

# A SELECTIVE NURR1/RXR ACTIVATOR FOR TREATING PARKINSON'S DISEASE

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## Introduction

### Nurr1 is a therapeutic target with strong rationale in Parkinson's disease

- Clinically relevant evidence supports the role of Nurr1 in PD pathophysiology
- Nurr1 is critical for the protection and survival of dopaminergic neurons
- Nurr1 is a major driver of dopaminergic neuron differentiation
- Nurr1 governs both dopaminergic phenotype and neurotransmission
- Nurr1 inhibits neuroinflammation

A drug targeting Nurr1 may delay the progression of or reverse the effects of Parkinson's disease and would address a major clinical need

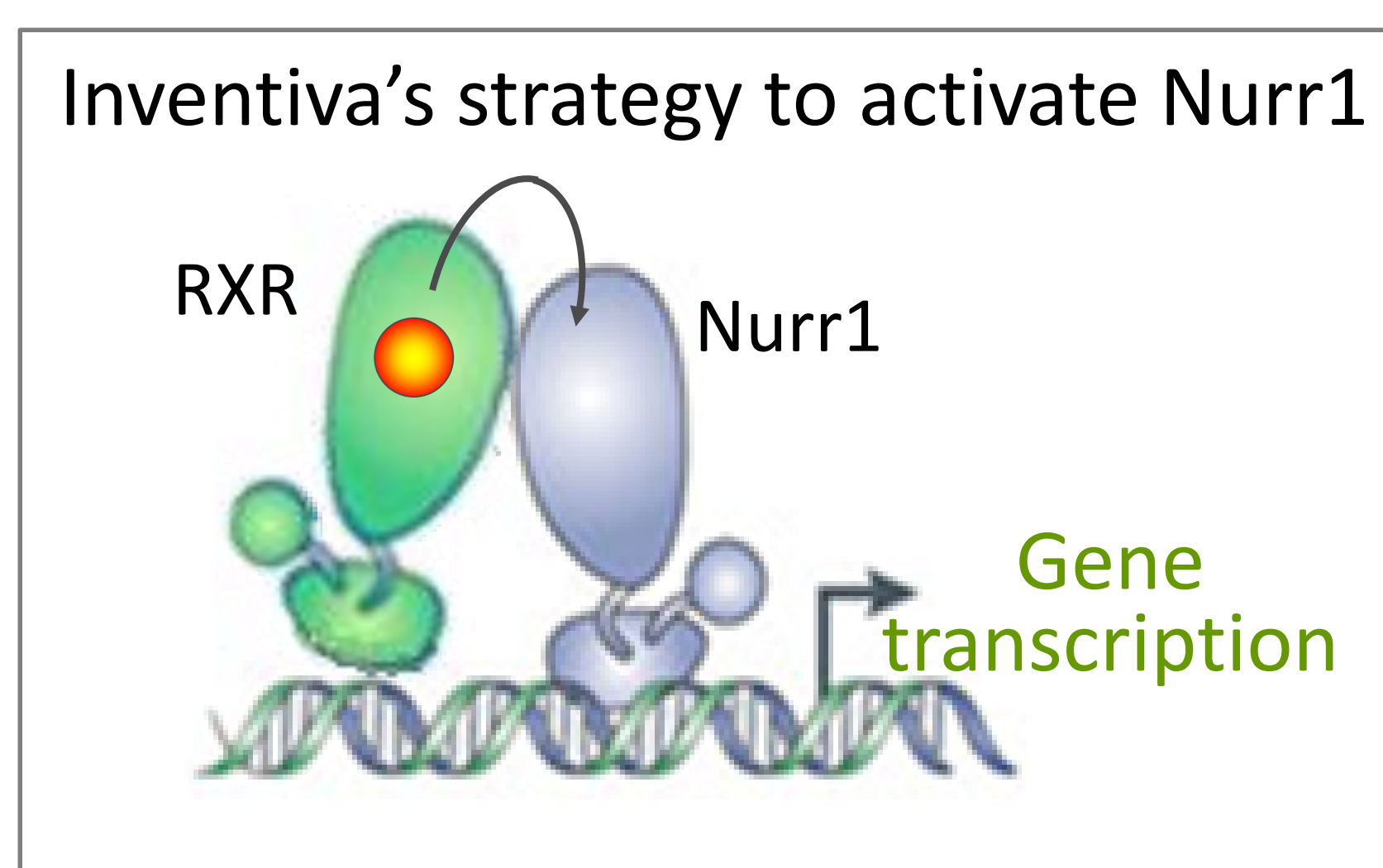
## Strategy to identify Nurr1 activators

