PRANA BIOTECHNOLOGY Limited

Metal Protein Attenuating Compounds (MPACs)

A Unique Approach to Unmet Medical Need in CNS Indications

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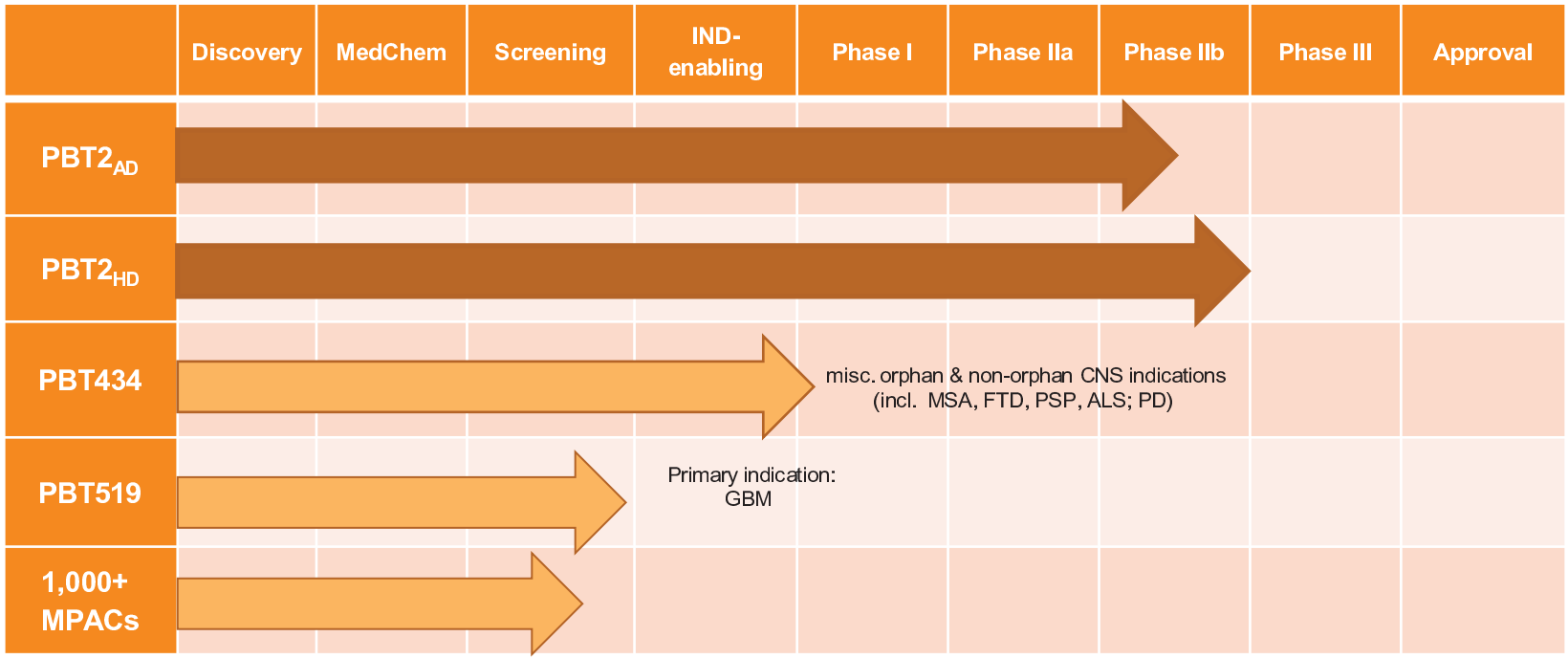
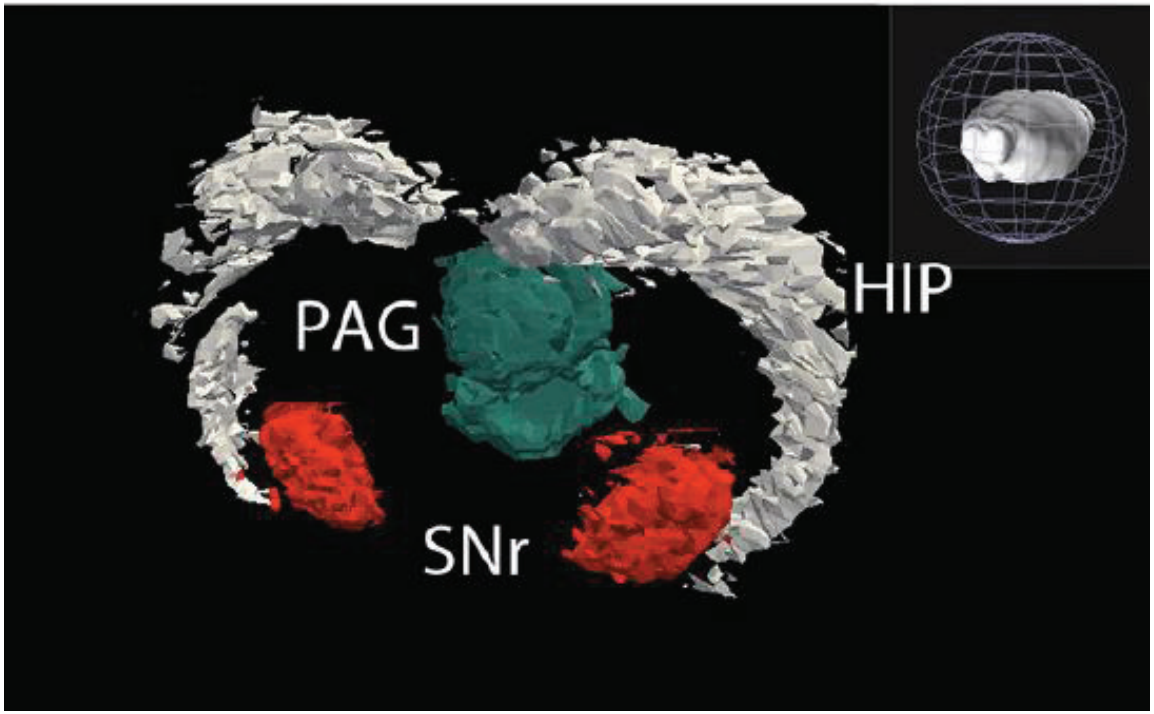
Safe Harbor Statement

