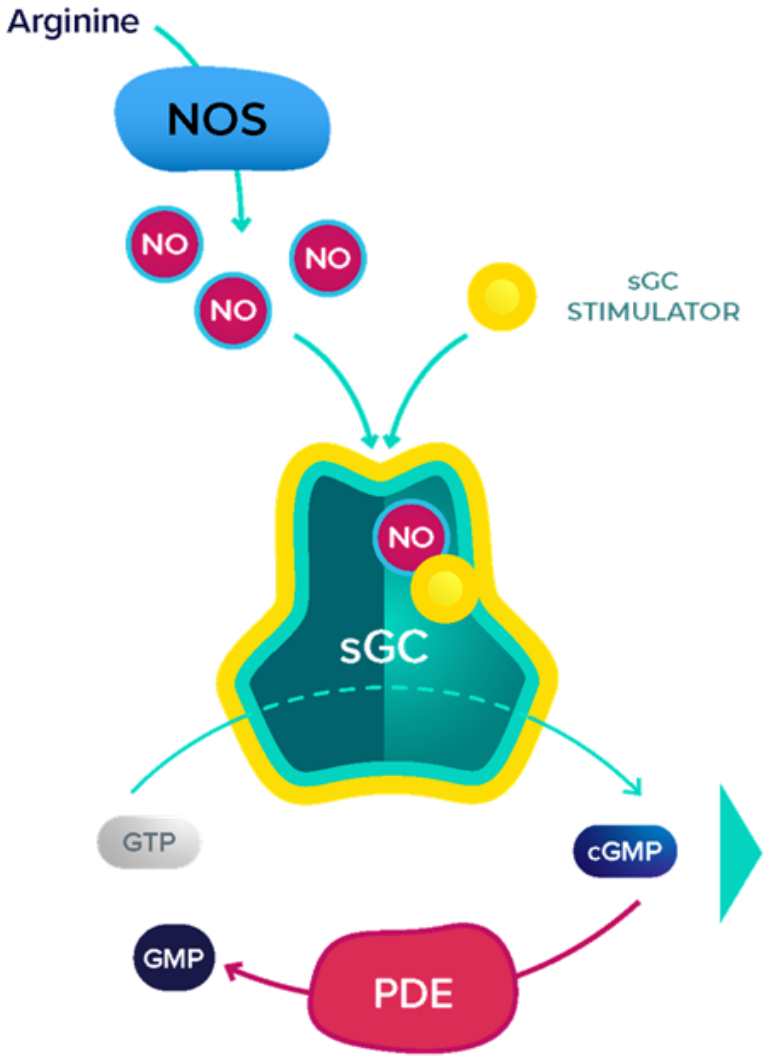
January 13, 2020

Creating breakthrough treatments for patients with serious and orphan diseases by harnessing the power of soluble guanylate cyclase (sGC)

Appendix

NO-sGC-cGMP signaling



Cyclic Nucleotide Gated Channels

Protein Kinase G

Phosphodiesterases

sGC Stimulation Can Increase

Local vasodilation / blood flow (e.g., vascular and smooth muscle relaxation)

Metabolism (e.g., AMPK activation)

Neuronal health and signaling (e.g., neuroprotection, LTP)

sGC Stimulation Can Decrease

Inflammation (e.g., TNFα signaling, EC activation)

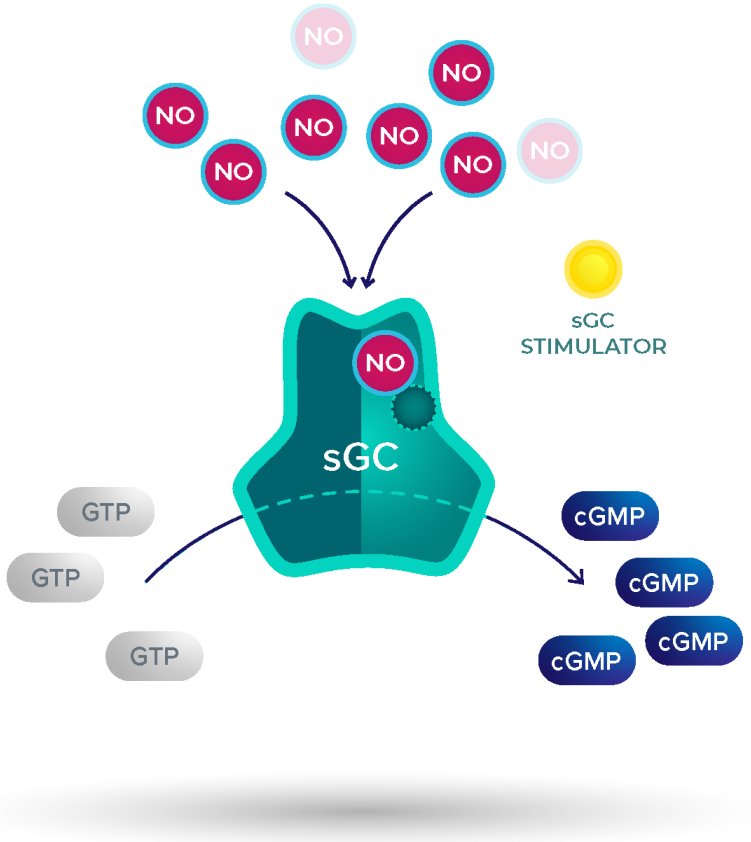
Fibrosis (e.g., TGFβ signaling)