- Nurr1 (NR4A2) forms with Nur77 and Nor1 a subclass of orphan nuclear receptors
- Nurr1's ligand binding pocket is obtruded
- Nurr1 (like Nur77) binds to DNA as monomers, homodimers or heterodimers with RXR $\alpha$  and RXR $\gamma$
- Nurr1/RXR heterodimers are activated by endogenous RXR ligands in embryonic CNS and promote the survival of dopaminergic neurons

Inventiva's strategy to discover Nurr1 activators was to identify RXR ligands that selectively activate Nurr1/RXR heterodimers

- Functional screening on a proprietary library of 300 000 compounds to identify RXR ligands that selectively activate Nurr1 / RXR heterodimers
- Five chemical series identified. Four series extensively worked on in lead optimization programs

IVA360 is most advanced lead compound



## Conclusion

- IVA360 is a first-in-class activator of Nurr1/RXR displaying consistent neuroprotective and restorative properties *in vitro* and *in vivo*
- Additional novel chemical series are being worked on with improved properties

Altogether, our work demonstrates that

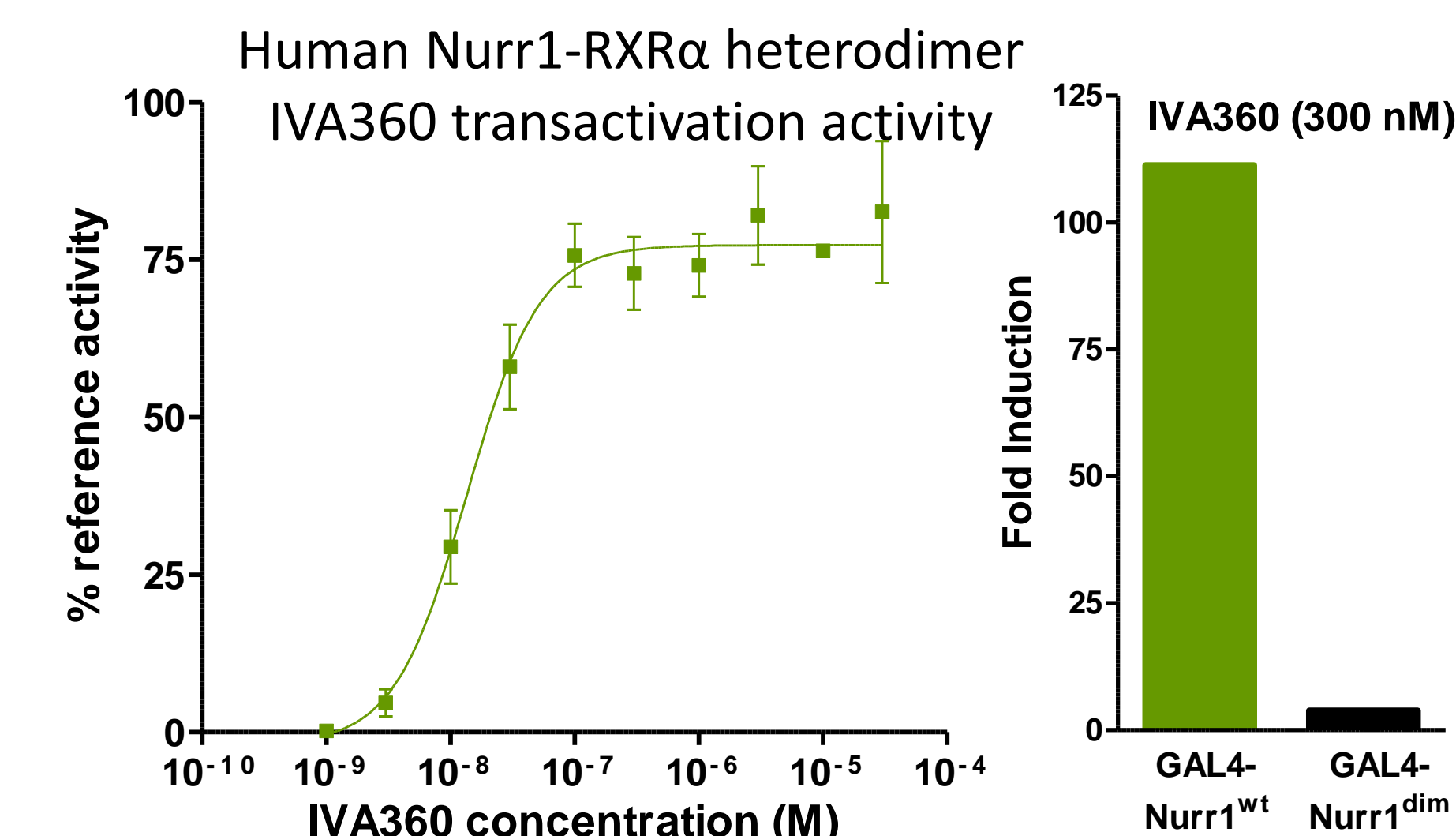
- Targeting Nurr1 via RXR is a valid approach to activate Nurr1 and thus induce neuroprotective activity
- Selective Nurr1/RXR activators devoid of pan-RXR-like liabilities can be obtained