This presentation may contain some statements that may be considered "Forward-Looking Statements", within the meaning of the US Securities Laws. Thus, any forward-looking statement relating to financial projections or other statements relating to the Company's plans, objectives, expectations or intentions involve risks and uncertainties that may cause actual results to differ materially. For a discussion of such risks and uncertainties as they relate to us, please refer to our 2015 Form 20-F, filed with the US Securities and Exchange Commission, in particular Item 3, Section D, titled "Risk Factors."

Pipeline of Proprietary MPACs Positions Prana as Speciality Player in CNS (Orphan, non-Orphan)



Metals are Highly Enriched and Tightly Regulated in the Healthy Brain



Metals concentrate in specific brain structures, reflecting metal functions in specialised neuronal activities.

Grey: zinc, Red: iron, Green: copper

Hare, D.J. et al. Anal. Chem. 2012

Metal Dyshomeostasis Provides Link Between AD and HD Pathology

	Alzheimer's	Huntington's
Aggregated protein deposits	✓	✓
Brain atrophy	✓	✓
Altered metal homeostasis	✓	✓
Disease-relevant metal-dependent pathways	✓	✓

PNAS
Proceedings of the National Academy of Sciences of the United States of America

Xiao G *et al*, PNAS (2013); DOI: 10.1073/pnas.1308535110
Huntington disease arises from a combinatory toxicity of polyglutamine and copper binding

Numerous CNS Disorders Are Characterised By Altered Metal Homeostasis

Loss of effective regulation of brain metals causes:

- ***Dysregulation of metal-responsive pathways involved in protein activation, trafficking and clearance***
  - ***Accumulation of misfolded proteins***
- ***Aberrant interaction of metals with misfolded proteins***
  - ***Promotion of aggregation and toxicity***

reviewed in: Zatta et al Trend Pharm Sci 2009

Therapeutic Challenge:

