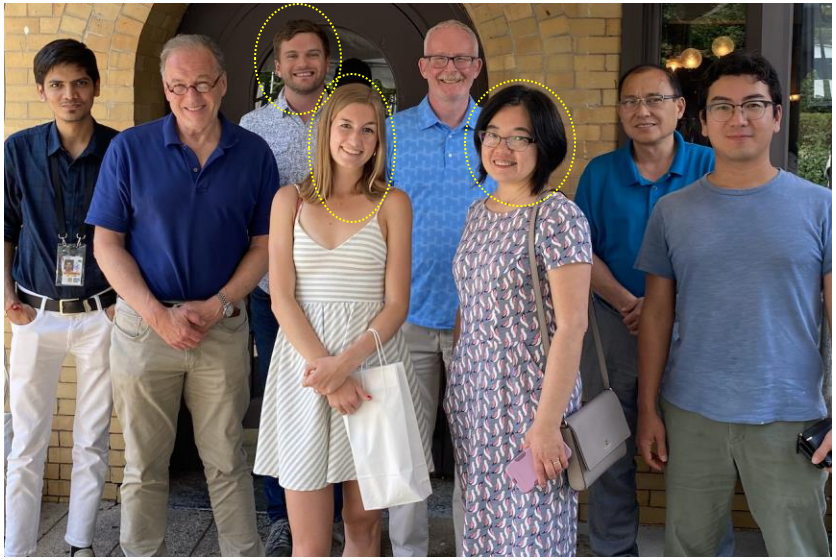
GLP-1 AND NEURODEGENERATIVE DISEASES

Drug Design & Development Section, Translational Gerontology Branch, NIA, NIH, Baltimore, MD



Left to right: Pathik Parekh, Nigel Greig, Elliot Glotfelty, David Tweedie, Katie Kopp Yazhou Li, Weiming Luo, Buka Batsaikhan

Key collaborators:

Barry Hoffer
Case Western Univ., USA (TBI & PD)

Deb Lahiri
Indiana Univ. USA (AD)

Kumar Sambamurti
MUSC, USA (AD)

Yun Wang
NHRI, Taiwan (PD & stroke)

Yuan-Hao Chen
National Defense Medical Center, Taiwan (PD)

Tom Foltynie
Univ. London, UK (PD)

Dilan Athauda
Univ. London, UK (PD)

Sonia Gandhi
Univ London, UK (PD)

Chaim Pick
Tel Aviv Univ., Israel (TBI)

Richard DiMarchi
Indiana Univ., USA (TBI)

Jin Jung
Peptron, S Korea (TBI/PD)

Conflict of interest statement

The National Institutes of Health (NIH), USA, has patent rights on the use of GLP-1 agonists for the treatment of neurodegenerative disorders (inventors: Greig and colleagues).

All rights have been assigned by Greig and colleagues in entirety to NIH.

Greig and colleagues have no financial or any other conflicts of interest.

There are commonalities between type 2 diabetes mellitus (T2DM) and neurodegenerative disorders – especially related to insulin resistance and cellular dysfunction/death mechanisms.

Hence, a drug efficacious in T2DM may be effective in neurodegenerative disorders for which useful drugs are unavailable.

Individuals with T2DM prescribed GLP-1R agonists (incretin mimetics) and gliptins (DPP-4 inhibitors) are 36-60% less likely to develop PD (Brauer et al., *Brain.* 143:3067-76, 2020)

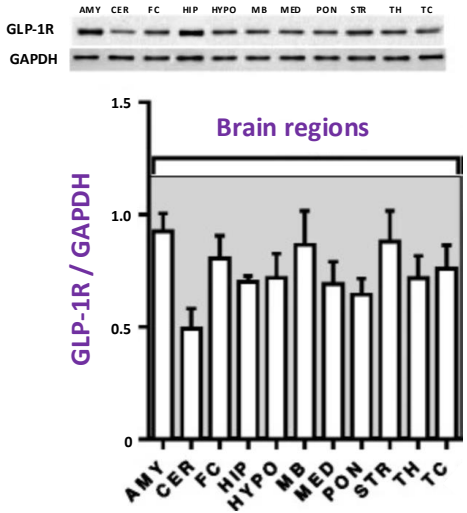
US Veterans prescribed GLP-1R agonists have a reduced risk of neurocognitive disorders – including AD and dementia (Xie, Choi, Al-Aly, *Nature Med*. 31: 951-62, 2025)

Outline

- GLP-1R brain expression
- GLP-1R agonists in neurodegeneration - brief history
- GLP-1R target across age/disease
- GLP-1R agonists in Parkinson's disease preclinical models…. clinical studies
- Potential directions ahead

GLP-1R Expression in Brain

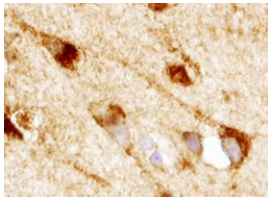
A Present across brain areas



GLP-1R distribution male ferrets (n=3, SEM)
Lu et al., *J Transl Med*. 12: 327, 2014.

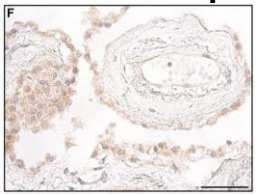
B Present on neurons

Human hippocampus



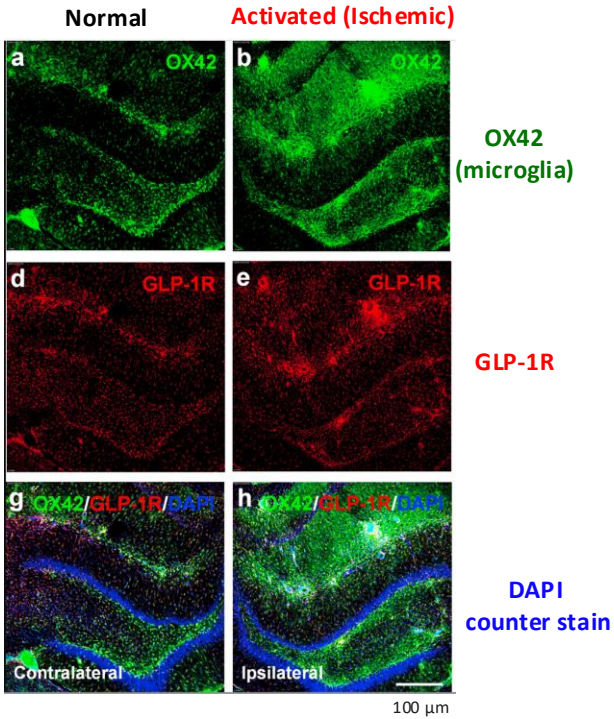
Biotechne MAB28141

C Present on epithelial cells of the choroid plexus



MAB3F52
Botfield et al., *Sci Transl Med.* 9:eaan0972, 2017.

D Present on microglia (and astrocytes)



GLP-1R distribution rat hippocampus 48 hr after ischemia, Jia et al., *Pharmacol Res.* 102: 276–285, 2015.

GIPR expression: neurons, microglia, astrocytes, oligodendrocytes
GcgR expression: neurons, microglia.

Incretin mimetic studies in neurodegeneration

GLP-1R agonists to mitigate neurodegenerative disorders: 2002 onwards
(Perry et al., *J Pharmacol Exp Ther*. 300:958-66, 2002 & 302:881-8, 2002).

Perry & Greig 2002 (NIA/NIH)

Neurotrophic/protective/anti-inflammatory actions in cellular & animal models: AD, PD, Multiple system atrophy, ALS, Huntington's disease, peripheral neuropathy, TBI, ischemic stroke, idiopathic intracranial hypertension

Questions:

..... but do these actions translate to human disease?

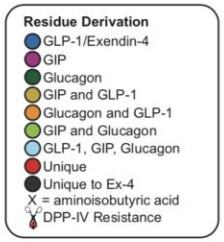
..... which agonists should best be evaluated?

..... when in the disease process?

