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MEETING ABSTRACT

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In vivo systems pharmacology of IRL752, a novel compound for treatment of BPSD and cognitive impairment in dementia, enhancing prefrontal synaptic activity by modulation of dopamine transmission

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In Alzheimer’s disease (AD) and other forms of dementia, impaired cortical monoamine transmission is a core feature associated with progressive cognitive decline and behavioural and psychiatric symptoms (BPSD). Available medications can improve cognition by enhancing cortical synaptic activity, by increasing acetylcholine (ACh esterase inhibitors), or by low-affinity NMDA receptor antagonism presumably acting extrasynaptically (memantine). Also, antipsychotic drugs are used, largely off-label, to control BPSD. The efficacy on cognitive functions is limited, and antipsychotics are associated with severe side effects. Furthermore, there are indications that anti-dopaminergic compounds may be detrimental with respect to phenotype and rate of decline in neurodegenerative disorders including AD.

IRL752 was discovered using a phenotypic screening approach, based on broad data arrays generated in vivo (gene expression, monoamine biomarkers, behaviour). The in vivo profile was benchmarked against an in-house database covering most CNS compound classes. IRL752 displays a novel profile, with region-selective enhancement of cortical dopamine (DA) and norepinephrine (NE), and net effects in vivo addressing pathological dysregulations in multiple transmitter systems affected in dementia. IRL752 induces Arc mRNA in the frontal cortex, limbic and striatal areas. The effect on cortical Arc is interpreted as enhanced synaptic activity, secondary to increased DA or NE levels leading to downstream activation of DA D1 and/or α receptors. The increase of subcortical Arc is presumably related to activation of cortico-striatal pathways. The Arc expression profile by IRL752 resembles that of memantine. IRL752 also induces a modest increase in cortical ACh. Behaviourally, IRL752 does not affect motor activity patterns in normal rats, and does not enhance locomotor activity under the influence of psychostimulants. It reverses tetrabenazine-induced hypomotility, indicating efficacy in conditions with impaired dopamine transmission, and hence potential to improve motor function in dementia where mild parkinsonian features are frequently observed. IRL752 reverses deficits in novel object recognition in a subchronic PCP model, suggesting potential to enhance short-term memory. Furthermore, IRL752 reverses MK-801-induced hyperactivity, suggesting antipsychotic properties. Main receptor level targets involved in the effects of IRL752 are 5-HT7, α2 and σ1 receptors. IRL752 is currently in phase I.

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