

Prana presents unique drug platform at World Orphan Drug Congress

MELBOURNE, 22 April 2016: Prana Biotechnology Ltd (ASX PBT: NASDAQ PRAN) is attending the World Orphan Drug Congress, 2016, in Washington D.C., where it has delivered a presentation outlining its unique approach to treating age-related neurodegenerative disorders.

The congress brings together hundreds of the world's leading researchers and pharmaceutical companies to share experiences and discuss how to expedite access to orphan drugs for patients with rare diseases.

Prana Acting Vice President of Business Development, Dr Birgit Anderegg, presented to congress delegates Prana's approach to treating various neurological indications using its platform of Metal-Protein Attenuating Compounds.

"We're aiming to close therapeutic gaps by addressing unmet medical needs in orphan indications such as Huntington's disease and various atypical Parkinsonian movement disorders," Dr Anderegg said.

Prana's compounds target the metal induced build-up of toxic aggregated forms of proteins linked to neurodegenerative disorders, including alpha-synuclein, A-beta and tau.

Prana's PBT2 compound has received orphan drug designation from the European Commission and US Food and Drug Administration for Huntington's disease while its PBT434 compound has potential to treat a range of orphan disorders such as progressive supranuclear palsy, frontotemporal dementia and chronic traumatic encephalopathy.

PBT2 is currently on Partial Clinical Hold by the US FDA and the company continues to work on its substantive submission to reinstate clinical development in the United States. The company is continuing to explore opportunities outside of the US.

The presentation is attached.

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About Prana Biotechnology Limited

Prana Biotechnology was established to commercialise research into Alzheimer's disease and other major age-related neurodegenerative disorders. The Company was incorporated in 1997 and listed on the Australian Stock Exchange in March 2000 and listed on NASDAQ in September 2002. Researchers at prominent international institutions including The University of Melbourne, The Mental Health Research Institute (Melbourne) and Massachusetts General Hospital, a teaching hospital of Harvard Medical School, contributed to the discovery of Prana's technology.

For further information please visit the Company's web site at www.pranabio.com.

Forward Looking Statements

This press release contains "forward-looking statements" within the meaning of section 27A of the Securities Act of 1933 and section 21E of the Securities Exchange Act of 1934. The Company has tried to identify such forward-looking statements by use of such words as "expects," "intends," "hopes," "anticipates," "believes," "could," "may," "evidences" and "estimates," and other similar expressions, but these words are not the exclusive means of identifying such statements. Such statements include, but are not limited to any statements relating to the Company's drug development program, including, but not limited to the initiation, progress and outcomes of clinical trials of the Company's drug development program, including, but not limited to, PBT2, and any other statements that are not historical facts. Such statements involve risks and uncertainties, including, but not limited to, those risks and uncertainties relating to the difficulties or delays in financing, development, testing, regulatory approval, production and marketing of the Company's drug components, including, but not limited to, PBT2, the ability of the Company to procure additional future sources of financing, unexpected adverse side effects or inadequate therapeutic efficacy of the Company's drug compounds, including, but not limited to, PBT2, that could slow or prevent products coming to market, the uncertainty of patent protection for the Company's intellectual property or trade secrets, including, but not limited to, the intellectual property relating to PBT2, and other risks detailed from time to time in the filings the Company makes with Securities and Exchange Commission including its annual reports on Form 20-F and its reports on Form 6-K. Such statements are based on management's current expectations, but actual results may differ materially due to various factors including those risks and uncertainties mentioned or referred to in this press release. Accordingly, you should not rely on those forward-looking statements as a prediction of actual future results.



Metal Protein Attenuating Compounds (MPACs)