Data support further development of Nurr1/RXR activators as novel therapeutic agents with disease modifying potential in Parkinson's disease

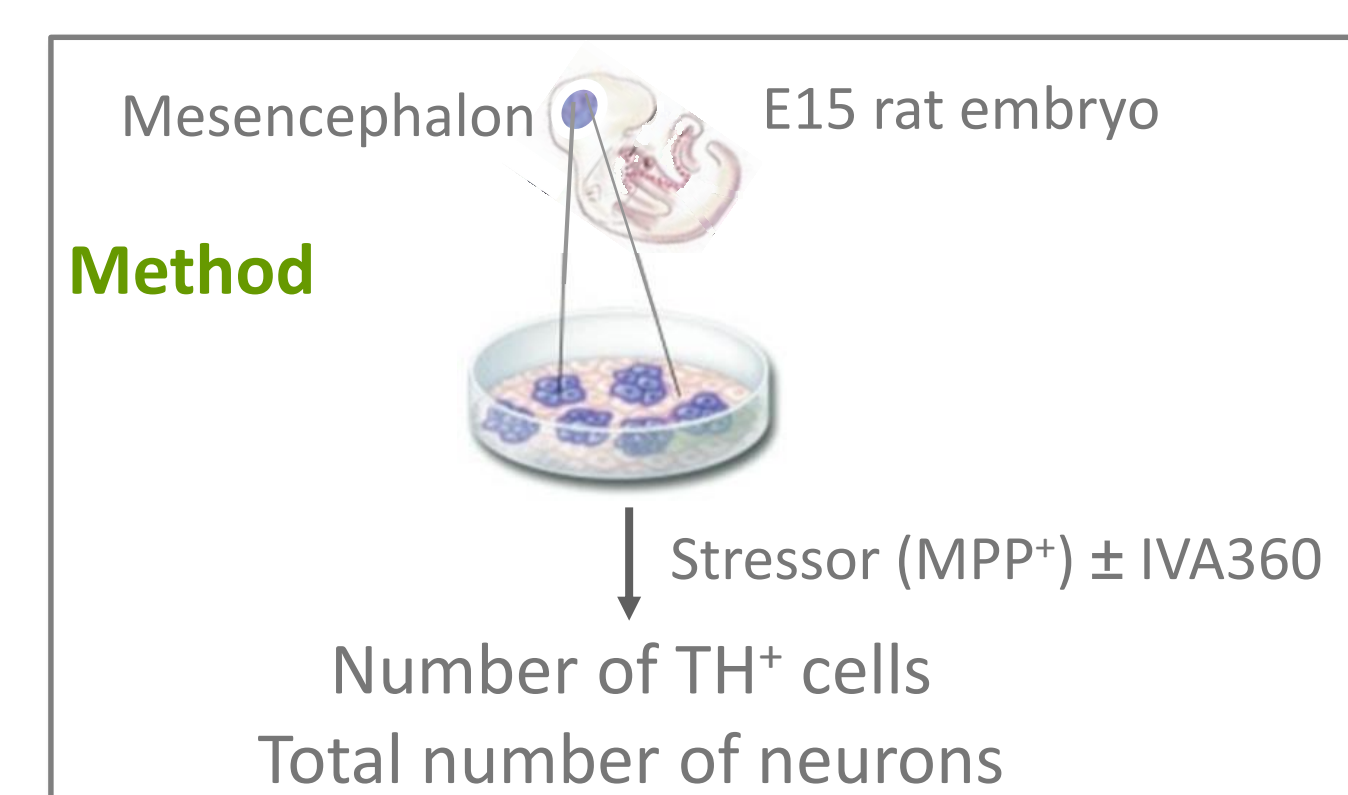
## Results

### IVA360 is a potent