NOS=nitric oxide synthase; cGMP=cyclic guanosine monophosphate; PDE=phosphodiesterase; GTP=guanosine triphosphate; GMP=guanosine monophosphate

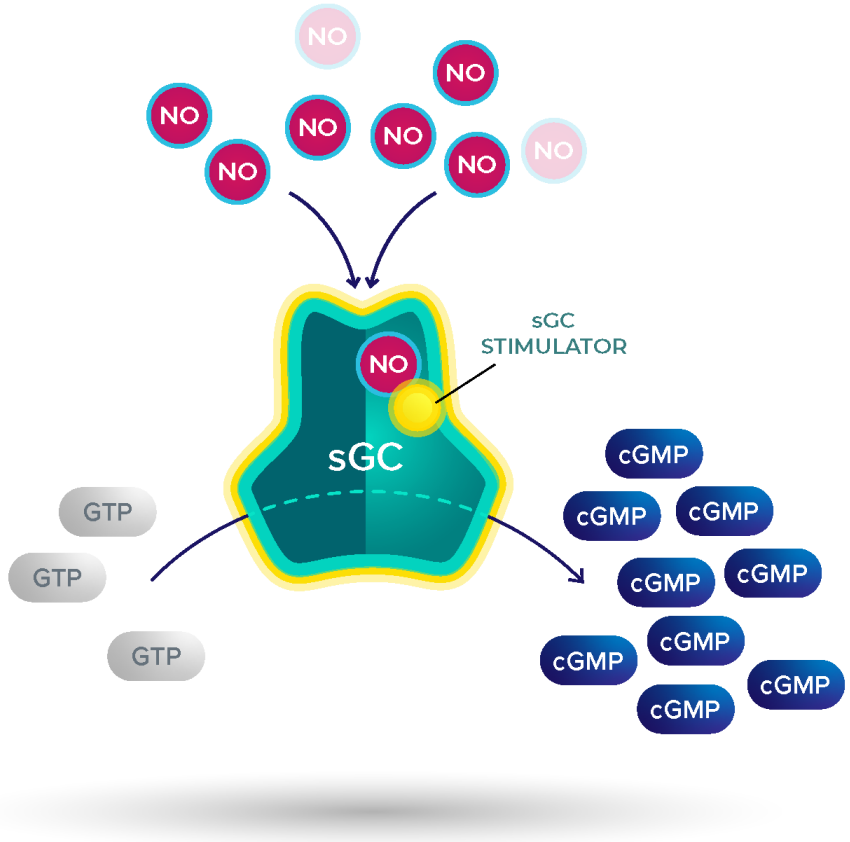
Reviewed in: Sandner et al. (2018) Soluble Guanylate Cyclase Stimulators and Activators. In: . Handbook of Experimental Pharmacology. Springer, Berlin, Heidelberg.

sGC stimulators are positive allosteric modulators that enhance NO-sGC-cGMP signaling

