Magic bullets or novel multimodal drugs with various CNS targets for Parkinson s disease?

Schapira *et al.* recently published an excellent overview of therapeutic targets for Parkinson s disease (PD) [1]. Traditional drug design efforts optimize drug specificity against one selected target. Disappointingly, such magic bullet drugs for CNS disorders, including PD and Alzheimer s disease (AD), have not been realized. Transcriptomics, proteomic profiling and genetic analyses indicate that PD is polyaetiological in origin, with multifactorial processes leading to neuronal death: any one of which can initiate neurodegenerative cascades. Braak s group[2] suggests that PD manifests in different stages, beginning with alterations in anterior olfactory structures and loss of smell, then initial subtle and subsequent increasingly severe changes in the substantia nigra and other nuclei of the basal midbrain and forebrain. Such changes result in a predisposition to depression among other neurological deficits associated with PD. In the final stages, lesions occur in the prefrontal cortex, with increasing cholinergic neuronal degeneration and onset of dementia. Thus, an emerging drug design concept for PD and AD therapeutics is to develop ligands that modulate the multiple drug targets available in these disorders. In this commentary, we present examples of novel multimodal drugs with various CNS targets (FIG. 1) that are in development for symptomatic and possibly neuroprotective neurorescue treatment of PD[3], which were not discussed by Schapira *et al.*

Ladostigil (TV3326; clinical Phase IIa) is one example of a multimodal drug for the treatment of AD and Lewy body disease (LBD). Ladostigil incorporates a carbamate moiety, which is associated with cholinesterase inhibition, into the pharmacophore of rasagiline (Azilect; Teva Pharmaceuticals). The carbamate moiety in ladostigil results in the inhibition of acetylcholinesterase and butyrylcholinesterase, whereas its propargylamine moiety is responsible for brain-selective monoamine oxidase (MAO) A and B inhibition, and interferes with the regulative processing of amyloid precursor protein. Ladostigil also possesses the *in vitro* and *in vivo* neuroprotection neurorescue mechanisms associated with the propargylamine moiety similar to rasagiline[4,5]. Preclinical studies show that ladostigil has antidepressant, anti-PD and anti-AD activities[6], and clinical development is planned for AD, LBD and PD dementia.

Other multifunctional drug examples include the brain-permeable iron chelator and MAOA/B inhibitor M30, and the dual adenosine A_{2A} antagonists and brain MAOB inhibitors. One major pathology of PD is the accumulation of iron in the substantia nigra pars compacta, which contributes to oxidative-stress-associated toxicity[7]. Interestingly, similar iron accumulation patterns also occur in 6-hydroxydopamine and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) parkinsonian models, whereby iron chelators attenuate the neurotoxicity of these agents. M30, currently undergoing

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development similar to ladostigil, possesses the MAO inhibitory and neuroprotective propargylamine moiety in the pharmacophore of the brain-permeable iron chelator VK-28. M30 and VK-28 prevents 6-hydroxydopamine and MPTP neurotoxicity. As a potent MAOA and MAOB inhibitor, M30 (unlike VK-28, which lacks MAO-inhibitor activity) increases brain levels of monoamine neurotransmitters. M30 may possess antidepressant activity that is due to MAOA inhibition, similar to non-selective MAO inhibitors and MAOA-selective inhibitors. In addition, the propargylamine moiety of M30 confers neuroprotection and neurorescue properties that ostensibly involve the regulation of the mitochondrial BCL-2 family of proteins and the activation of tyrosine kinase receptor signalling pathways, which is similar to rasagline[8].

In PD, dual mechanistic inhibition of MAOB and adenosine A_{2A} receptor antagonism may offer another novel therapeutic approach to prevent neuronal cell death. Studies with KW-6002, a potent A_{2A} receptor antagonist undergoing clinical trials, and (*E*)-8-(3-chlorostyryl)caffeine (CSC) show that both compounds are neuroprotective in the MPTP mouse model[9]. Similar compounds tested showed significant MAOB inhibition, which suggests that the neuroprotective properties of KW-6002 and CSC may partly be due to MAOB inhibition in the brain in synergy with A_{2A} receptor antagonism[10,11].