Restore metal homeostasis

+ Counteract protein misfolding

= Prevent pathophysiological consequences of aberrant protein binding

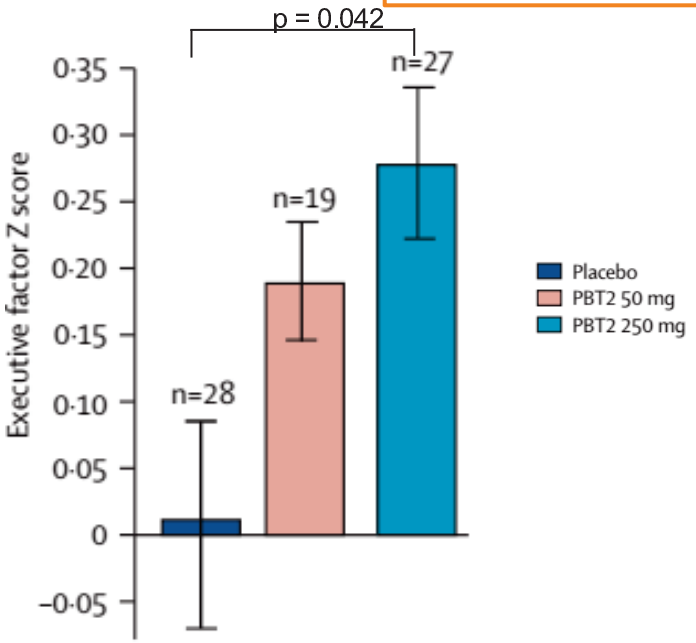
Metal Hypothesis
Clinically Validated in Across Independent Trials, Indications

PBT2 meets the Therapeutic Challenge:

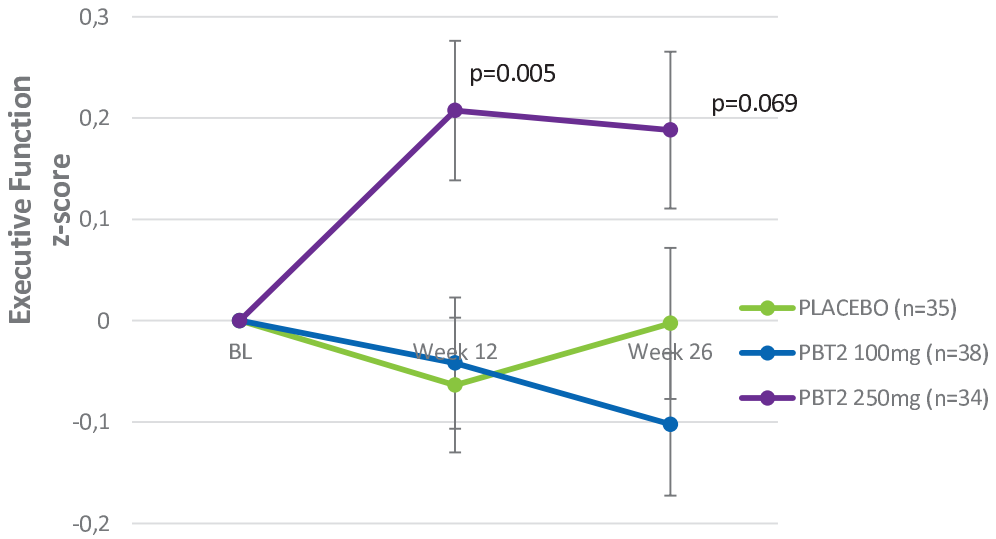
✓ *Restores metal homeostasis*

✓ *Counteracts protein misfolding*

= ***Prevents pathophysiological consequences of aberrant protein binding, even in cognitive readouts!***



Clinical Improvement of Executive Function in PBT2-treated Alzheimer's patients
3-months Phase IIa EURO study
Lannfelt L et al. Lancet Neurol 2008 & Erratum 2009