A Unique Approach to
Unmet Medical Need in CNS Indications

www.pranabio.com

ASX: PBT Nasdaq: PRAN

Birgit Andereg, Ph.D.
acting VP Business Development

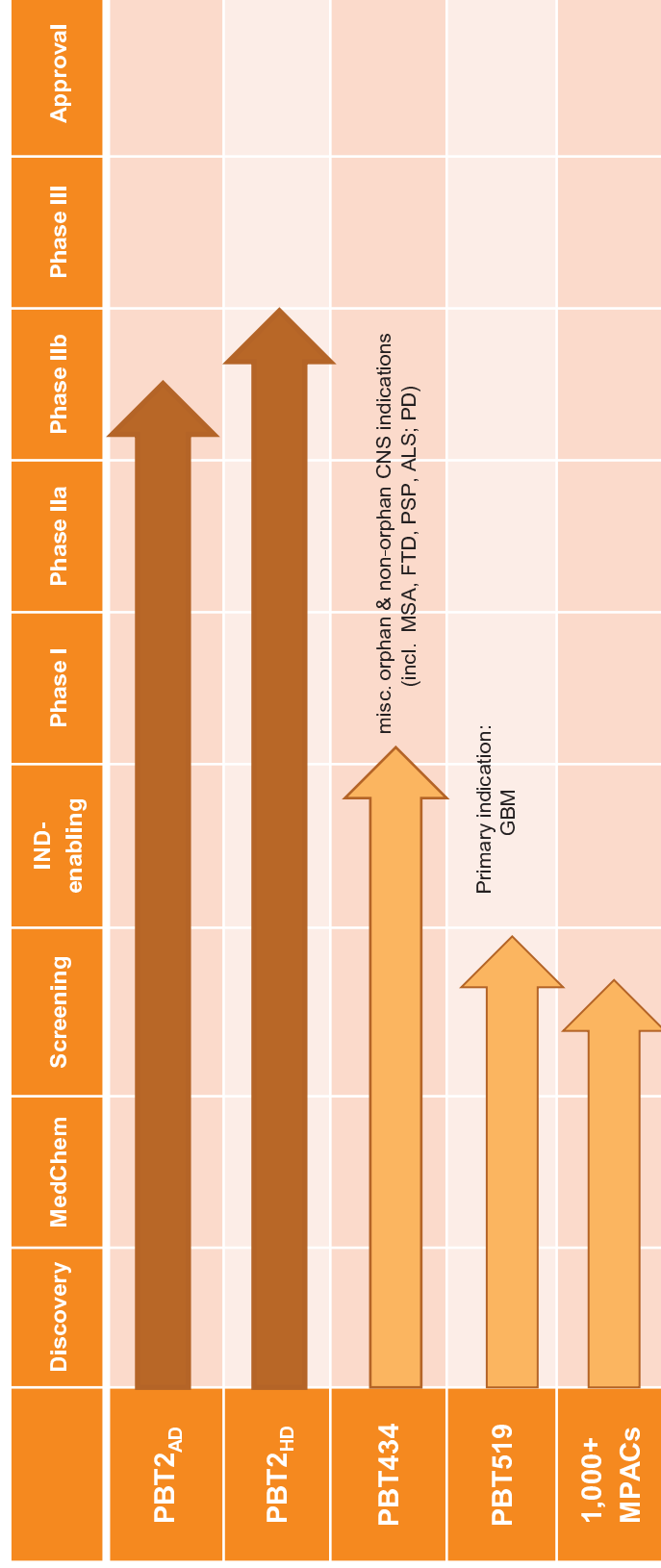


Safe Harbor Statement



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)



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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

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

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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

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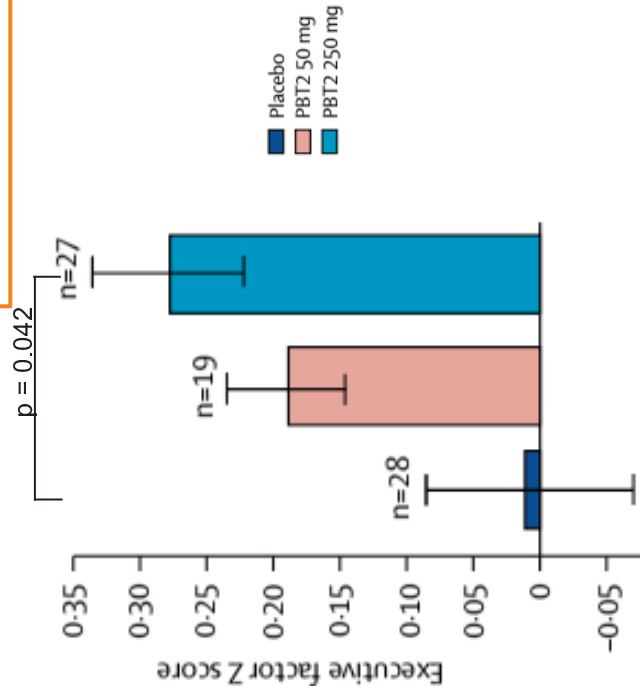
Metal Hypothesis

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!