The development of multifunctional drugs is not limited to PD and AD; this approach offers an exciting new concept with similar applications in drug development for treatment of depressive illness, schizophrenia, cardiovascular diseases, AIDS and cancer[12].

Moussa B. H. Youdim and Cornelis J. (Neels) Van der Schyf*

**Professor of Pharmacology, Professor of Life Sciences, Director of Eve Topf and NPF Centers of Excellence For Neurodegenerative Diseases Research, Technion-Rappaport Family Faculty of Medicine, Efron St, P.O. Box 9697, Haifa 31096, Israel.*

Chair and Professor of Pharmaceutical Sciences, Professor of Neurobiology, Northeastern Ohio Universities, College of Pharmacy and College of Medicine, 4209 State Route 44, Rootstown, Ohio 44272, USA.

e-mails: youdim@tx.technion.ac.il, cvanders@neoucom.edu

1. Schapira, A. H. *et al*. Novel pharmacological targets for the treatment of Parkinson's disease. *Nature Rev. Drug Discov.* **5**, 845 854 (2006).
2. Braak, H. *et al*. Pathology associated with sporadic Parkinson's disease where does it end? *J. Neural Transm. Suppl.* **70**, 89 97 (2006).
3. Van der Schyf, C. J., Gal, S., Geldenhuys, W. J. & Youdim, M. B. H. Multifunctional neuroprotective drugs targeting monoamine oxidase inhibition, iron chelation, adenosine receptors, and cholinergic and glutamatergic action for neurodegenerative diseases. *Expert Opin. Invest. Drugs* **15**, 873 886 (2006).

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4. Youdim, M. B. H., Maruyama, W. & Nao i, M. Neuropharmacological, neuroprotective and amyloid precursor processing properties of selective MAO -B inhibitor antiparkinsonian drug, rasagiline. *Drugs Today* **41**, 369 391 (2005).
5. Sagi, Y., Mandel, S., Amit, T. & Youdim, M. B. Activation of tyrosin e kinase receptor signaling pathway by rasagiline facilitates neurorescue and restoration of nigrostriatal dopamine neurons in post -MPTP-induced parkinsonism. *Neurobiol. Dis.* **25**, 35 44 (2007).
6. Youdim, M. B. H., Amit, T., Bar -Am, O., Weinreb, O. & Yogev-Falach, M. Implications of co -morbidity for etiology and treatment of neurodegenerative diseases with multifunctional neuroprotective neurorescue drugs; Ladostigil. *Neurotox. Res.* **10**, 181 192 (2006).
7. Zecca, L., Youdim, M. B. H., Riederer, P., Connor, J. R. & Crichton, R. R. Iron, brain ageing and neurodegenerative disorders. *Nature Rev. Neurosci.* **5**, 863 873 (2004).
8. Avramovich-Tirosh, Y. *et al*. Therapeutic targets and potential of the novel brain -permeable multifunctional iron chelator-monoamine oxidase inhibitor drug, M-30, for the treatment of Alzheimer's disease . *J. Neurochem.* **100**, 490 502 (2007).
9. Chen, J. F. *et al*. 8-(3-Chlorostyryl)caffeine may attenuate MPTP neurotoxicity through dual actions of monoamine oxidase inhibition and A2A recepto r antagonism. *J. Biol. Chem.* **277**, 36040 36044 (2002).
10 Castagnoli, N. Jr. *et al*. Monoamine oxidase B inhibition and neuroprotection: studies on selective adenosine A2A receptor antagonists. *Neurology* **61** (Suppl. 6), 62 68 (2003).
11. Petzer, J. P. *et al*. Inhibition of monoamine oxidase B by selective adenosine A2A receptor antagonists. *Bioorg. Med. Chem.* **11**, 1299 1310 (2003).
12. Van der Schyf, C. J., Geldenhuys, W. J. & Youdim, M. B. Multifunctional drugs with different CNS targets for neuropsychiatric disorders. *J. Neurochem.* **99**, 1033 1048 (2006).