NO - sGC - cGMP Signaling

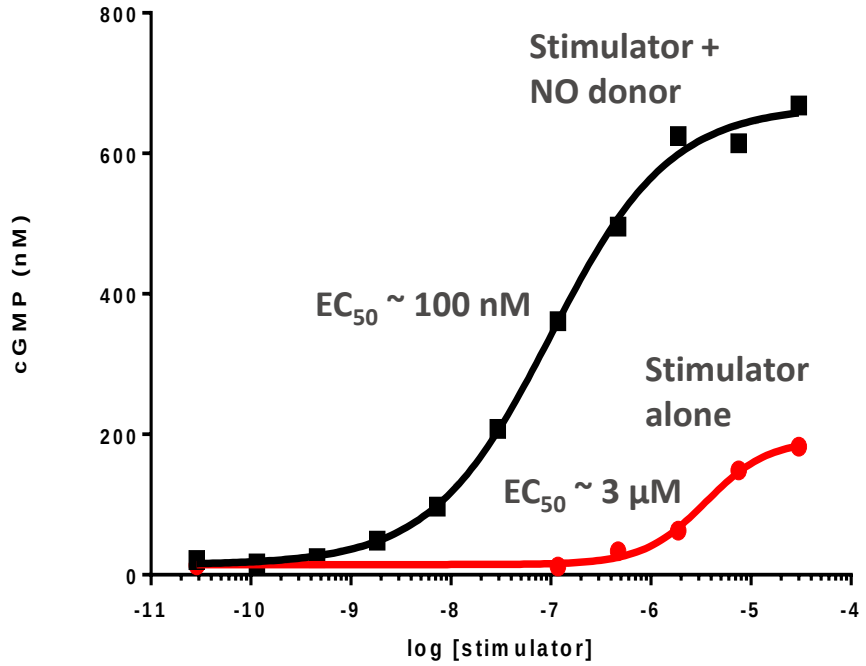


Stimulation of sGC

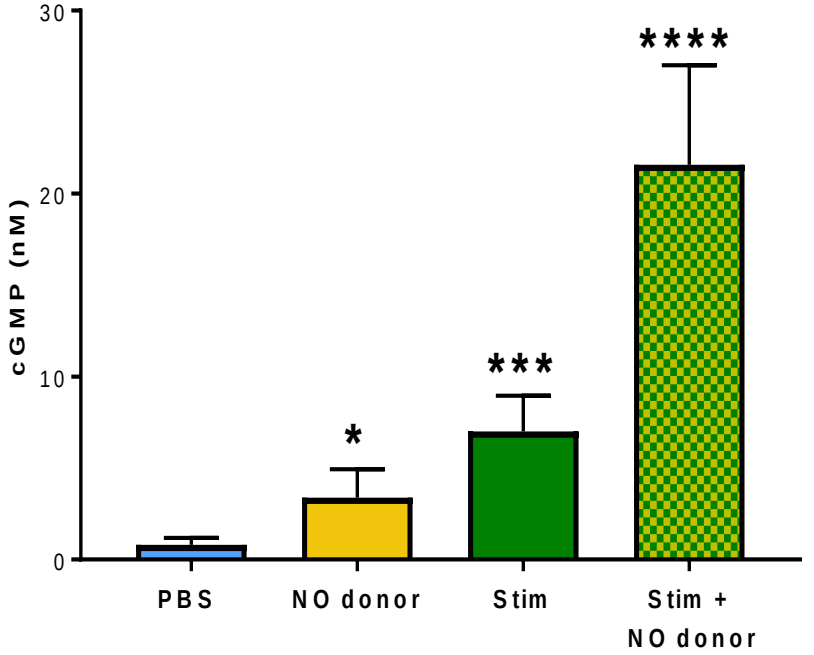


sGC stimulators act synergistically with NO

In vitro (HEK293 cells)



In vivo (rat liver/retrodialysis)

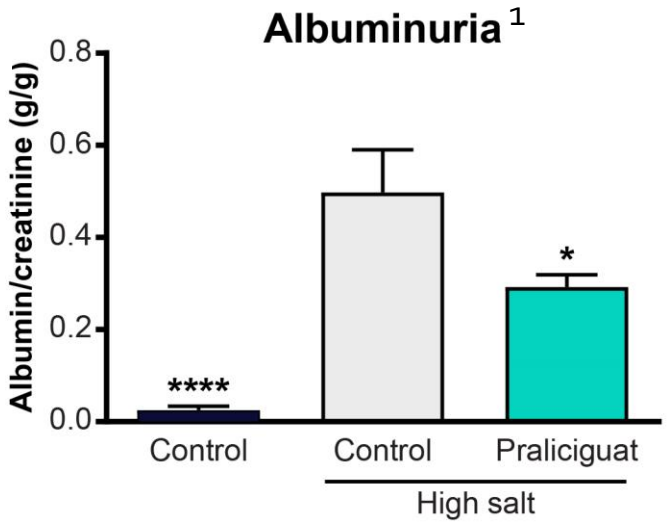


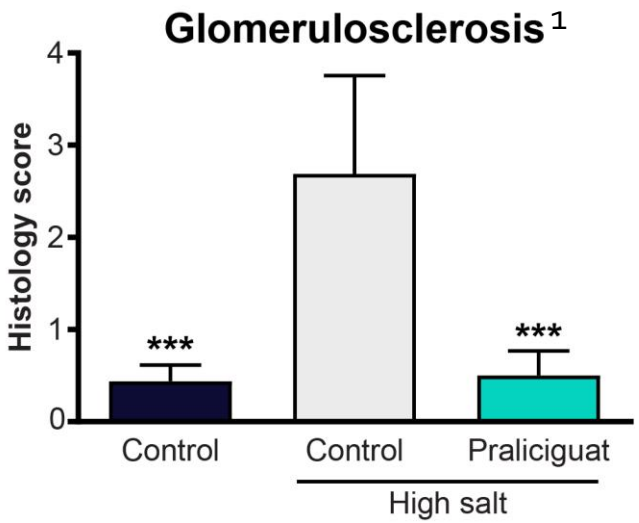
* p<0.05, *** p<0.001; **** p<0.0001 vs PBS

Preclinical data for praliciguat support potential utility in diabetic nephropathy

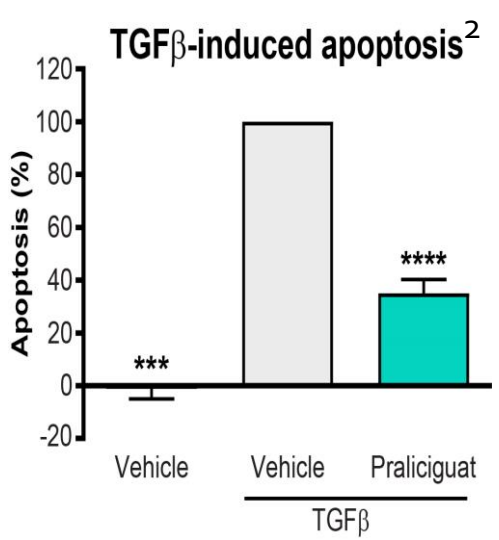
- Preservation of kidney function in multiple animal models†
- Corresponding effects on inflammation, fibrosis, and metabolism
- Anti-inflammatory and anti-fibrotic effects mechanistically separated from hemodynamic effects
- Positive effects on fasting glucose and lipids in ZSF1 rat model of diabetic nephropathy