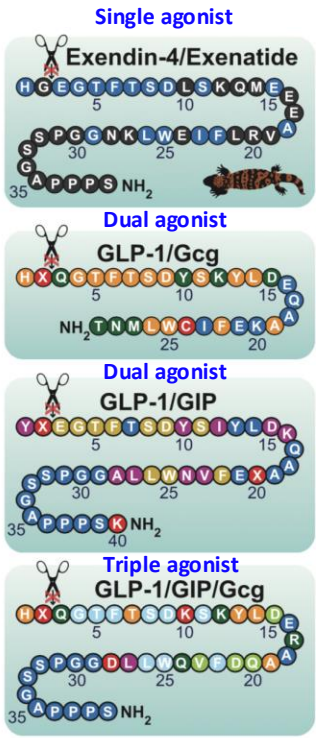
To gain a quick overview of the field:

Short perspective: Kopp KO et al., *Ageing Res Rev*. 98:102343, 2024
(5 to 10 min read)

Katie Kopp
(NIA/NIH)



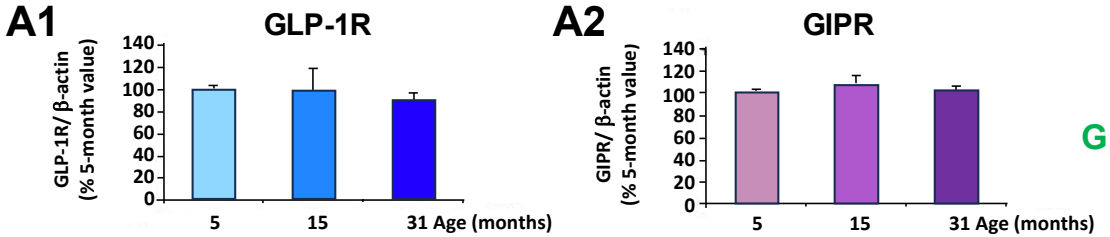
Current monomeric GLP-1 based receptor agonists



Drug target availability across age and disease:

Receptors for glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)

Rodent brain



GLP-1R/GIPR expressed across age in brain

Seong-Jin Yu
(NHRI Taiwan)

Yazhou Li
(NIA/NIH)

Yu SJ et al. *Geroscience*. 46: 4349-71, 2024

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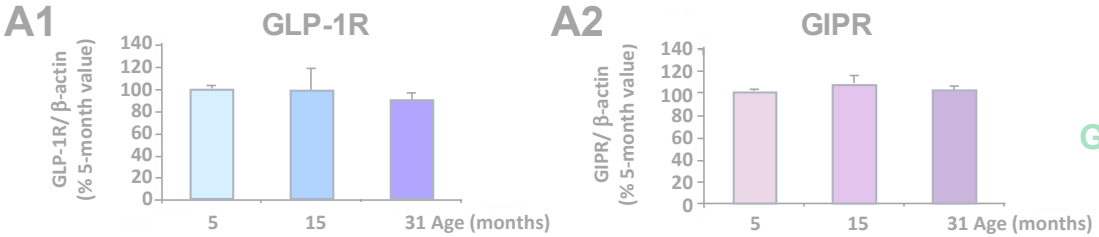
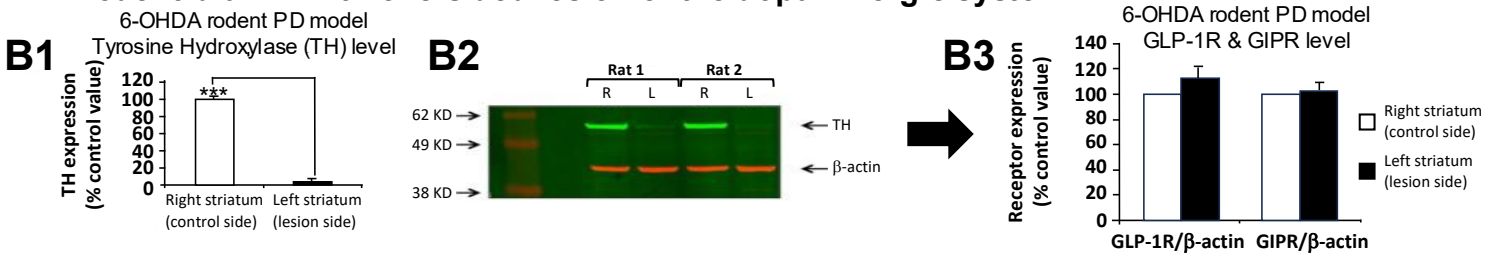


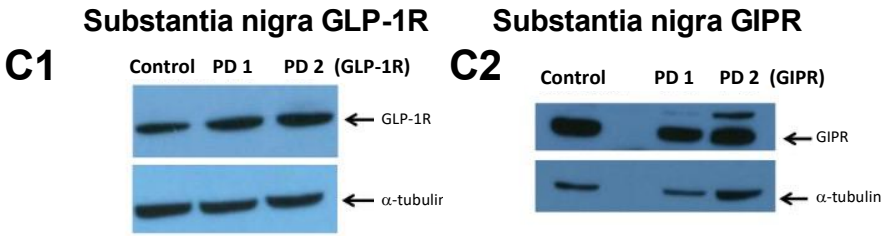
GLP-1R/GIPR expressed across age in brain

Rodent brain – with one-sided lesion of the dopaminergic system



GLP1R/GIPR expressed in the disease state in PD rodent model

Human brain: control vs. Parkinson's disease



GLP-1R/GIPR expressed in human PD brain

Seong-Jin Yu (NHRI Taiwan)

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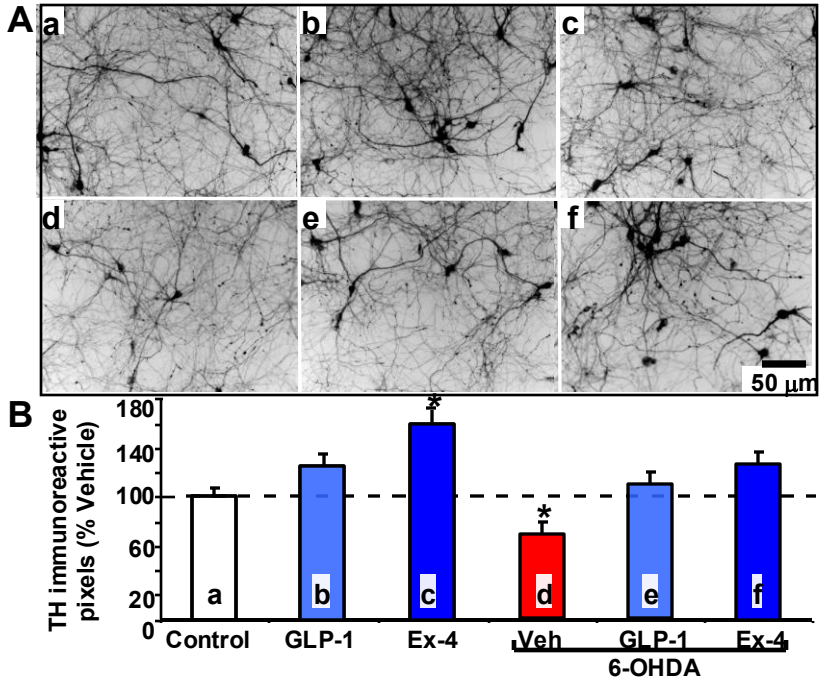
Yu SJ et al. *Geroscience*. 46: 4349-71, 2024

Consequences of GLP-1R mediated neurotrophic actions: stronger phenotype



Tyrosine hydroxylase activity: Ventral mesencephalic (VM) (dopaminergic) primary neurons challenged with GLP-1/Ex-4 (100 nM) +/- 6-OHDA

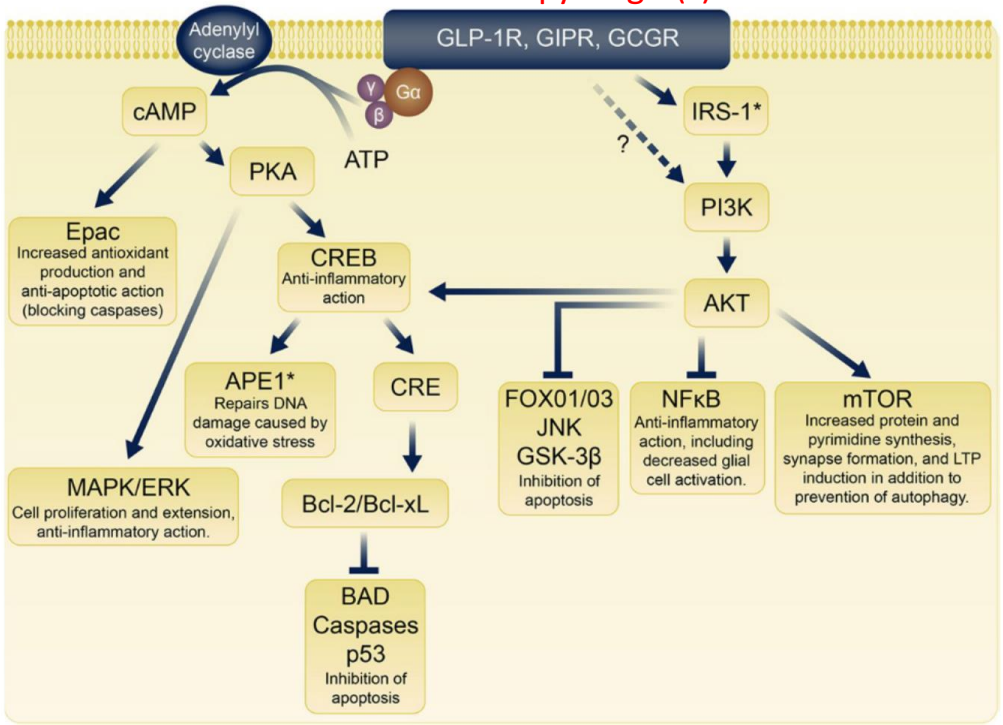
Significantly different from control ($p<0.05$)
Li Y, *PNAS* 106: 285-90