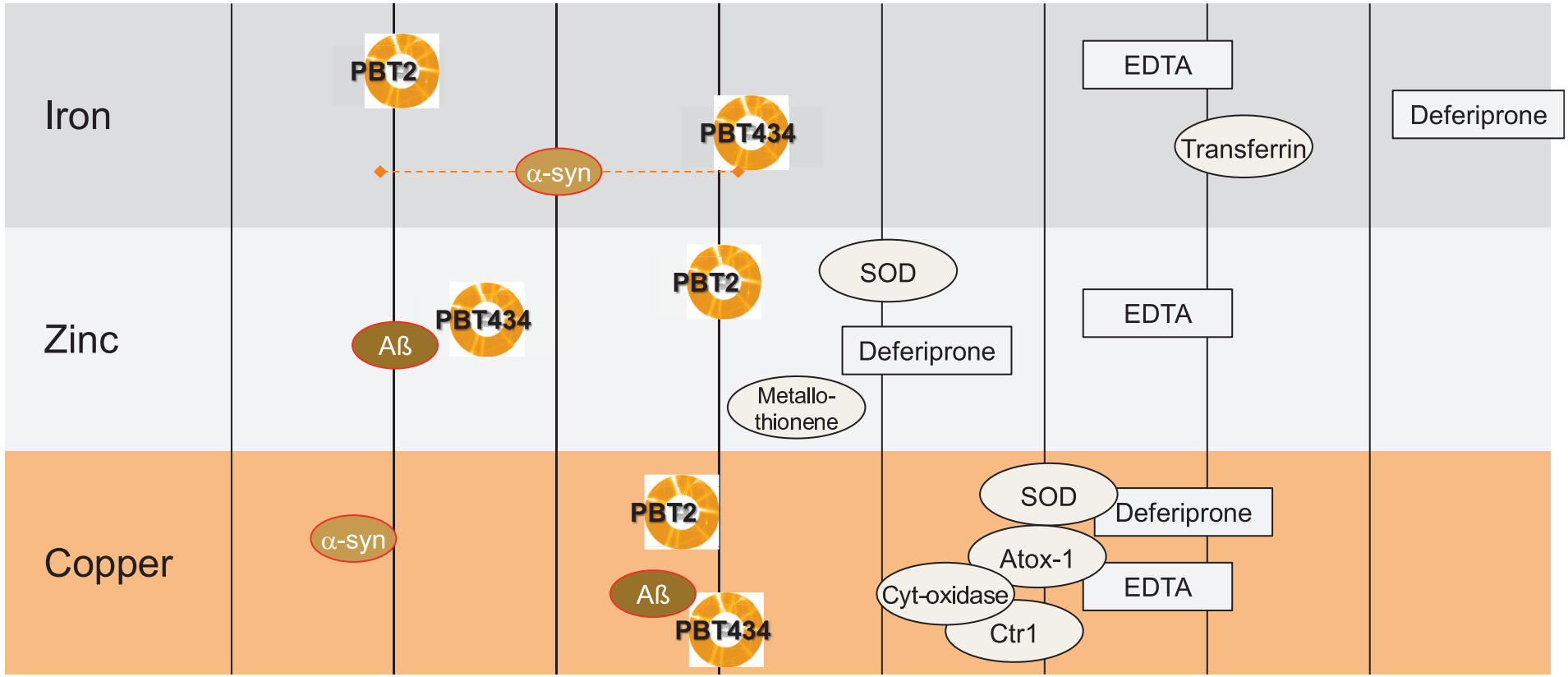
Clinical Improvement of Executive Function in PBT2-treated Huntington's patients
6-months Phase II REACH2HD study

Post-hoc analysis of mild HD patients identified significant benefit of 250mg PBT2 in Exec Function z-score vs base line at 26-week time point, too (p = 0.038)

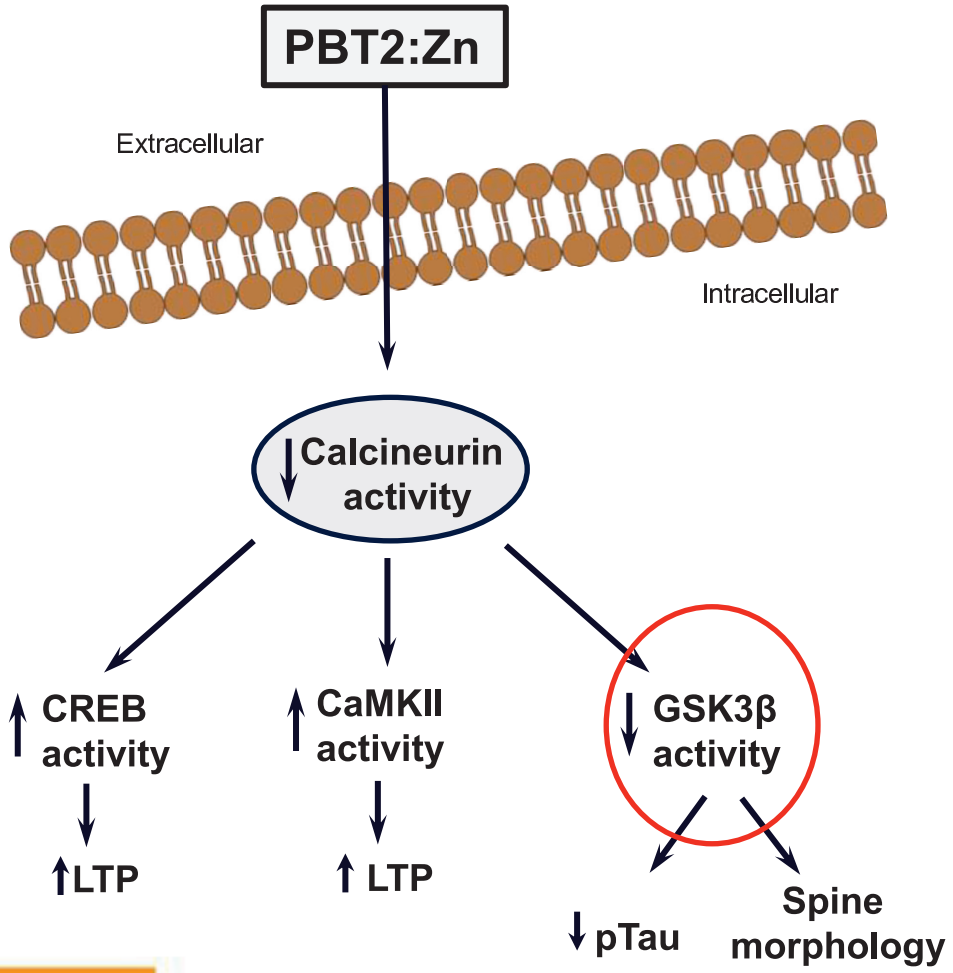
Further MPAC MoA Aspects of Disease-Relevance