Kidney Protection



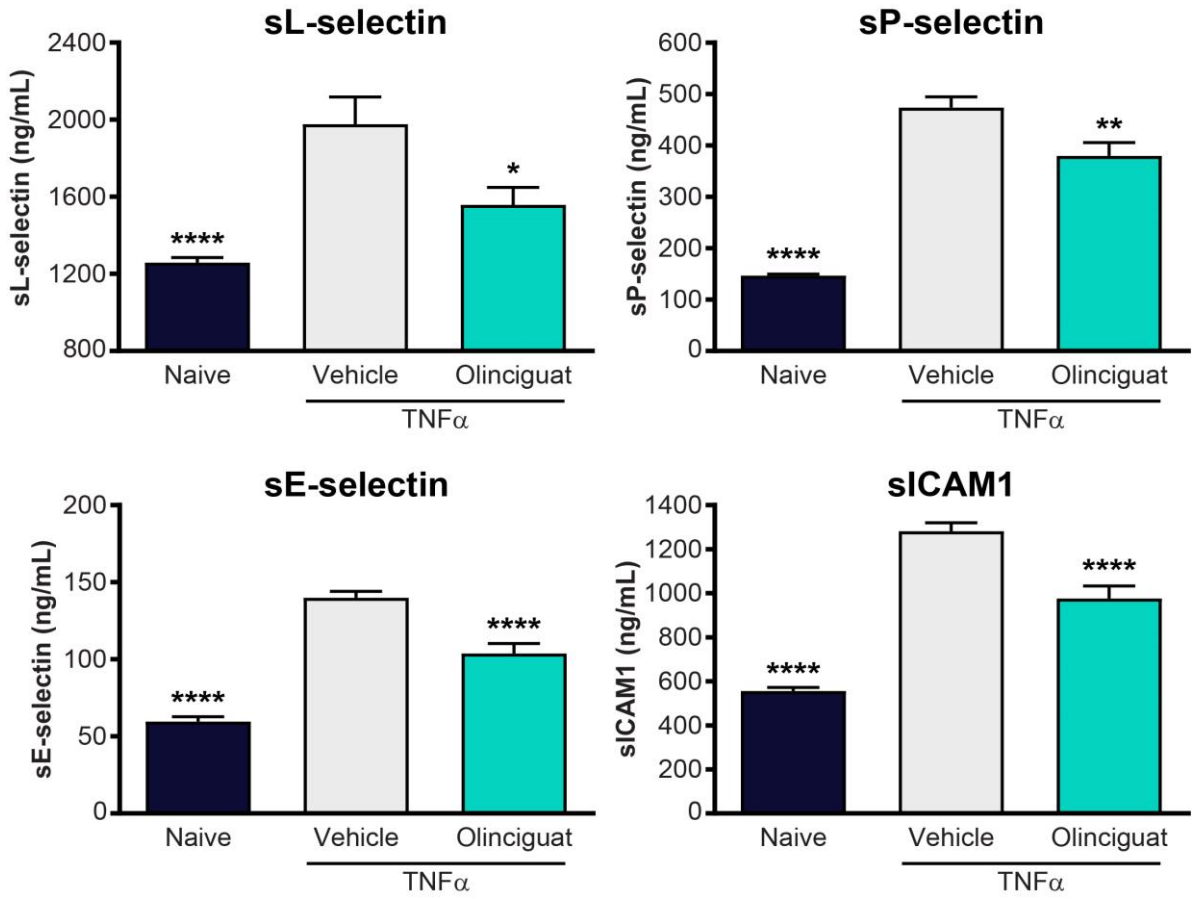


Anti-Fibrotic



† Dahl salt-sensitive rat model of hypertension and ZSF1 rat model of DN, 1. * p<0.05, *** p<0.001; **** p<0.0001 vs High-salt control in Dahl salt-sensitive rat model; 2.*** p<0.001; **** p<0.0001 vs TGFβ-vehicle in human renal proximal tubule epithelial cells in cell culture

Lower expression of cellular adhesion molecules associated with olinciguat treatment in preclinical model†