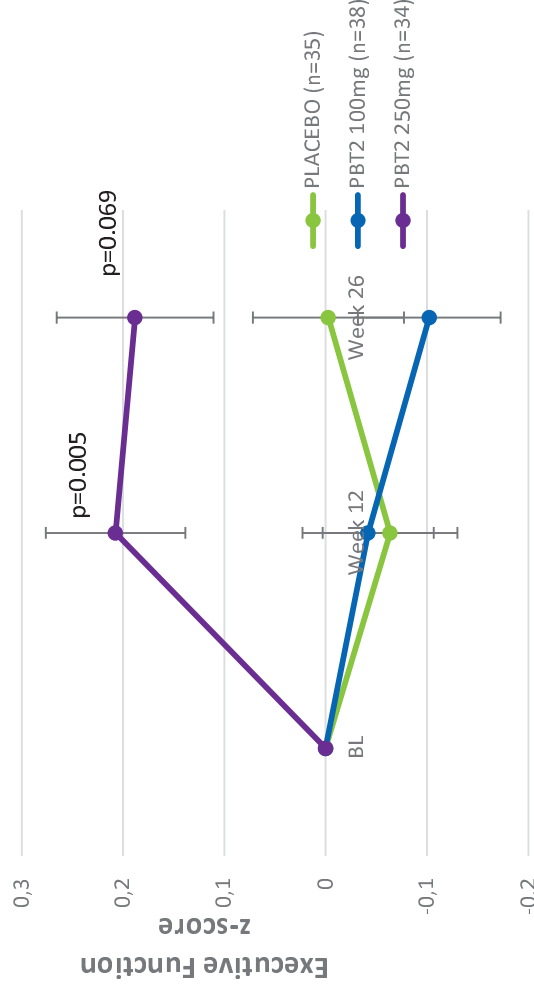


Clinical Improvement of Executive Function in

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)

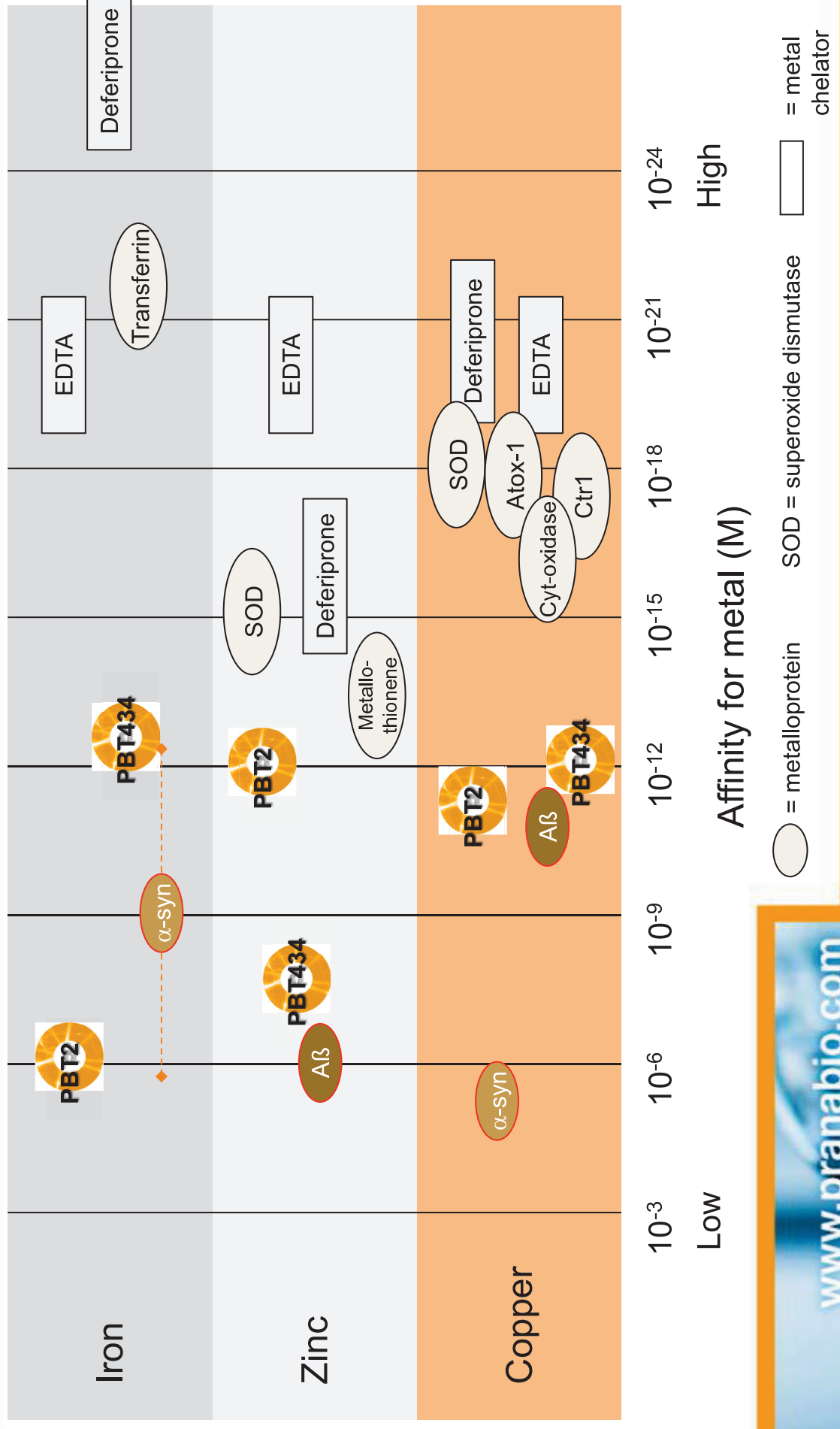
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Further MPAC MoA Aspects of Disease-Relevance