Nurr1/RXR activator

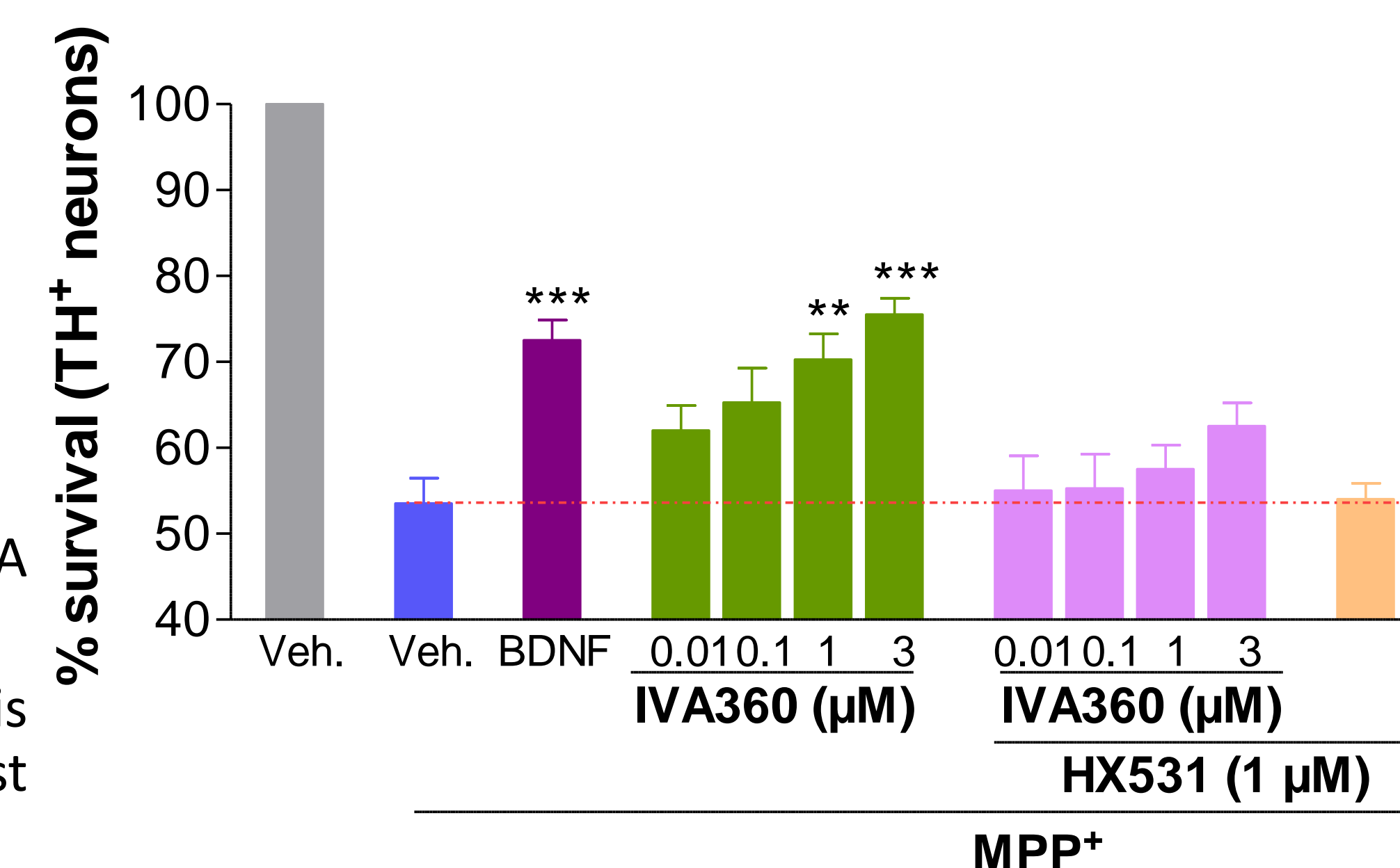
- IVA360 is a RXR ligand
- IVA360 activates human and mouse Nurr1/RXR heterodimers
- IVA360 activates Nurr1/RXR heterodimers in a Nurr1-dependent manner