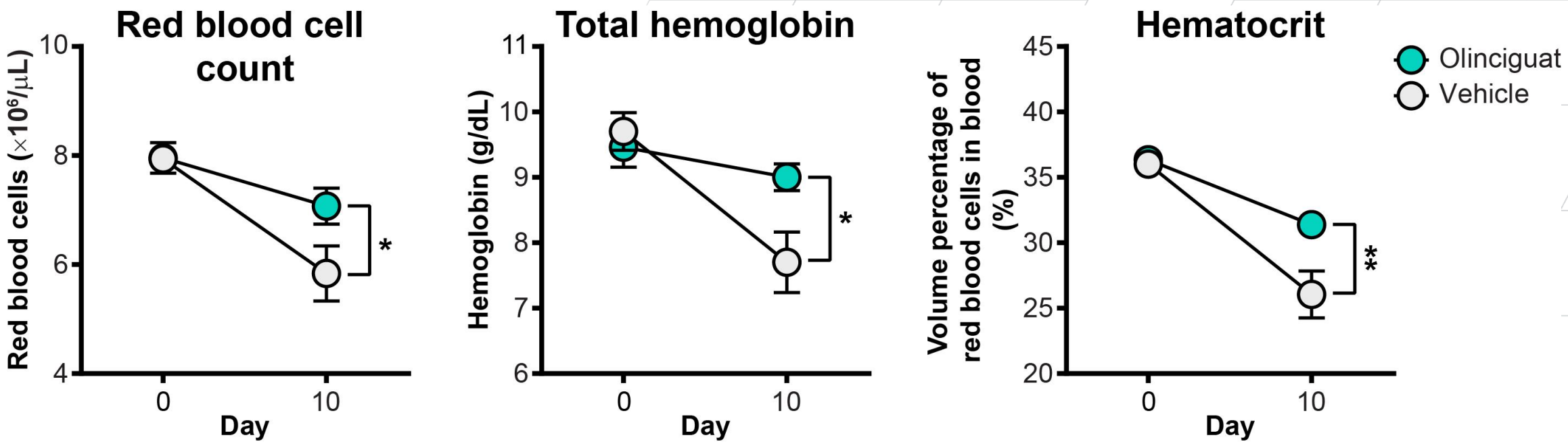


1h predose olinciguat followed by treatment with TNFα in normal mice

Reducing vascular inflammation via blockade of specific adhesion receptors is a clinically validated approach to reducing painful crises (e.g. crizanlizumab)

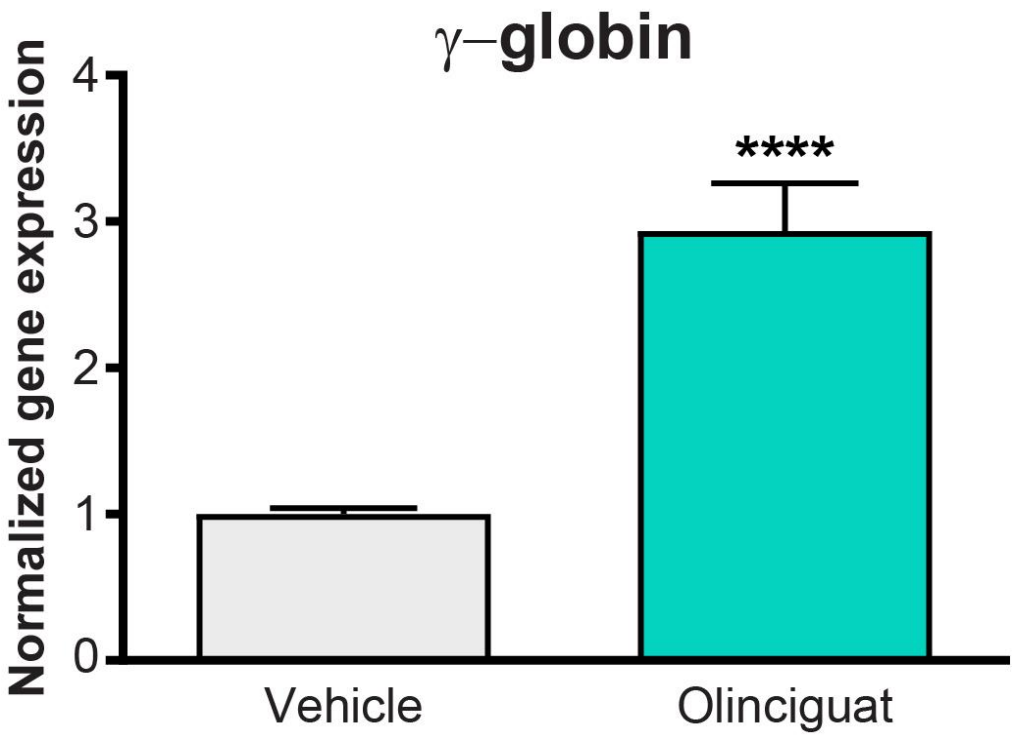
† in models of vascular inflammation, * p<0.05, ** p<0.001; **** p<0.0001 vs TNFα-vehicle

In a preclinical model of SCD, progression of hemolytic anemia was ameliorated in olinciguat treated mice



*p<0.05; ** p<0.01 Olinciguat vs Vehicle at Day 10

Greater normalized expression of the γ-globin subunit of fetal hemoglobin in cell culture treated with olinciguat



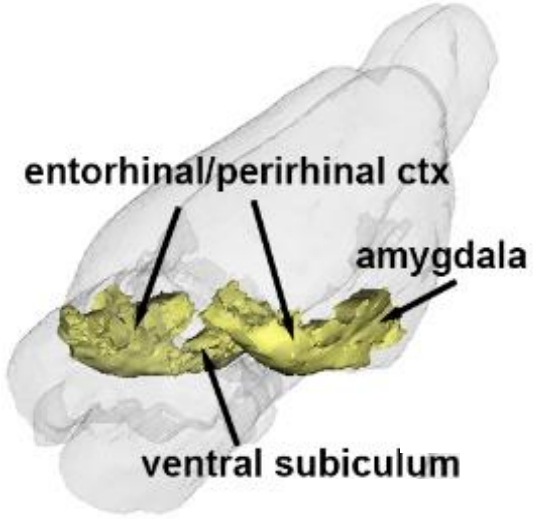
Treatment of K562 cells with vehicle or olinciguat for 7 days in cell culture