Choline *acetyltransferase activity:*
Motor neurons
Li Y, *PLoS One* 7(2):e32008

Yazhou Li
(NIA/NIH)

Key signaling pathways in neurons activated by incretins – particularly by GLP-1R activation – can be determined in cell culture

Incretin-based therapy target(s) – Class B GPCR

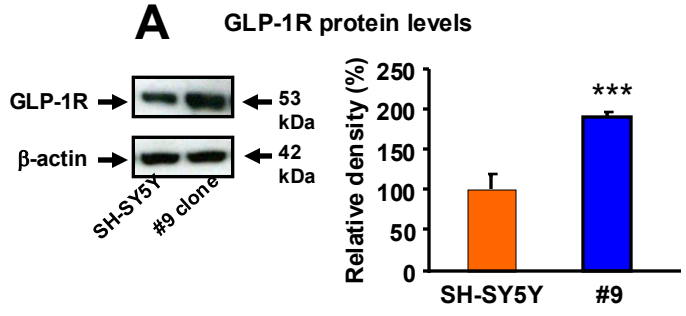


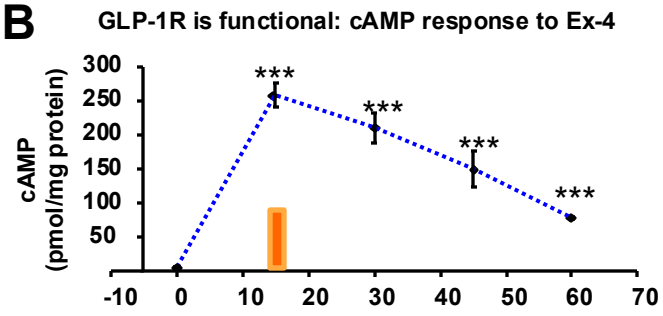
Markers of these pathways can be used in human studies as biomarkers of target engagement by assaying brain derived exosomes from plasma

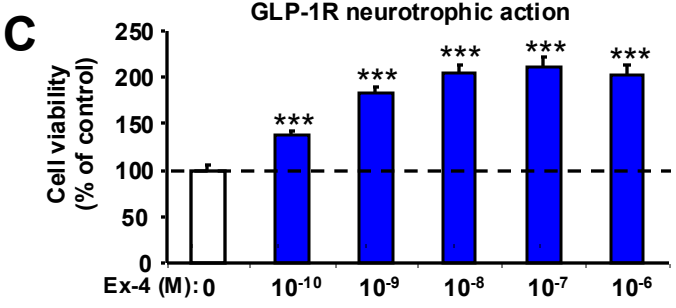
Athauda et al., *JAMA Neurol.* 76:420-9, 2019.

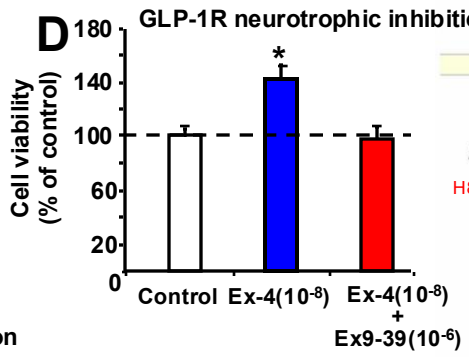
Athauda & Foltynie, *Neuropharmacology*. 136(Pt B): 260-70, 2018
Glotfelty et al., *ACS Pharmacol. Transl. Sci.*, 2: 66-91, 2019
Kopp et al., *Pharmacol Res.* 186: 106550, 2022.

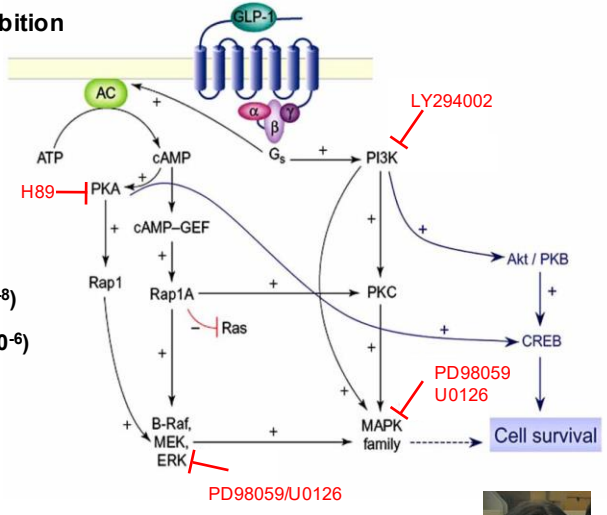
GLP-1R signaling pathways underpinning neurotrophic/protective actions

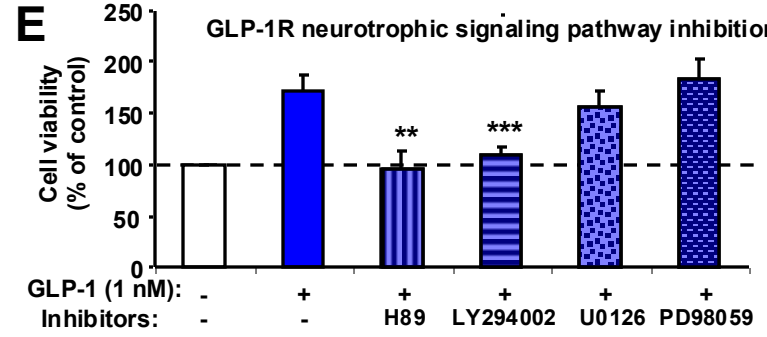










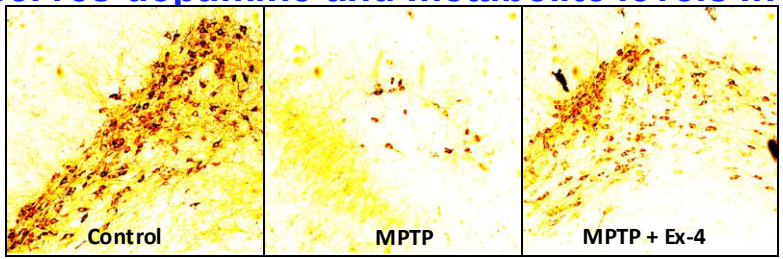


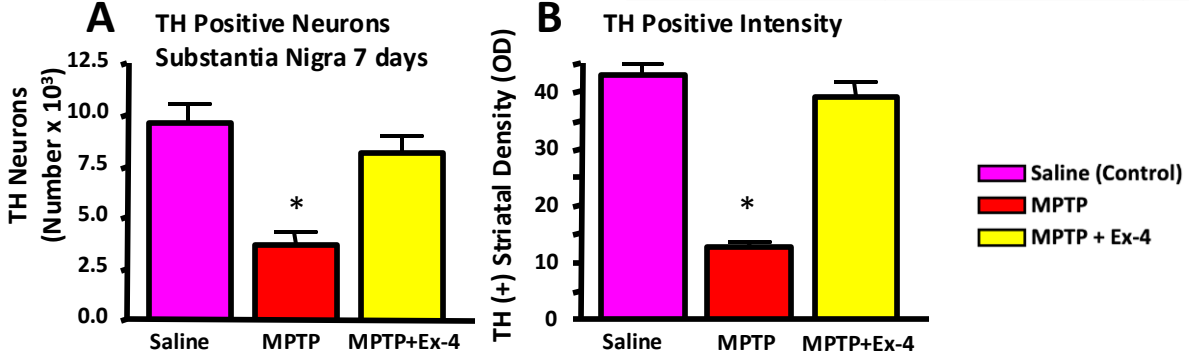
Inhibitors
H89: PKA
LY294002: PI3K
UO126: MAPK/ERK - MEK
PD98059: MEK 1/2

Yazhou Li
(NIA/NIH)

Li et al., *J Neurochem.* 113:1621-31
Li et al., *J Neurochem.* 159: 867-86

GLP-1R stimulation protects tyrosine hydroxylase (TH) positive neurons from MPTP toxicity and preserves dopamine and metabolite levels in striatum





MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

TH-immunoreactive neurons were quantified in the substantia nigra @ 7 days

*Significant difference between MPTP vs. controls and MPTP + Exendin-4 ($p<0.05$, Bonferroni t test). No difference between control & MPTP + Exendin-4

Li et al, *PNAS* 106:1285-90, 2009

(https://www.sfn.org/meetings/past-and-future-annual-meetings/abstract-archive/Abstract-Archive-Details?AbsYear=2005&AbsID=14808)

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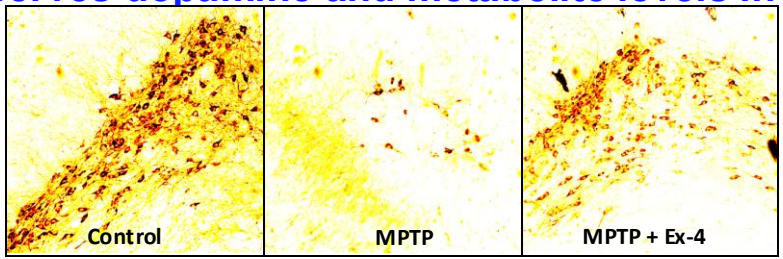
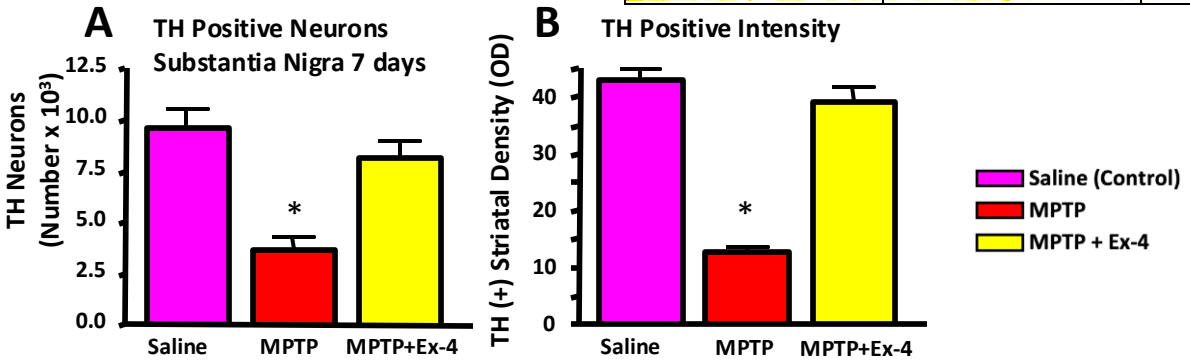




MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

TH-immunoreactive neurons were quantified in the substantia nigra @ 7 days

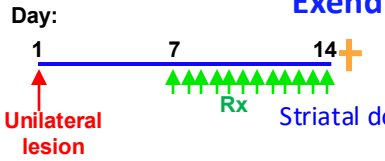
Dopamine (DA), dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were quantified by HPLC

*Significant difference between MPTP vs. controls and MPTP + Exendin-4 ($p<0.05$, Bonferroni t test). No difference between control & MPTP + Exendin-4

Li et al, *PNAS* 106:1285-90, 2009

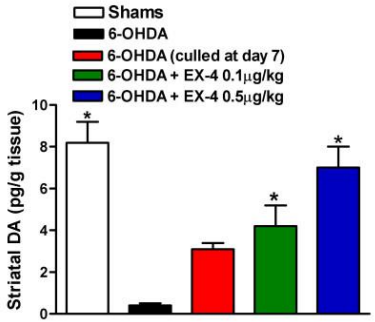
(https://www.sfn.org/meetings/past-and-future-annual-meetings/abstract-archive/Abstract-Archive-Details?AbsYear=2005&AbsID=14808)

Exendin-4 is regenerative in 6-OHDA & LPS-induced toxicity of dopaminergic neurons

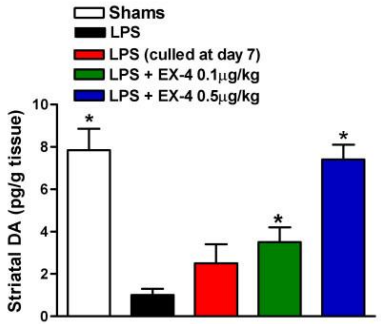


Striatal dopamine (DA) content

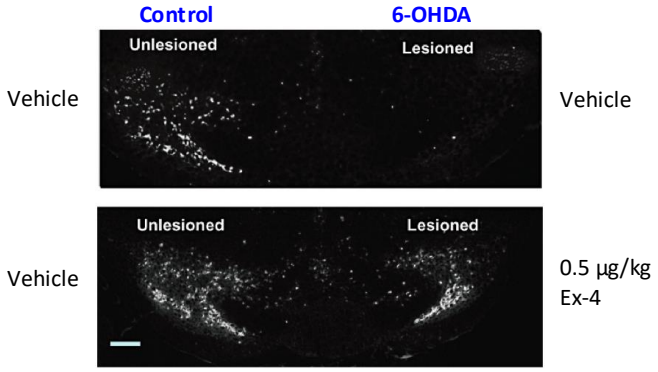
6-OHDA



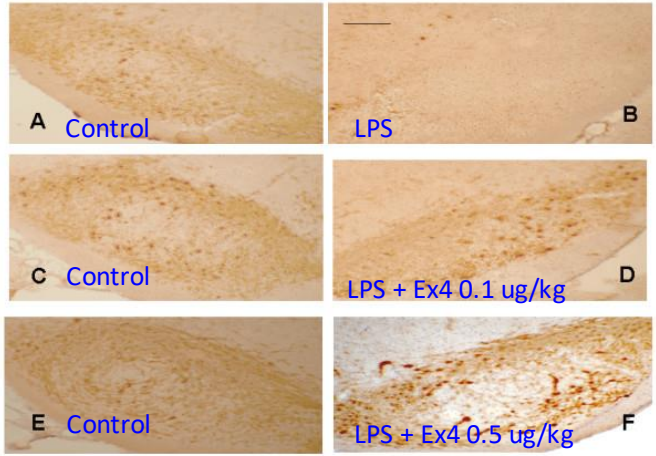
LPS



Ex-4 (0.1 and 0.5 ug/kg) on striatal tissue DA content in 6-OHDA (*upper*) or LPS (*lower*) lesioned rats. Ex-4 was given BID for 7 days, starting 7 days *after* toxin injection. *indicates significant differences from toxin ($p < 0.01$, n=6 per group).

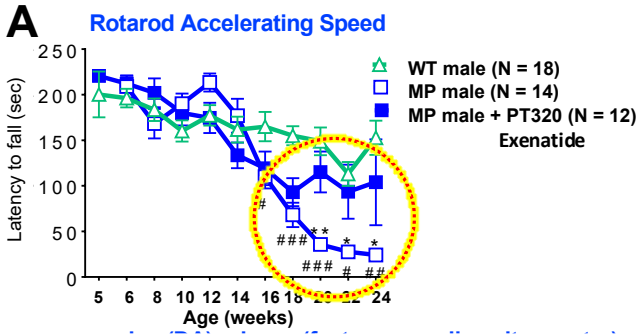


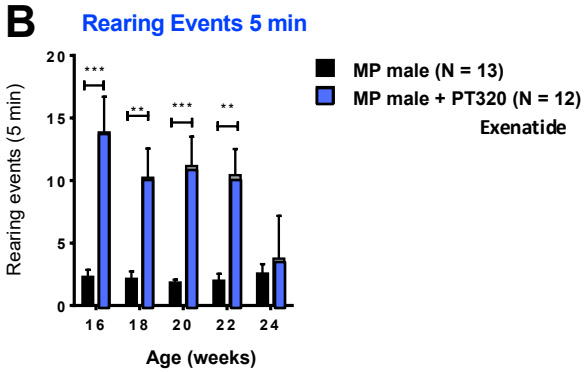
Photomicrographs: rat nigral sections:
6-OHDA/ Fluorogold (*upper*),
LPS immuno-stained for tyrosine hydroxylase (*lower*)