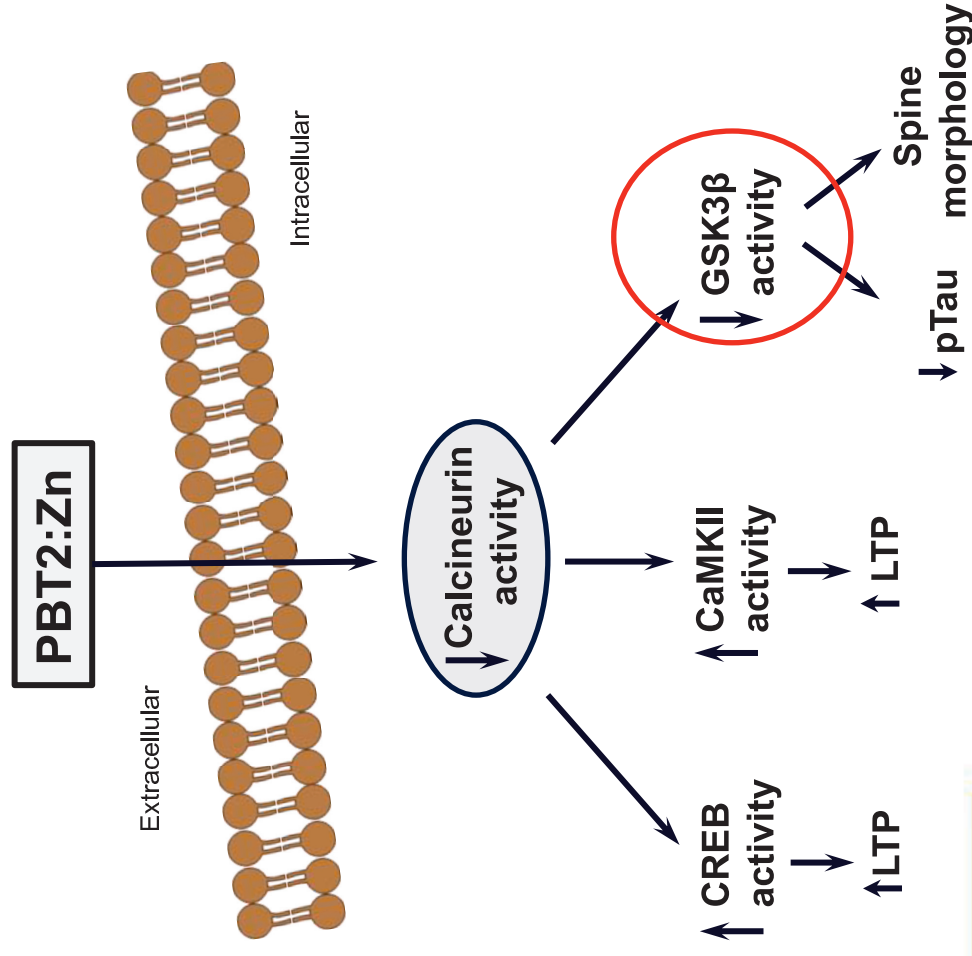
PATHWAYS AFFECTED BY MPACS' METAL RE-DISTRIBUTION

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