Increasing fetal hemoglobin is a clinically validated approach to the treatment of sickle cell disease (i.e. hydroxyurea)*

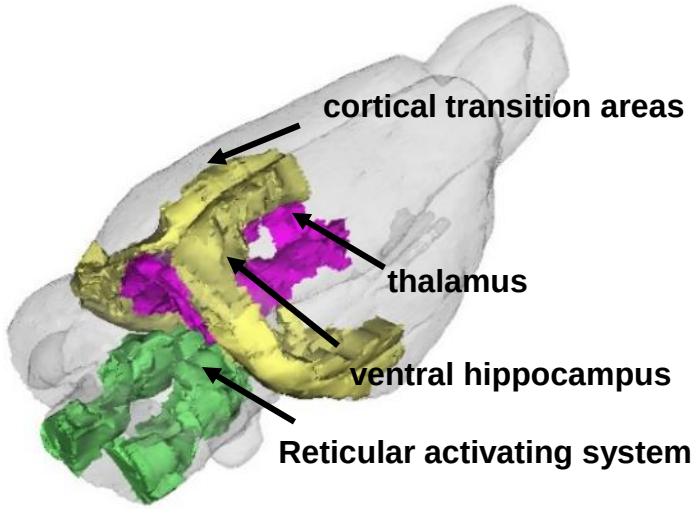
** In patients with SCD, higher HbF levels are associated with reduced rates of VOC, decreased frequency of acute chest syndrome and attenuation of other complications of SCD*
**** p<0.0001 vs vehicle

Increased blood flow to brain areas associated with memory and arousal in rats treated with IW-6463

Cerebral Blood Flow | Neuroinflammation | Neuroprotection | Cognitive Function



sGC stimulator: Peripherally Restricted



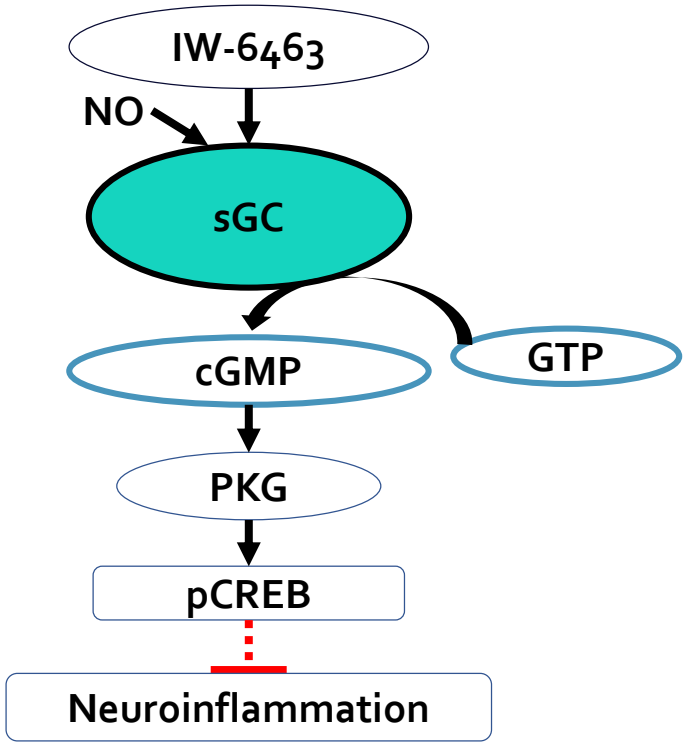
IW-6463: CNS-penetrant

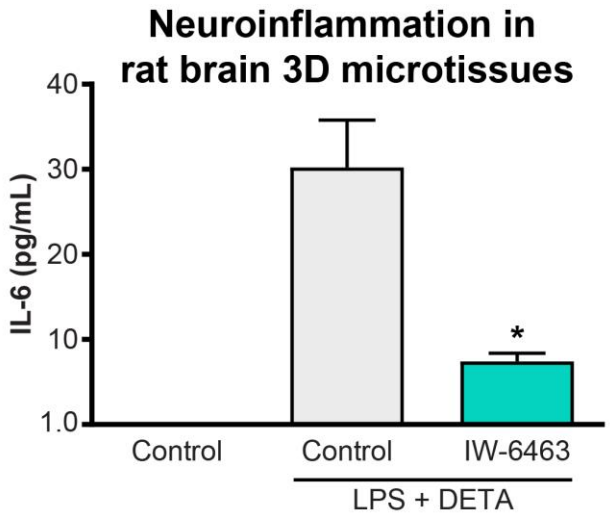
- Increased blood flow to areas associated with memory and arousal in normal rats by fMRI BOLD imaging -

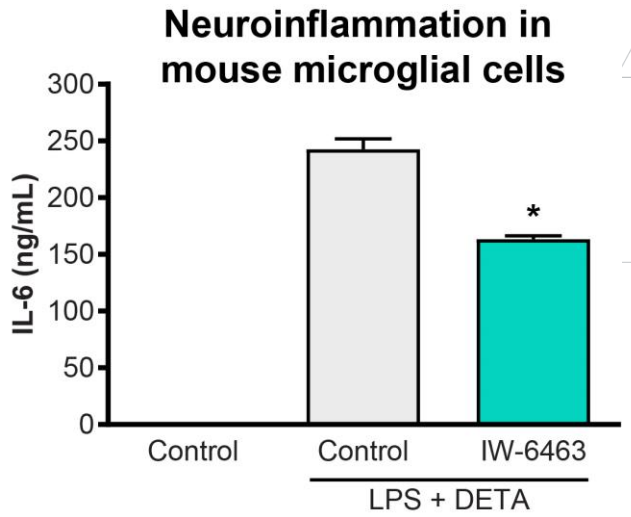
Note: data provided in this slide is based on preclinical models