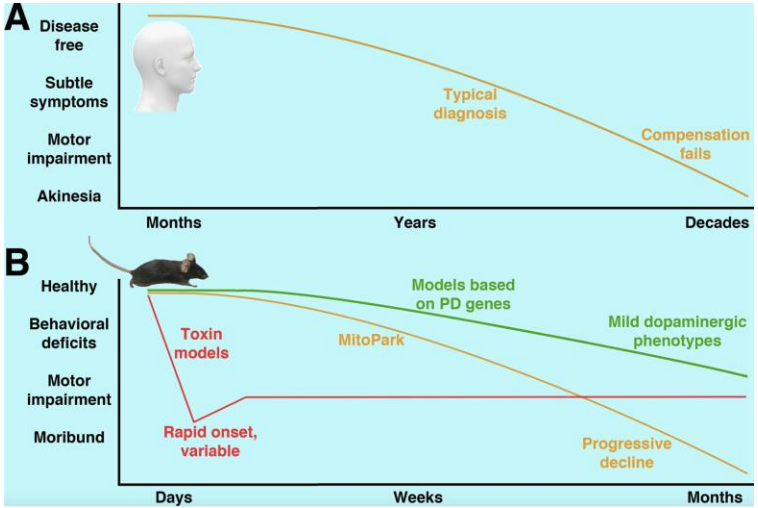


Harkavyi A, Whitton PS. *Br J Pharmacol.* 159 :495-501, 2010

MitoPark (MP) mouse, a progressive PD model involving deleted mitochondrial transcription factor TFAM (respiratory chain function) in midbrain DA neurons: PT320 (Exenatide) delays disease progression across multiple parameters







Beckstead & Howell. *Exp Neurol*. 341: 113707, 2021

Yuan-Hao (Howard) Chen
National Defense Medical Center, Taiwan

Wang et al., *ACS Pharmacol Transl Sci* 4: 858-69, 2021

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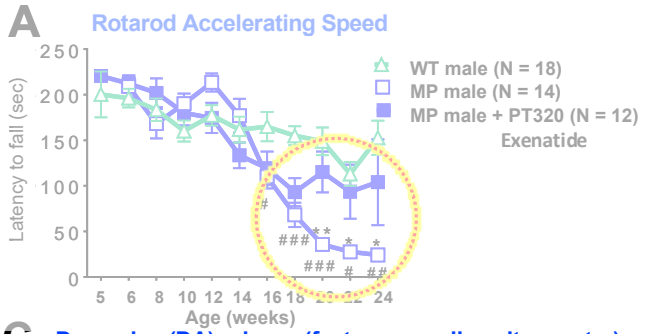

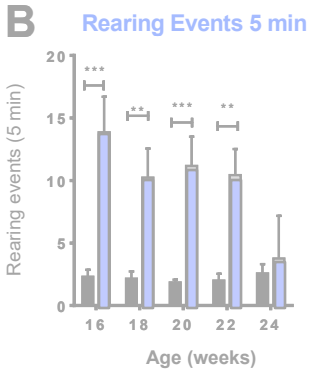

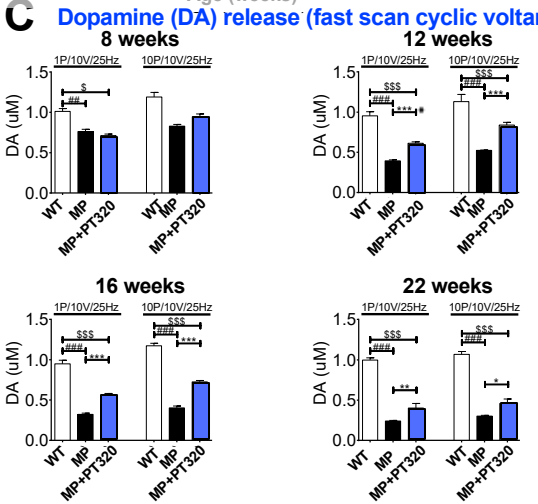

MP male + Vehicle

MP male + PT320
Exenatide

Yuan-Hao (Howard) Chen
National Defense Medical Center, Taiwan

Wang et al., *ACS Pharmacol Transl Sci* 4: 858-69, 2021

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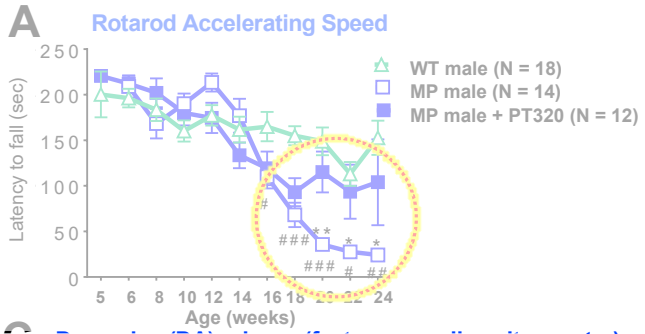
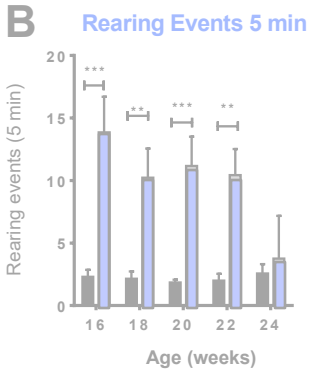
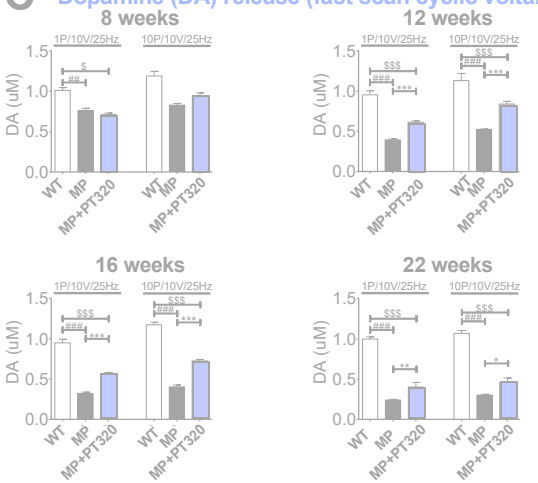
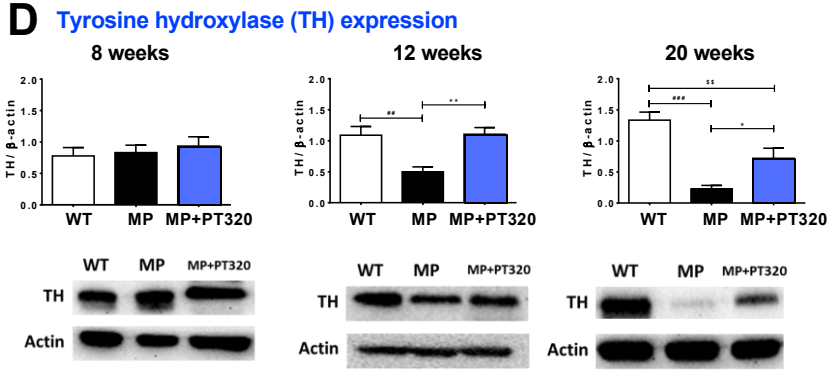






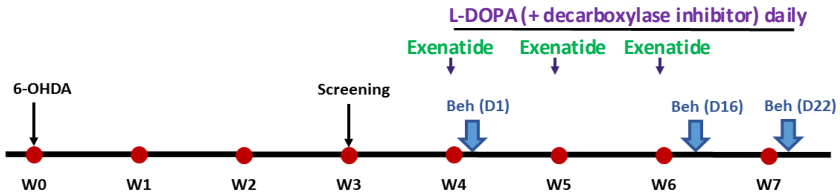


Yuan-Hao (Howard) Chen
National Defense Medical Center, Taiwan

Wang et al., *ACS Pharmacol Transl Sci* 4: 858-69, 2021

Replicated MitoPark mouse PD Exenatide study and attenuated mitochondrial dysfunction (Wang et al., *J Biomed Sci.* 31: 38, 2024)

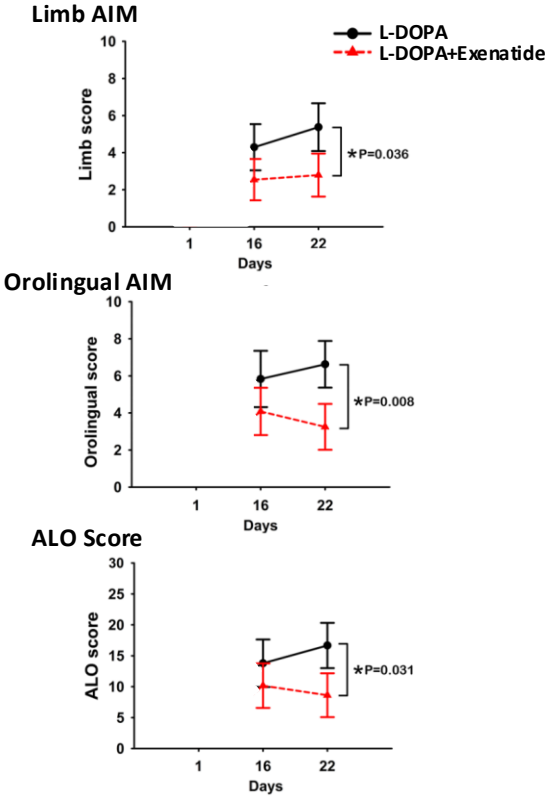
Sustained release Exenatide (Ex-4) mitigates L-DOPA-induced dyskinesia in a rat 6-OHDA model of PD



Synopsis: L-DOPA increased abnormal involuntary movements (AIMs) of limbs and axial as well as the sum of all dyskinesia scores (ALO) over 3 weeks. Exenatide significantly reduced all AIM scores.