- Proprietary structural data demonstrate a different binding mode of Inventiva ligands to the RXR ligand binding pocket



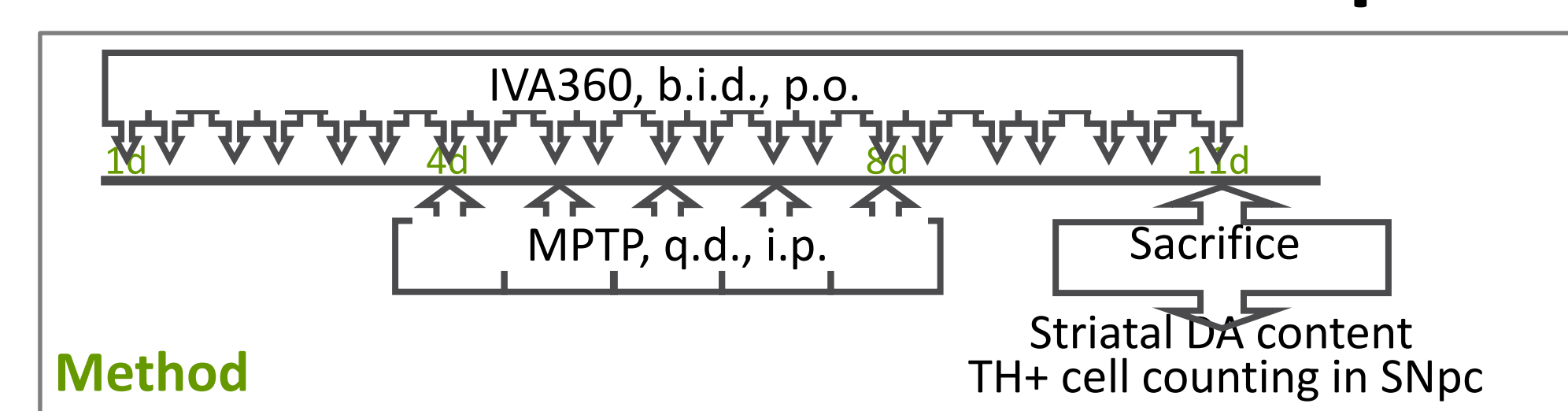
### IVA360 induces dopaminergic neuron survival *in vitro*