Anti-inflammatory neuroprotective effects in mice treated with IW-6463

Cerebral Blood Flow | **Neuroinflammation** | Neuroprotection | Cognitive Function





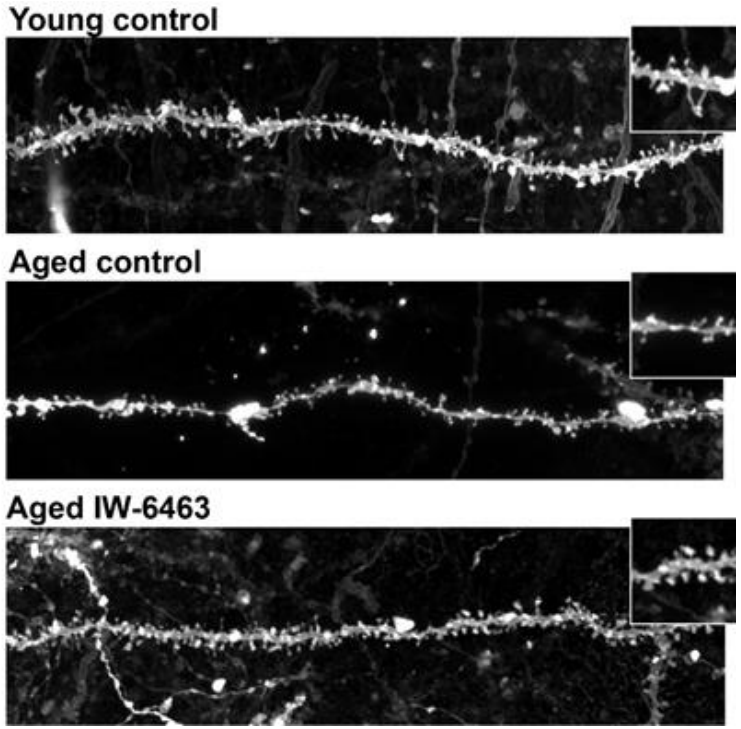


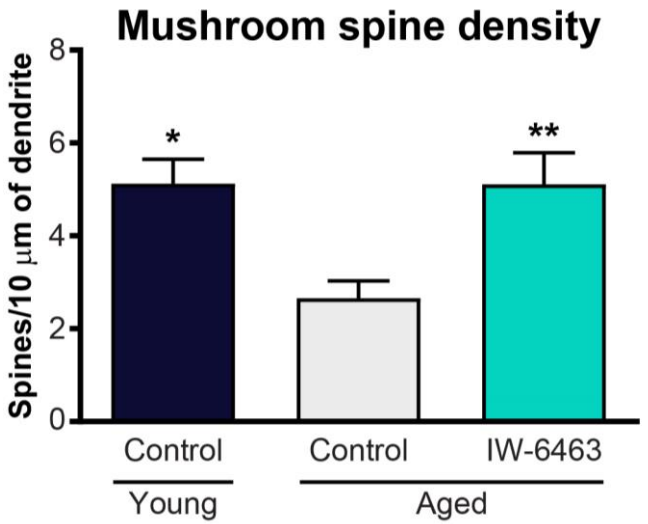
- Increased cGMP and pCREB in rat brain 3D microtissues -
- Decreased inflammatory cytokines in rodent microglial cultures and brain 3D microtissues -

*Note: data based on IW-6463 pretreatment in preclinical models, *p<0.05 vs LPS + DETA Control*

Neuroprotective effects in mice treated with IW-6463

Cerebral Blood Flow | Neuroinflammation | **Neuroprotection** | Cognitive Function





- Synaptic spine density in aged mice at same level observed in young mice -

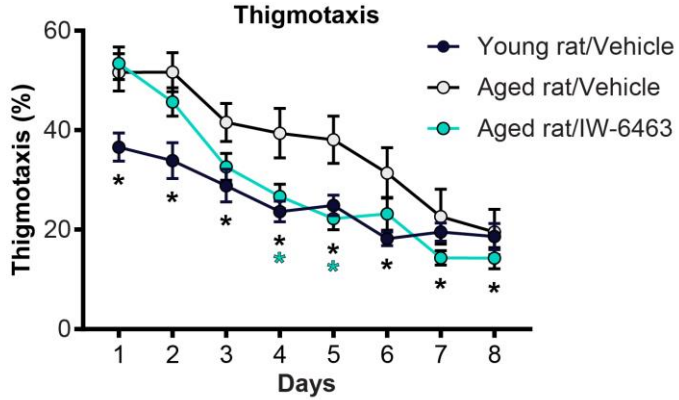
Note: data provided in this slide is based on preclinical models