Competing interests statement

M.B.H.Y. declares competing financial interests. Ladostigil was designed by M.B.H.Y . and M. Weinstock and was supported and co-developed with Teva Pharmaceutical Co ., Israel. M.B.H.Y. will receive numeration if the drug is successful. M30 is being developed by Varinel Inc ., USA. No part of the work on M30 was supported by them, but M.B.H.Y. will receive numeration if it is successful .

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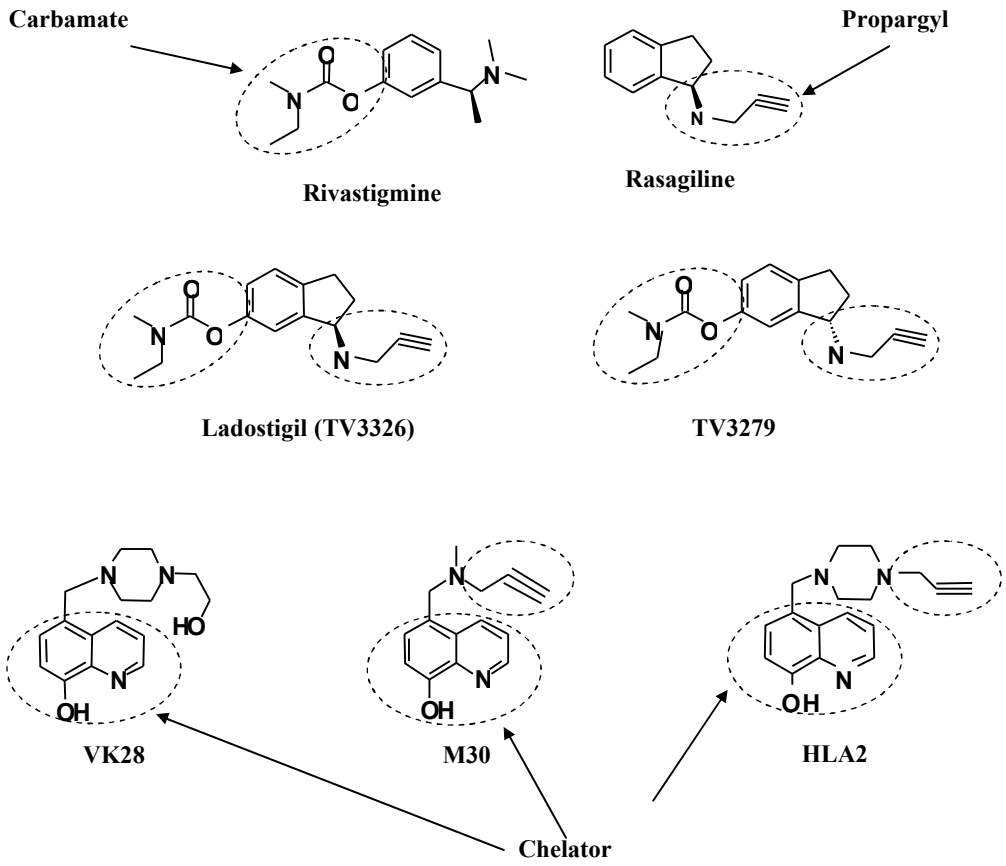

Figure 1 | **The structures of neuroprotec tive multifunctional drugs ladostigil and M30 depicting their derivation from monoamine oxidase (MAO) B inhibitor, rasagiline and iron chelator-radical scavenger, VK-28.** Ladostigil possesses the acetylcholinesterase and butyrlcholinesterase inhibitor moiety, carbamate and the MAO inhibitory and neuroprotective propargyl moiety. M30 has the iron -chelating pharmacophore moiety of VK-28 and the MAO inhibitory and neuroprotective propargyl moiety.

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