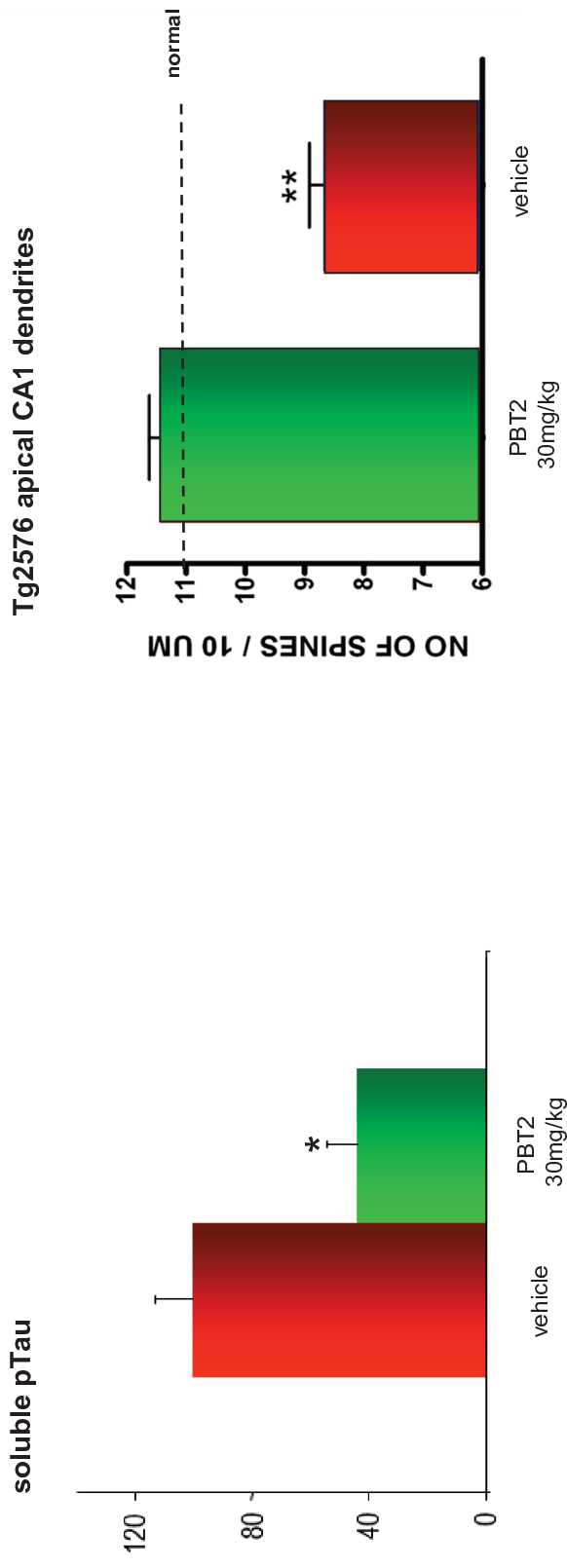


MPAC-Driven Metal Re-Distribution Triggers Disease-Relevant Signalling Pathways



EXAMPLE 1:

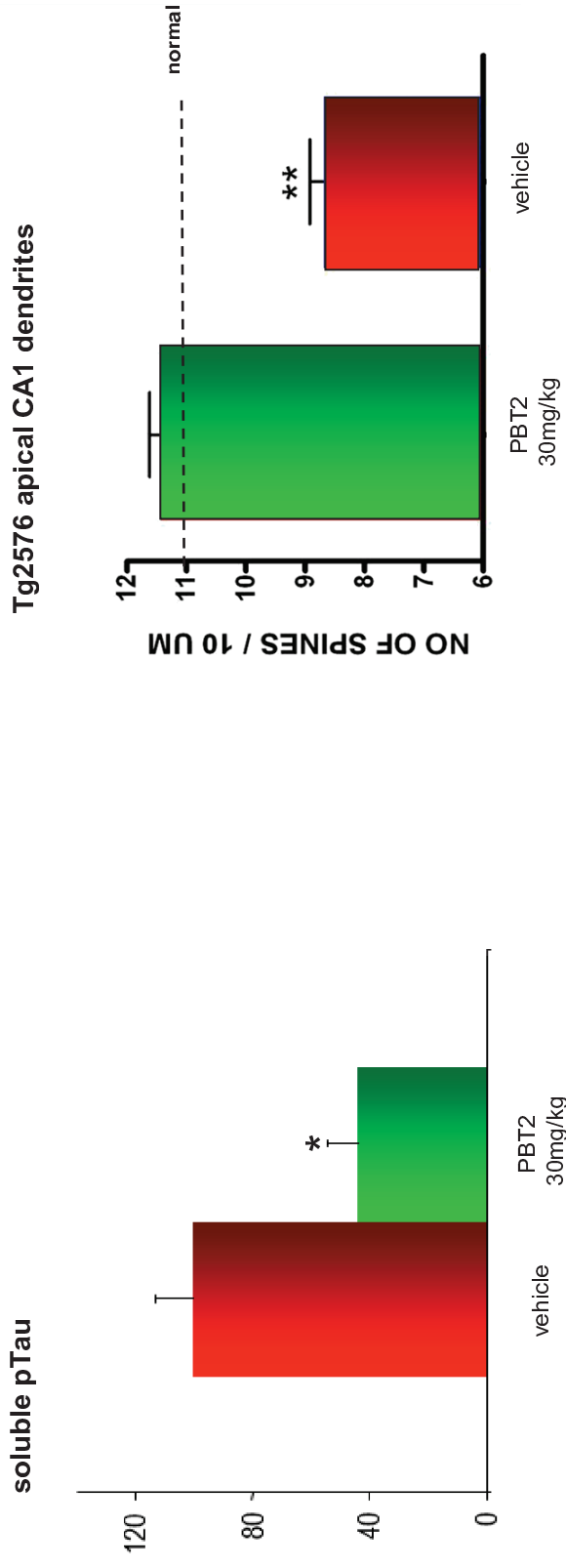
PTB2 Activates Pathways of Neuronal Plasticity



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

EXAMPLE 1:

PTB2 Activates Pathways of Neuronal Plasticity



**nature
medicine**

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

NATURE MEDICINE VOLUME 20 | NUMBER 8 | AUGUST 2014

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

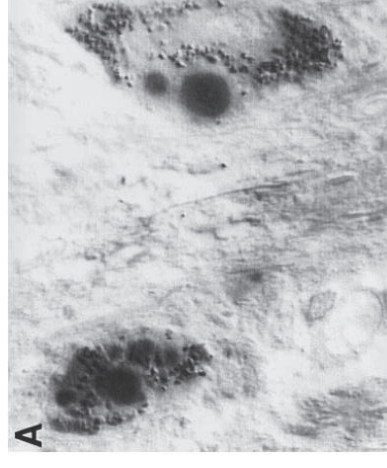
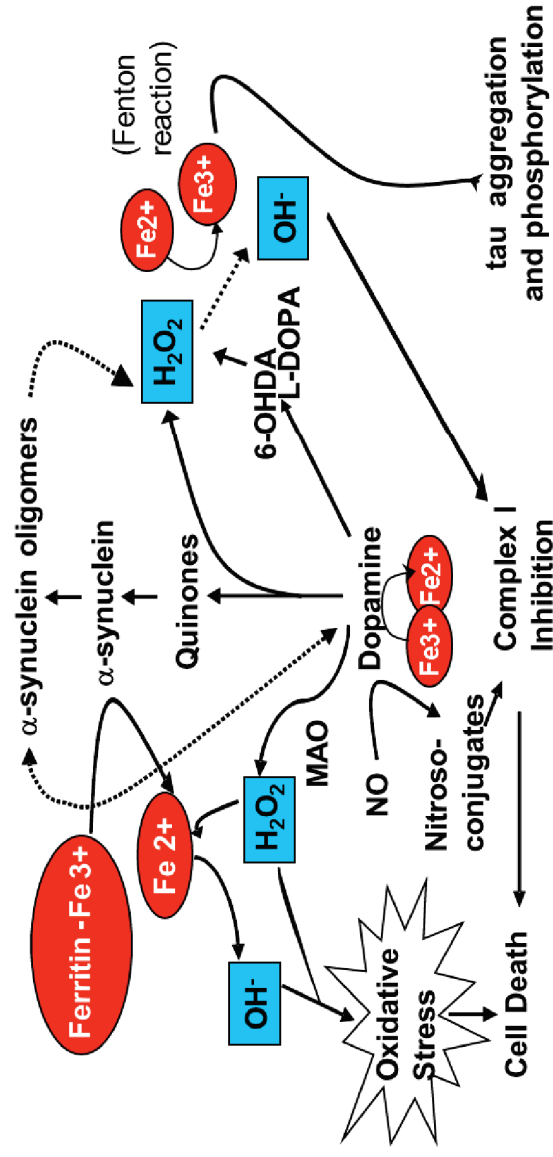
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Adlard et al Neuron 2008