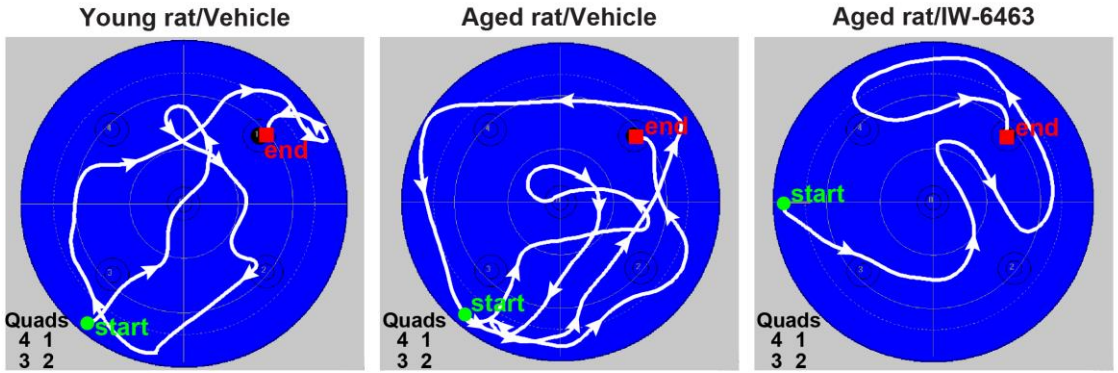
**p<0.05 vs. control aged mice*
***p<0.01 vs. control aged mice*

Improved cognitive function in rats treated with IW-6463

Cerebral Blood Flow | Neuroinflammation | Neuroprotection | **Cognitive Function**

Thigmotaxis: tendency to stay close to walls when exploring open spaces, which is associated with cognitive dysfunction and interferes with maze solving

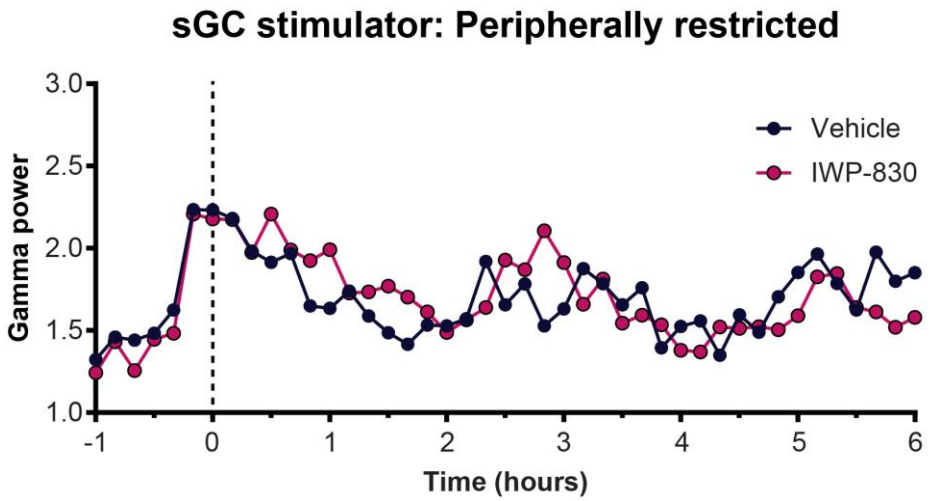


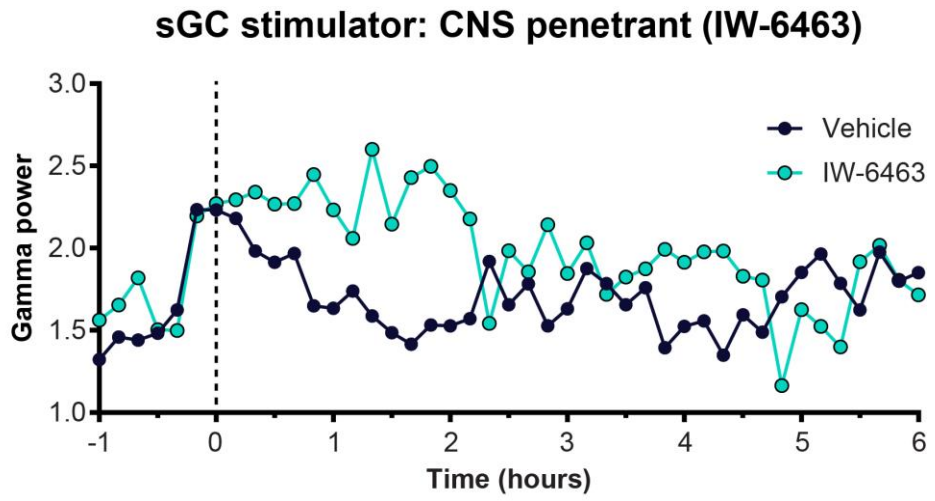


- Positive effect on cognitive function in multiple animal models, including both aged and pharmacologically impaired rats -

Note: data provided in this slide is based on preclinical models

Cortical brain activity greater in rats treated with IW-6463





- Opportunity for Early Clinical Proof of Pharmacologic Effects –

- Pharmacological effects of IW-6463 can be assessed clinically using translational non-invasive methods including EEG, MRS, ASL, and fMRI BOLD -

Note: data provided in this slide is based on preclinical models