Types of AIMs:
(i) **Limb** - Random uncontrollable forelimb movements contralateral to the lesion.
(ii) **Orolingual** - Excess chewing and jaw movements + tongue protrusion
(iii) **Axial** - Dystonic postures or choreiform twisting of neck and upper body towards the contralateral side.

ALO score - sum of all AIMs (axial, limb and orolingual).

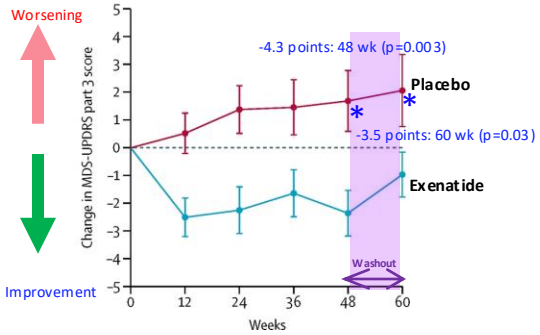


Yu et al., *Front Neurosci.* 14:785, 2020

Replicated mitigation of L-DOPA-induced dyskinesia in MitoPark mouse PD model with Exenatide (Kuo et al., *Int J Mol Sci.* 24: 4687, 2023)

Exenatide once weekly vs. placebo in Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Athauda et al., *Lancet* 390(10103): 1664-75, 2017

A **Major Finding**: significant change in MDS-UPDRS part 3 between groups



MDS-UPDRS part 3: time-dependent change in score of Exenatide vs. placebo groups. Data are means for off-medication state. Error bars are SEM
MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale
Mattis-Dementia Rating scale – no significant effect

Interpretation: Exenatide had positive effects on motor scores in PD, which were sustained beyond the period of exposure.

Whether Exenatide affects underlying disease pathophysiology or simply induces long-lasting symptomatic effects is uncertain.

Further clinical evaluation is warranted

Exenatide concentrations: Serum 543.3 pg/ml, CSF 11.7 pg/ml. (**CSF/serum ratio: 2%**)

Tom Foltynie
UCL, London, UK

Dilan Athauda
UCL, London, UK

Exenatide once weekly vs. placebo in Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Athauda et al., *Lancet* 390(10103): 1664-75, 2017

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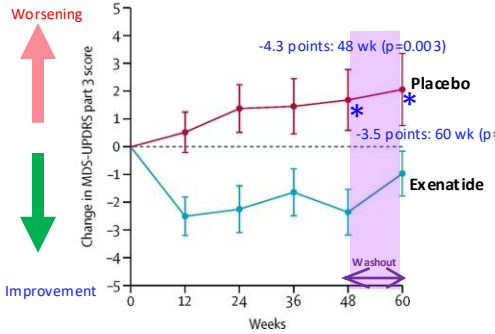
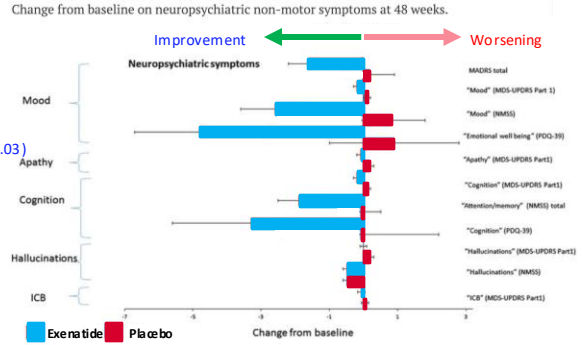


B **Further Finding**: post-hoc analysis suggests improvement in select non motor functions (*J Parkinsons Dis*. 8(2):247-58, 2018).



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MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale
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C Evaluation of neuronal exosomes from plasma samples demonstrated efficacy was associated with changes in the insulin signaling pathway (IRS-1 phosphorylated at tyrosine (Y), and serine (S) residues 616 and 312), with Exenatide-mediated changes were evident in the Akt and m-TOR pathways (Athauda et al., *JAMA Neurol* 76:420-9, 2019).

D 24-Month Exenatide Phase 3 clinical trial in moderate PD (Exenatide PD3; 194 patients, NCT04232969)

Tom Foltynie
UCL, London, UK

Dilan Athauda
UCL, London, UK

Recent PD clinical trials:

Wassilios Meissner et al., (the French Clinical Research Network for PD and Movement Disorders) Phase 2 12-month Lixisenatide study + washout of early PD (<3 years), 78 Lixi, 78 placebo) – *N Engl J Med* 390: 1176-85, 2024

Outcome: significant improvement in MDS-UPDRS part 3 (primary outcome measure) – which remained following 2-month washout period.

Elliot Hogg et al., (Cedar Sinai, LA, CA): Phase 2 52-week Liraglutide study in PD (≥ 2 years duration, 42 liraglutide, 21 placebo) - *Lancet* preprint.

Outcome: required L-DOPA dose higher in Placebo group
No change in MDS-UPDRS part 3 (primary outcome – motor examination)
Significant improvement in (i) non-motor symptom scale (NMSS; primary outcome), (ii) MDS-UPDRS part 2 (motor experience/daily living) (2nd outcome)

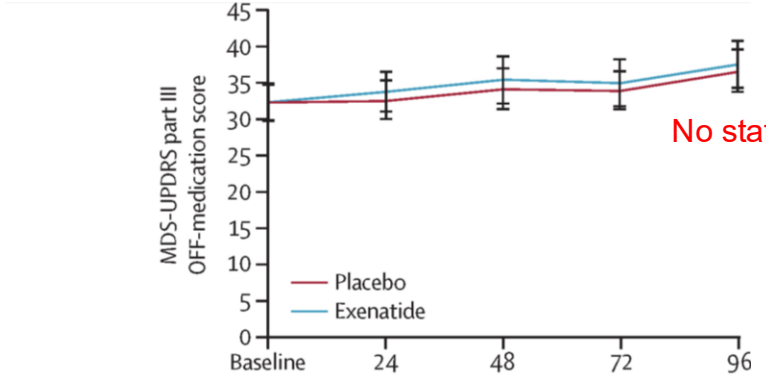
Peptron (S. Korea): Phase 2 48-week Exenatide (PT320) study in early PD (≥ 2 years, 99 patients) – *Dec. 2022 press release*

Outcome: No change in MDS-UPDRS part 3 (primary outcome – motor examination)
Significant improvement in K-PDQ-39 (Quality of life/health status measure)

Clinical studies

24-Month Exenatide Phase 3 multi-center CT in moderate PD (Exenatide PD3; 194 patients, NCT04232969, UCL, London, UK)

Primary measure: change in MDS-UPDRS part 3 between groups (OFF-dopaminergic medication score)



No statistical difference

No change in MDS-UPDRS part III OFF-medication score over 96 weeks

No change in MDS-UPDRS on medication or neuropsychological battery.

Exenatide well tolerated. Mean plasma levels: 1142 pg/mL; CSF: 11.3 pg/mL

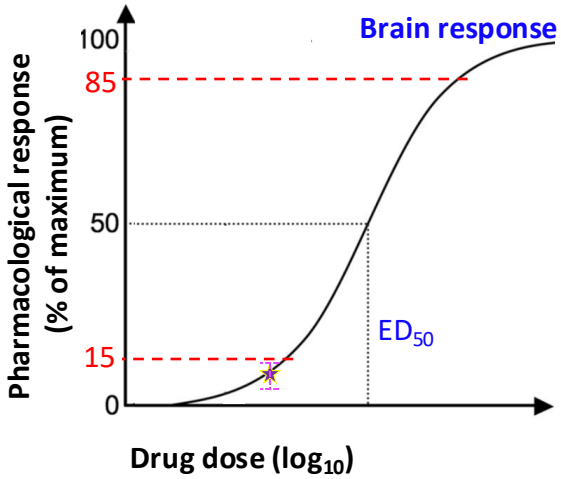
Tom Foltynie
UCL, London, UK

Vijiaratnam et al., *Lancet*. 405(10479): 627-36, 2025.

What's going on?