PATHWAYS AFFECTED BY MPACS' METAL RE-DISTRIBUTION

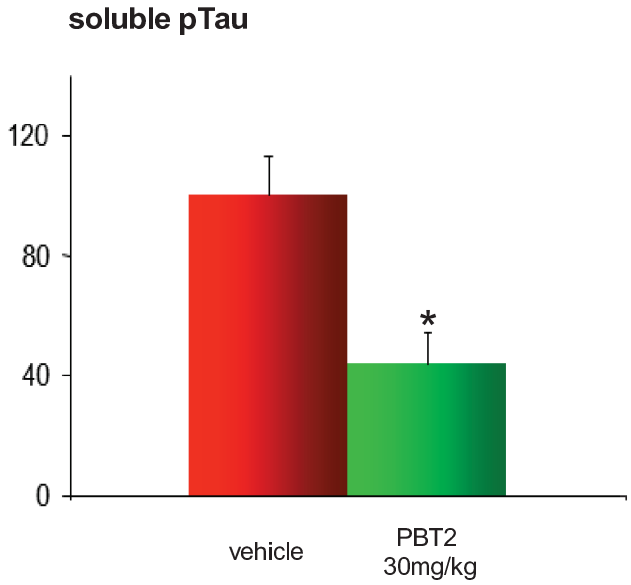
MPACs Compete w/ Toxic Misfolded Proteins, But Not w/ High-Affinity Physiological Ligands