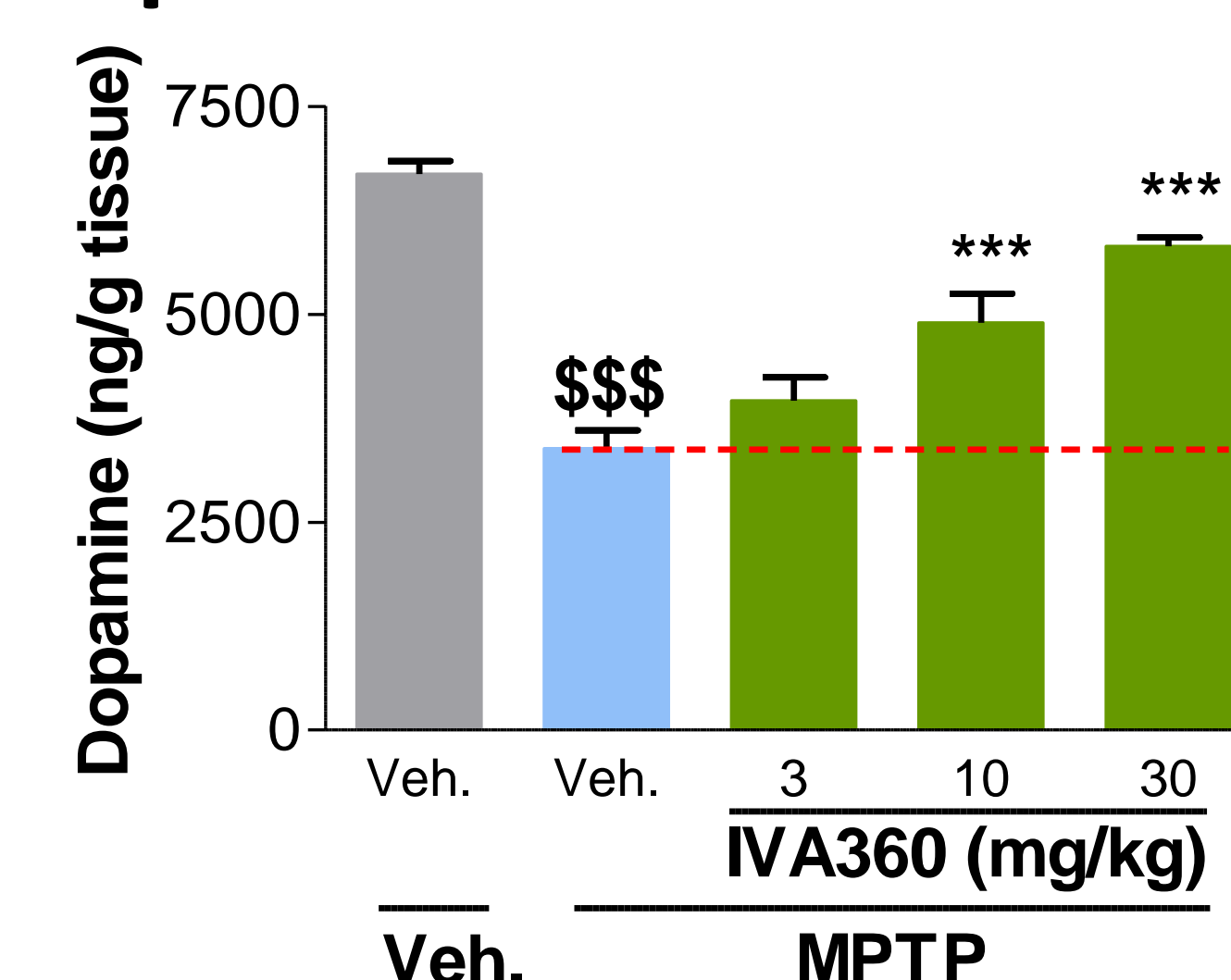
- IVA360 has protective effects on TH<sup>+</sup> DA neurons when administered with MPP<sup>+</sup>
- The neuroprotective effect of IVA360 is mediated by RXR as the RXR antagonist HX531 blocked the effect of IVA360