Classical sigmoidal drug dose-response curve:
Largely linear between 15% - 85% response

Hypothesis:
Likely – we are at the bottom of the sigmoidal dose-response curve ★ for PD human trials



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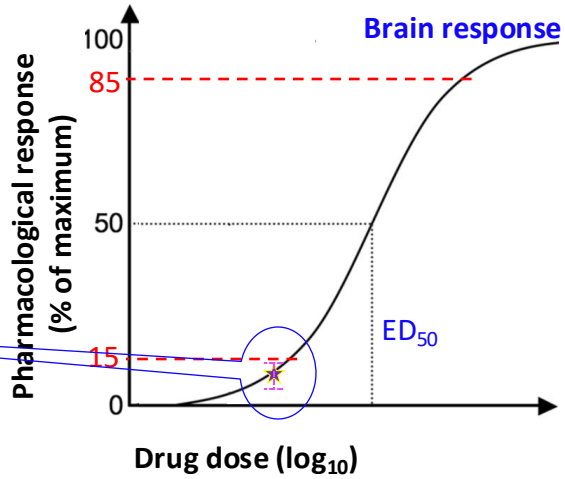

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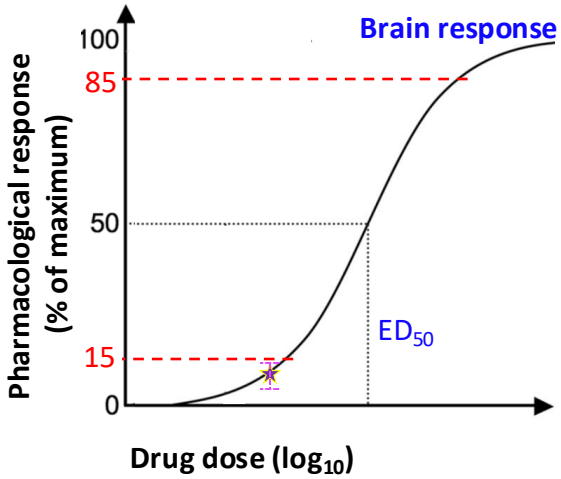
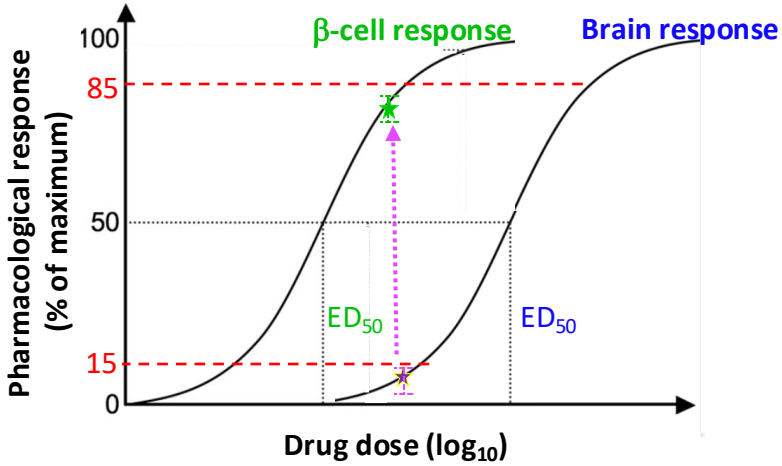
The PD clinical trial dose was selected from T2DM – where it generates actions at the top of the sigmoidal dose-response curve★

We need to:
Either increase drug dose (if tolerated)

Or combine effective drugs (synergy)

Or both



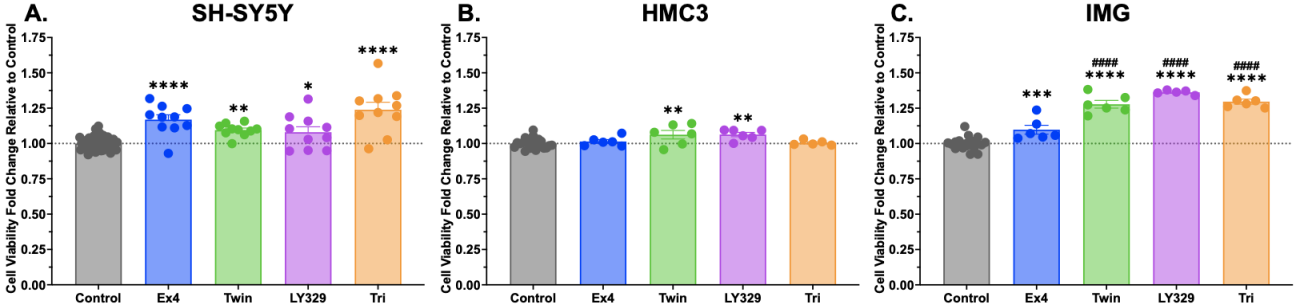


Concentration at GLP-1RA very different between β-cell and brain

Can dual/triple agonists offer more in neurological disorders?

Single: GLP-1
Dual: GLP-1+GIP
Dual: GLP-1+GIP
Triple: GLP-1+ GIP+Gcg

Neurotrophic responses across immortal neuronal cell types are generally greater for dual/triple agonists

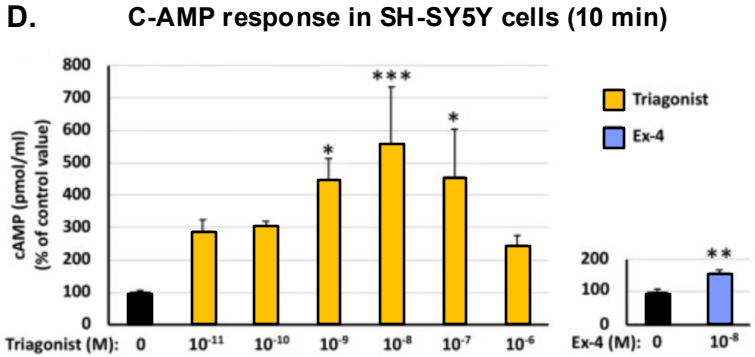


Immortal cell lines
SH-SY5Y: neuronal (human)
HMC3: microglial (human)
IMG: microglial (murine)

Threshold equimolar concentration to achieve neurotrophic action (10 nM for 48 hr)

Vs. Control
* p<0.05
**p<0.01
***p<0.001

Vs. Single GLP-1
# p<0.05
##p<0.01
###p<0.001



Tri-Agonist provides a substantially greater cAMP response than a single GLP-1RA

Kopp et al., *Biomolecules* 14: 872, 2024

Katie Kopp (NIA/NIH)

Can dual/triple agonists offer more in neurological disorders?

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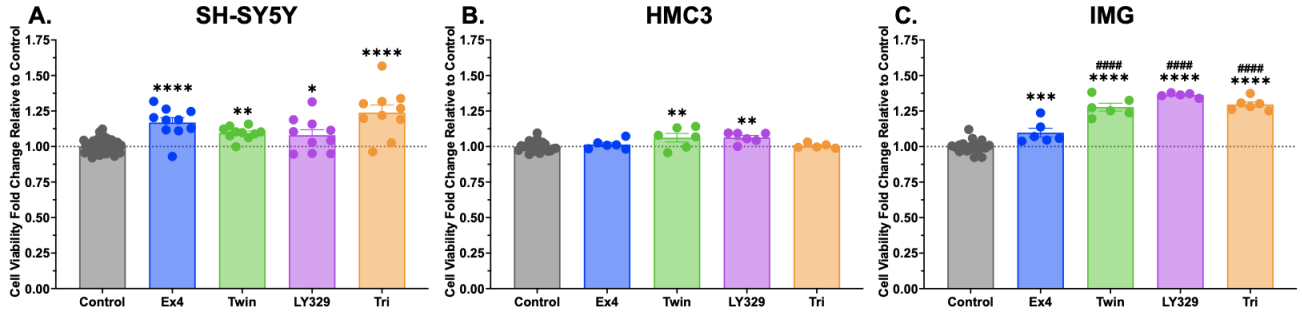

Immortal cell lines
SH-SY5Y: neuronal (human)
HMC3: microglial (human)
IMG: microglial (murine)

SH-SY5Y neuronal cells: each component of a Tri-Agonist provides neurotrophic action