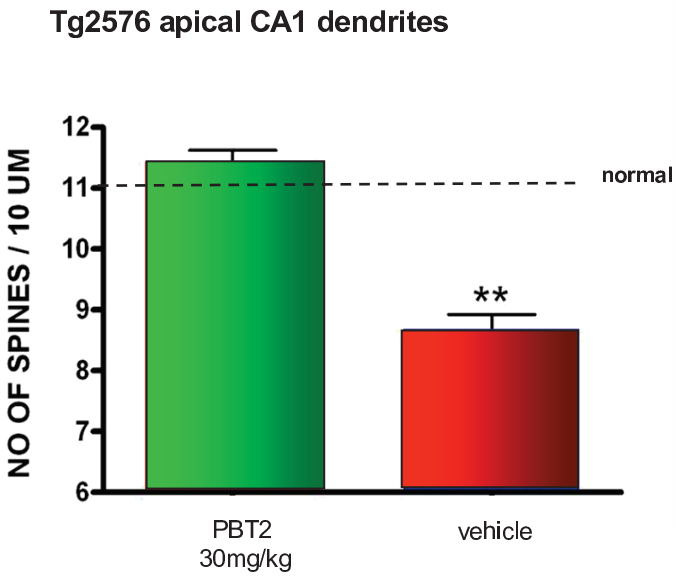


MPAC-Driven Metal Re-Distribution Triggers Disease-Relevant Signalling Pathways



EXAMPLE 1:
PTB2 Activates Pathways of Neuronal Plasticity



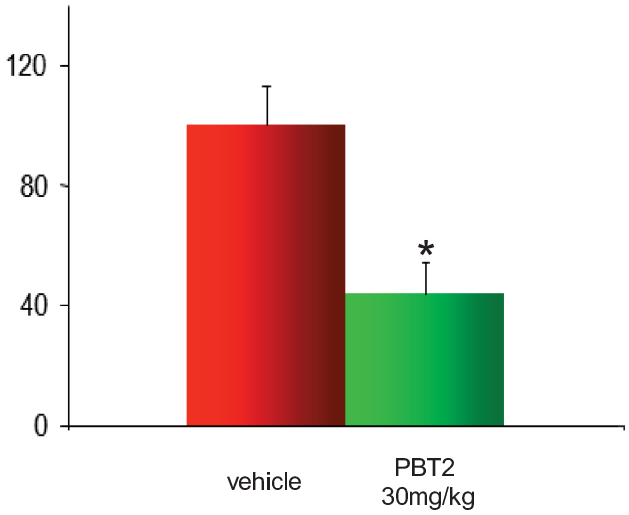


* $p \leq 0.03$
** $p \leq 0.009$

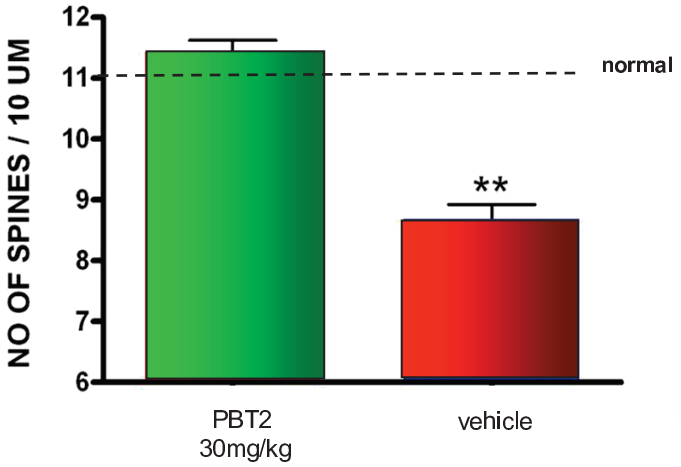
Adlard et al Neuron 2008

EXAMPLE 1:
PTB2 Activates Pathways of Neuronal Plasticity

soluble pTau



Tg2576 apical CA1 dendrites



nature medicine

Huntington's disease is a four-repeat tauopathy with tau nuclear rods

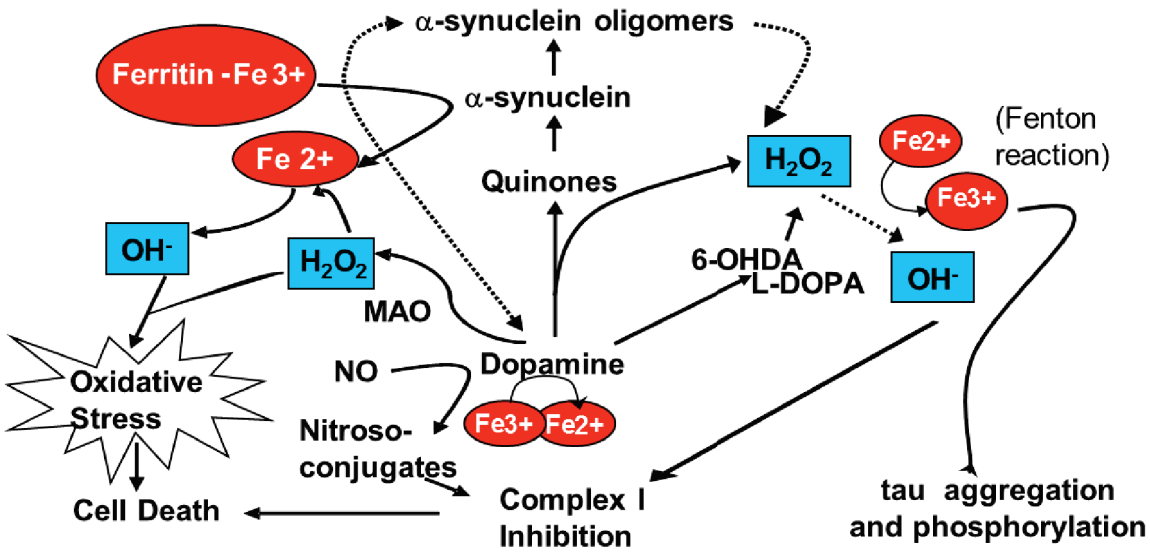
NATURE MEDICINE VOLUME 20 | NUMBER 8 | AUGUST 2014

* $p \leq 0.03$
** $p \leq 0.009$

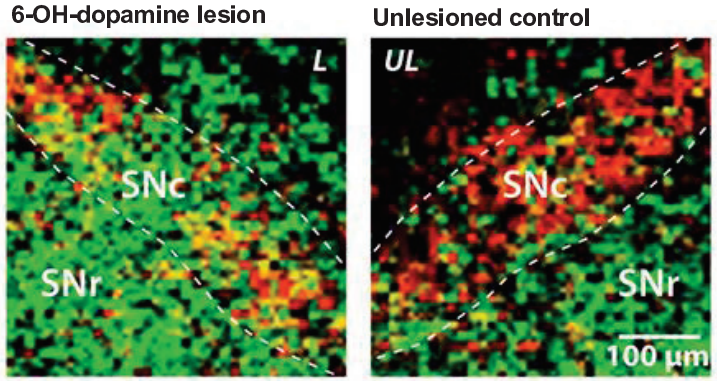
Adlard et al Neuron 2008

MPAC-Driven Metal Re-Distribution Restores Signalling in Parkinsonism