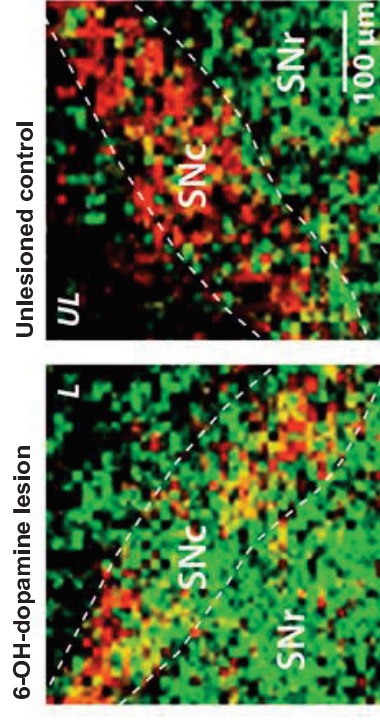
MPAC-Driven Metal Re-Distribution Restores Signalling in Parkinsonism



Pathological pathways of Fe dyshomeostasis



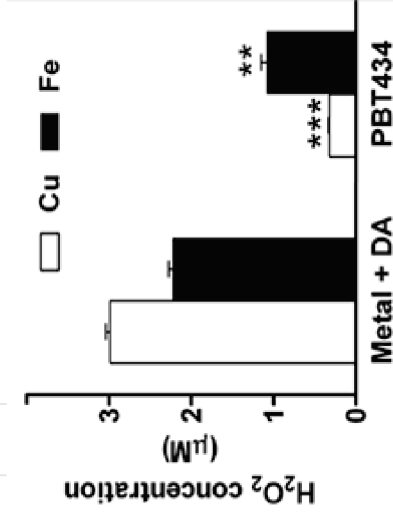
Altered brain iron distribution in PD, MSA, DLB and PSP patients. Here, strong labelling of the Lewy bodies in neurons of the SNpc in a PD patient



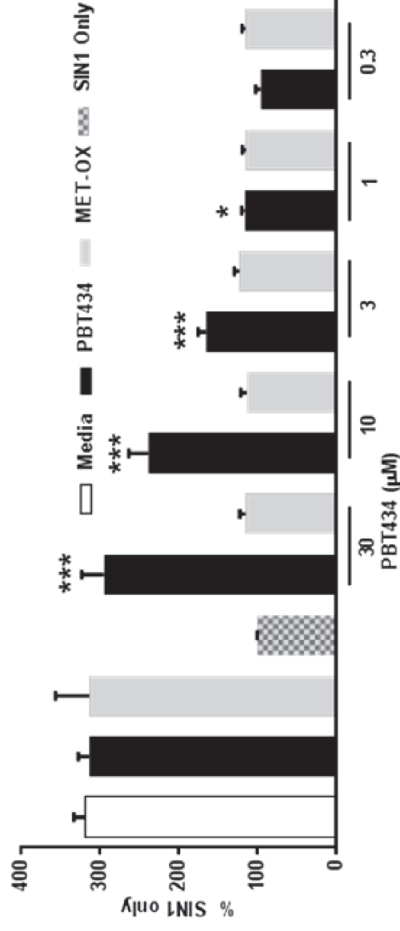
Iron colocalises with dopamine in the substantia nigra in PD in vivo model. Mouse brain SN sections; iron-staining (red), tyrosine hydroxylase-staining (yellow)