Vs. Control
* p<0.05
**p<0.01
***p<0.001

Vs. Single GLP-1
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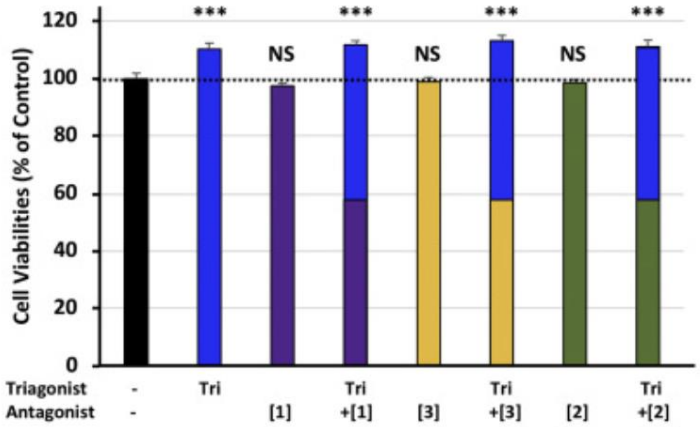
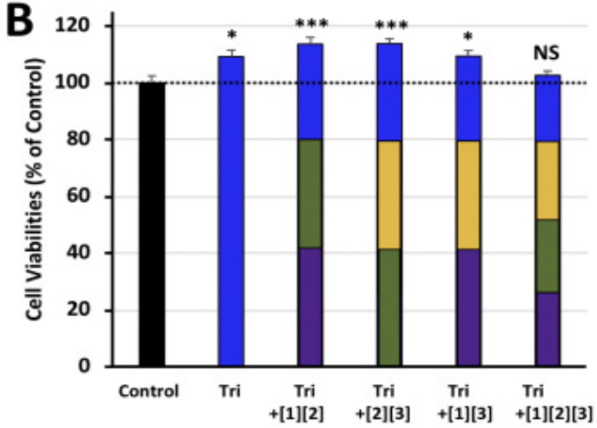




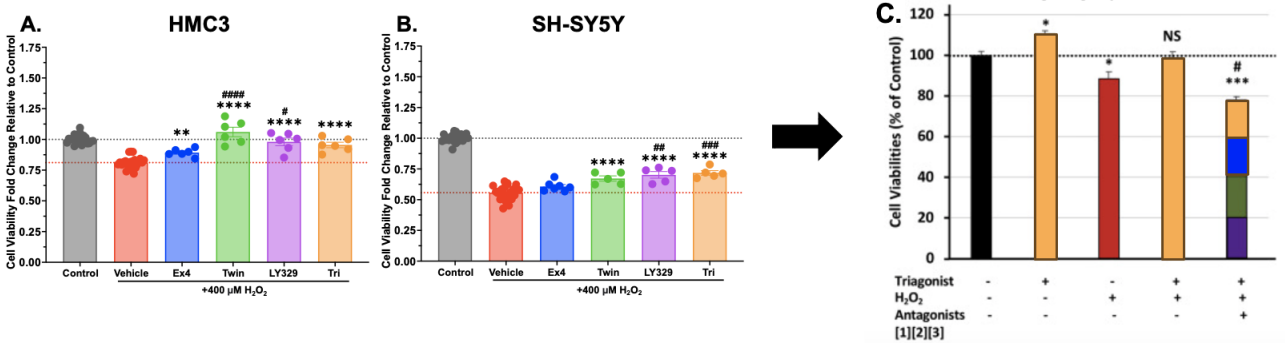
Inhibitors:

[1] GLP-1R: Ex-9-39
[2] GcgR: DesGlucagon
[3] GIPR: GIPRx

Can dual/triple agonists offer more in neurological disorders?

Neuroprotective response across immortal neural cell types is generally greater with dual/Tri Agonists

H_2O_2
Oxidative stress



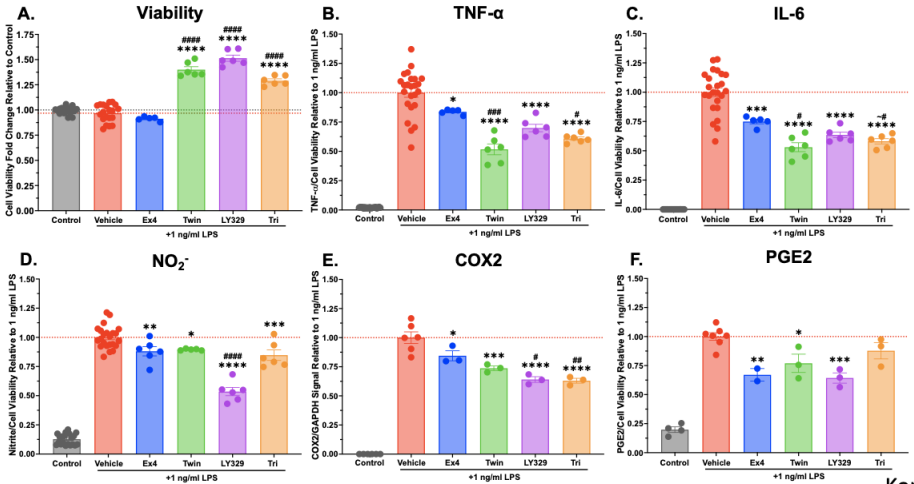
Inhibitors:

[1] GLP-1R: Ex-9-39
[2] GcgR: DesGlucagon
[3] GIPR: GIPRx

- Vehicle
- **Single**: GLP-1
- **Dual**: GLP-1+GIP
- **Dual**: GLP-1+GIP
- **Triple**: GLP-1+GIP+Gcg

Anti-inflammatory response across microglial cells is generally greater with dual/Tri Agonists

LPS
Inflammatory stress



Vs. Vehicle
* p<0.05
**p<0.01
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Vs. Single GLP-1
# p<0.05
##p<0.01
###p<0.001

Katie Kopp
(NIA/NIH)

Kopp et al., *Biomolecules* 14: 872, 2024

Generally – Dual/Tri Agonists have better activity vs. a single GLP-1RA in neurodegenerative animal models – when evaluated at a clinically translatable dose…… but this depends on the brain uptake of the selected agonist.

For example, in a mouse concussive TBI model – **5-fold lower** dual agonist (twincretin) dose was required for similar efficacy vs. single GLP-1RA liraglutide

ELSEVIER
Experimental Neurology
Volume 288, February 2017, Pages 176-186

Research Paper

Novel GLP-1R/GIPR co-agonist "twincretin" is neuroprotective in cell and rodent models of mild traumatic brain injury

Ian A. Tamargo [a], Miaad Bader [b], Yazhou Li [a], Seong-Jin Yu [c], Yun Wang [c], Konrad Talbot [d], Richard D. DiMarchi [e], Chaim G. Pick [b f], Nigel H. Greig [a]

Tamargo et al. *Exp Neurol.* 288: 176-86, 2017

ELSEVIER
Experimental Neurology
Volume 324, February 2020, 113113

Research paper

Neurotrophic and neuroprotective effects of a monomeric GLP-1/GIP/Gcg receptor triagonist in cellular and rodent models of mild traumatic brain injury

Yazhou Li [a], Elliot J. Glotfelty [a b], Inbar Namdar [c], David Tweedie [a], Lars Olson [b], Barry J. Hoffer [d], Richard D. DiMarchi [e], Chagi G. Pick [c], Nigel H. Greig [a]

Li et al. *Exp Neurol.* 324: 113113, 2020

frontiers in Cell and Developmental Biology
ORIGINAL RESEARCH
published: 10 January 2020
doi: 10.3389/fcell.2019.00356

Neuroprotective Effects and Treatment Potential of Incretin Mimetics in a Murine Model of Mild Traumatic Brain Injury

Miaad Bader[1], Yazhou Li[2], David Tweedie[2], Nathan A. Shlobin[3], Adi Bernstein[1], Vardit Rubovitch[1], Luis B. Tovar-y-Romo[2,4], Richard D. DiMarchi[5], Barry J. Hoffer[6], Nigel H. Greig[2] and Chaim G. Pick[1,7,8]*

Bader et al. *Front Cell Dev Biol.* 7:356, 2020

Likewise, Christian Hölscher has found dual agonists superior in murine models of Parkinson's & Alzheimer's disease
(Hölscher C. *Neuropharmacology*. 253:109952, 2024)

Collaborators

Richard DiMarchi
Indiana Univ., USA

Chaim Pick
Tel Aviv Univ., Israel

Summary

- GLP-1-based receptor agonists (RAs) have been evaluated across multiple preclinical neurodegenerative and neuropsychiatric disorders models since 2002 – and, largely, have been found highly promising.

- Dual/Triple RAs are generally more potent than single GLP-1RAs (but brain uptake is important)

- Multiple actions underpin efficacy in preclinical models (neurotrophic, neuroprotective/antiapoptotic, anti-inflammatory, insulin resensitization, neurogenesis, mitochondrial, autophagy, ….. others)
…… do any of these translate into human studies and how can they be measured? (Biomarkers)

- Single GLP-1RA human clinical trials in Parkinson's disease are demonstrating promise…but results are mixed - and Alzheimer's disease clinical trials are ongoing

- Other neurological disorder clinical trials should be considered (…….. TBI, ischemic stroke, peripheral neuropathy…….. substance abuse …… neuropsychiatric disorders?????)

Future

- Dual/Triple RAs ….. DPP-4 inhibitors and combination chemotherapy …. small MW compounds?

Concerns

- Selecting the best agent(s)….**brain entry?** / when to initiate treatment in the disease process?