Pathological pathways of Fe dyshomeostasis



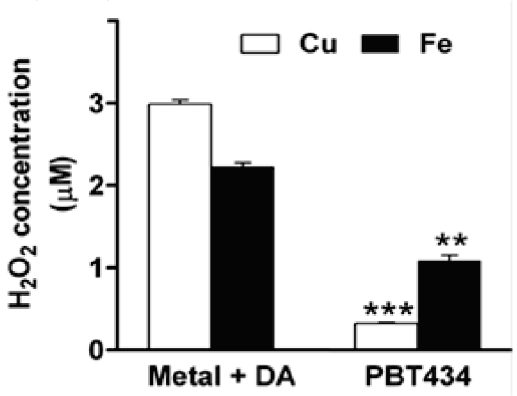
Altered brain iron distribution in PD, MSA, DLB and PSP patients. Here, strong labelling of the Lewy bodies in neurons of the SNpc in a PD patient



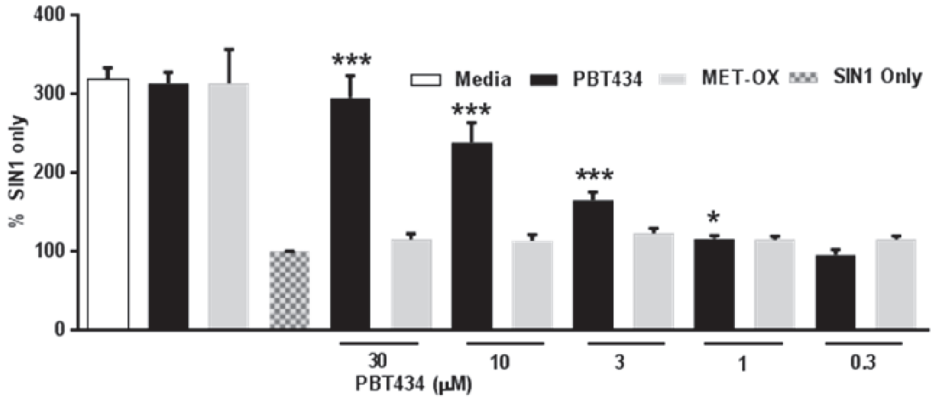
Iron colocalises with dopamine in the substantia nigra in PD *in vivo* model. Mouse brain SN sections; iron-staining (red), tyrosine hydroxilase-staining (yellow)

Doble PA et al Chem Sci 2014

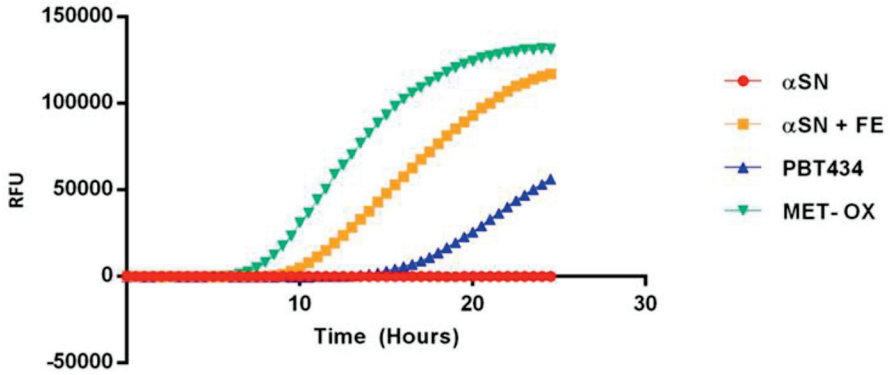
EXAMPLE 2: PBT434 Reduces Neuronal Stressors in Parkinsonism



PBT434 inhibits metal-mediated oxidative stress



PBT434 prevents toxicity by nitrosative stress by a metal-binding mechanism. SIN1: peroxynitrite generator; Met-Ox: non-metal binding PBT434 analogue