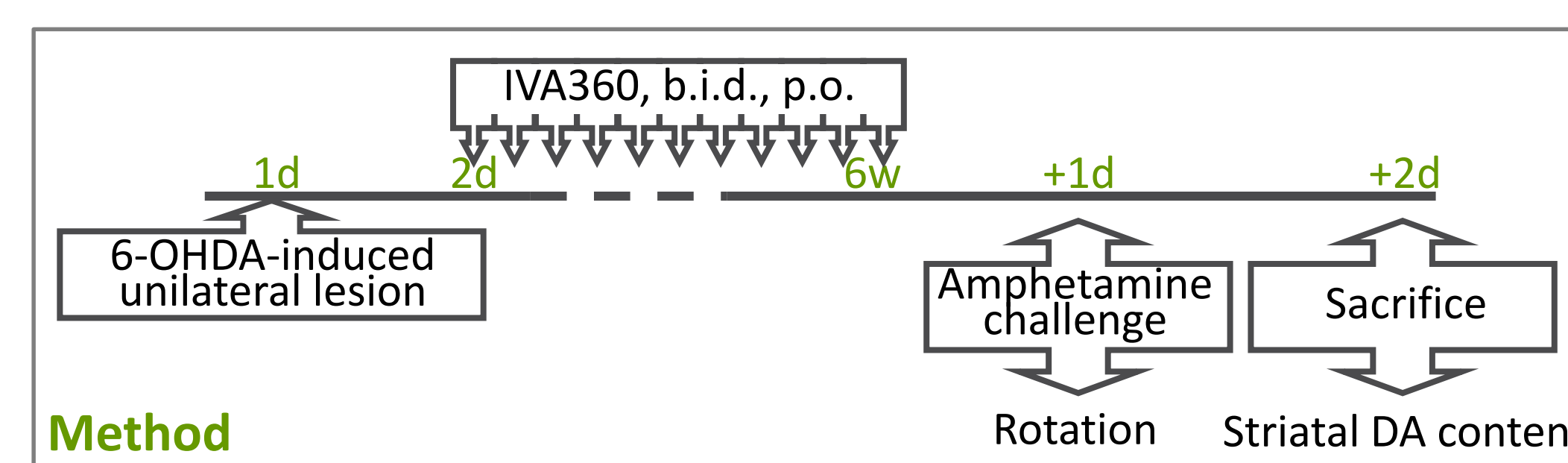
### IVA360 blocks MPTP-induced dopamine depletion in mice



- IVA360 dose-dependently blocks MPTP-induced dopamine reduction
- IVA360 dose-dependently blocks a stringent MPTP-induced dopamine level depletion and dopaminergic cell (TH<sup>+</sup>) loss (not shown)



### IVA360 restores full motor activity in the rat 6-OHDA model



- IVA360 dose-dependently restores striatal dopamine levels
- IVA360 dose-dependently abolishes amphetamine-induced unilateral rotation (circling behavior)

Chronic treatment with IVA360 after 6-OHDA-induced lesion translates into full recovery of functional/motor activity in the rat 6-OHDA model