Doble PA et al Chem Sci 2014

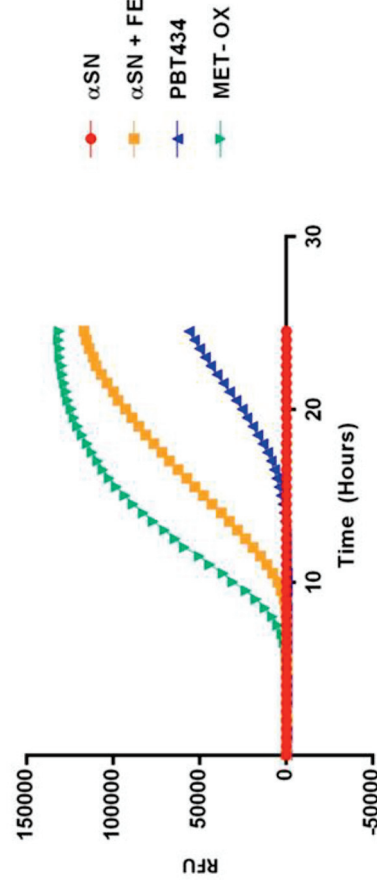
EXAMPLE 2: PBT434 Reduces Neuronal Stressors in Parkinsonism



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 aggregation. Met-Ox: non-metal binding PBT434 analogue

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Market Approval and Market Access

STRATEGIC & TACTICAL ASPECTS

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



Company Name	Product Names	Description	Partners	Milestones	Effect
Valeant	Xenazine, tetraabenazine	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 & antiinflammatory	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	2 nd -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

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



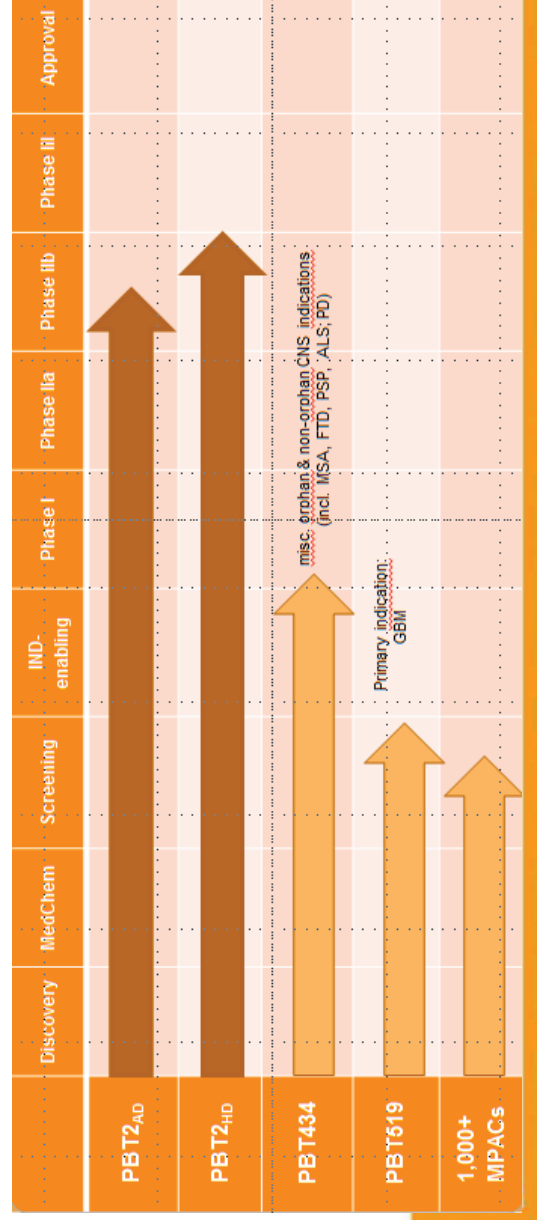
	tau	α -Syn
Aggregation disorders caused by respective protein/pathway	PSP, FTD, CBD, CTE	MSA, PD _{non-orphan}
Reduction of protein aggregation, deposition <i>in vivo</i>	PET brain rTg4510 mice	SNpc, TgA53T mice
Reduction, prevention of elevated iron levels <i>in vivo</i>		SNpc, Acutely lesioned MPTP model
Preservation of neuronal viability, prevention of neuronal loss <i>in vivo</i>		SNpc, Acutely lesioned MPTP model
Beneficial effect on cognition, motor function <i>in vivo</i>	Y-Maze rTg4510 mice	Hind Limb Claspings 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 uncharted orphan disorders of protein misfolding & aggregation: MSA, PSP, FTD, CTE, CBD etc.
- ✓ by addressing brain disorders related to metal dyshomeostasis, e.g. ALS, GMB



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