PBT434 delays onset and reduces degree of iron-mediated αSyn aggegation. Met-Ox: non-metal binding PBT434 analogue

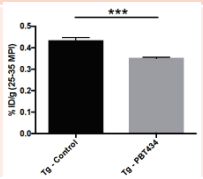
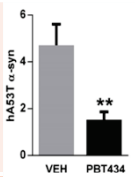
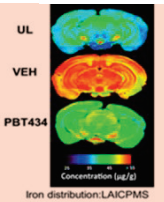
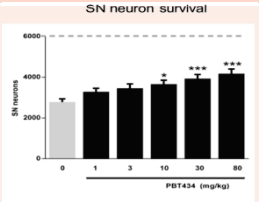
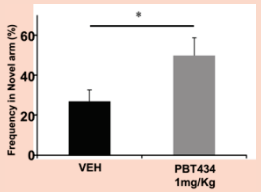
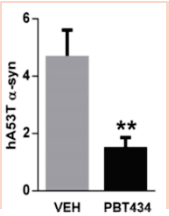
Market Approval and Market Access

STRATEGIC & TACTICAL ASPECTS

PBT2 Has a Clear Value-Generating Edge within the HD Environment

Company Name	Product Names	Description	Partners	Milestones	Effect
Valeant	Xenazine, tetrabenazine	Selective inhibitor of vesicular monoamine transporter (VMAT2)	Chiesi; HLu; Temmler	Marketed. Phase IV ongoing	Symptomatic Chorea
Auspex	SD-809 (Austedo)	Inhibitor of vesicular monoamine transporter 2 (VMAT2; SLC18A2)	Teva	Pre-registration	Symptomatic Chorea
Raptor	Procysbi, RP103	Cysteamine bitartrate delayed-release Alleged copper-chelating properties & BDNF		Phase II/III Formally negative (trend)	Disease mod UHDRS-TMS
Prana	PBT2	Metal protein-attenuating cmpd (MPAC)		Phase II/III	Disease mod **cognition**, function CGI
Active Biotech	Laquinimod	Oral quinoline-3-carboxamide immunomodulator Neuroprotective & antiinflammatrory	Teva	Phase II	Disease mod UHDRS-TMS, **cognition**, function, caudate volume
Vaccinex	VX-15 (primary: cancer)	Humanized Ab against semaphorin	Teva	Phase II (initiated in July 2015)	Disease mod ?? Motor symptoms
Isis	ISIS-HTTRx	2nd-generation antisense oligonucleotide targeting Huntingtin	Roche CHDI	Phase I (initiated in July 2015)	Disease mod. Motor symptoms
Neurosearch	Huntexil, pridopidine	Dopamine stabilizer	Teva	Phase II (or II/III?)	Symptomatic UHDRS-TMS
Omeros	OMS824	PDE10 inhibitor		Phase II, suspended Oct 2014 (pre-clinical issues)	Symptomatic UHDRS-TMS, **cognition**
Ipsen	BN82341	Multi-target hybrid molecule		Phase II	Symptomatic
Pfizer	PF-02545920	PDE10A inhibitor		Phase II	Symptomatic UHDRS-TMS Chorea, CGI

PBT434 Has Potential in an Exceptionally Broad Array of CNS Orphan Disorders

	tau	α-Syn
Aggregation disorders caused by respective protein/pathway	PSP, FTD, CBD, CTE	MSA, $PD_{non\text{-}orphan}$
Reduction of protein aggregation, deposition *in vivo*	✓  PET brain rTg4510 mice	✓  SNpc, TgA53T mice
Reduction, prevention of elevated iron levels *in vivo*		✓  SNpc, Acutely lesioned MPTP model
Preservation of neuronal viability, prevention of neuronal loss *in vivo*		✓  SNpc, Acutely lesioned MPTP model
Beneficial effect on cognition, motor function *in vivo*	✓  Y-Maze rTg4510 mice	✓  Hind Limb Clasping TgA53T mice

First-To-Market, First-in-Class Opportunities Across the Pipeline of Prana MPACs

Target Product Profile aims at closing "therapeutic gaps" …

- ✓ by addressing unmet medical need in orphan (HD) and non-orphan (PD; AD) indications:
  - ✓ PD, atypical parkinsonian: Motor and/or cognitive benefits
  - ✓ HD, AD: Cognitive benefit, esp. "Executive Function"
- ✓ by tapping into completely unchartered orphan disorders of protein misfolding & aggregation: MSA, PSP, FTD, CTE, CBD etc.
- ✓ by addressing brain disorders related to metal dyshomeostasis, e.g. ALS, GMB