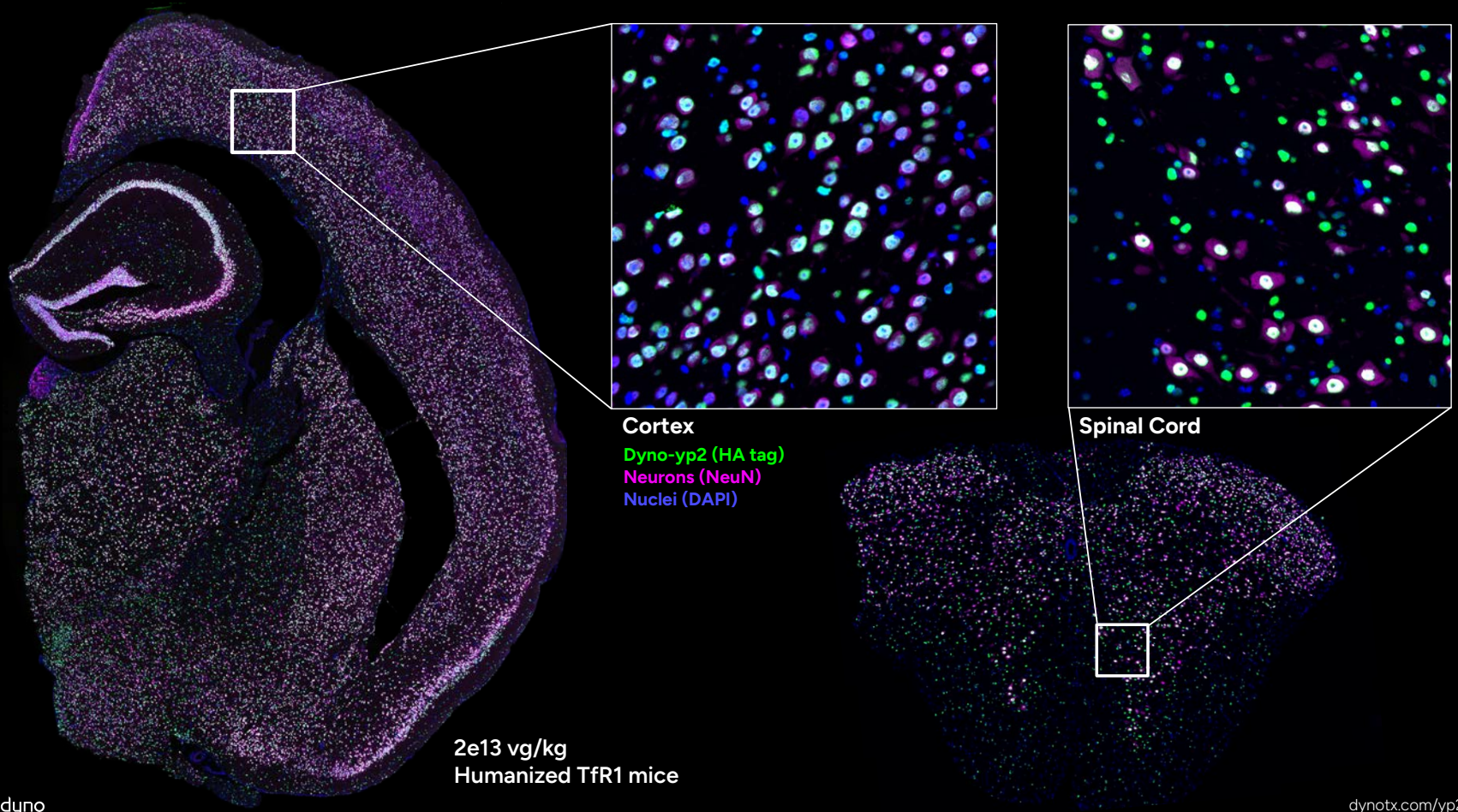
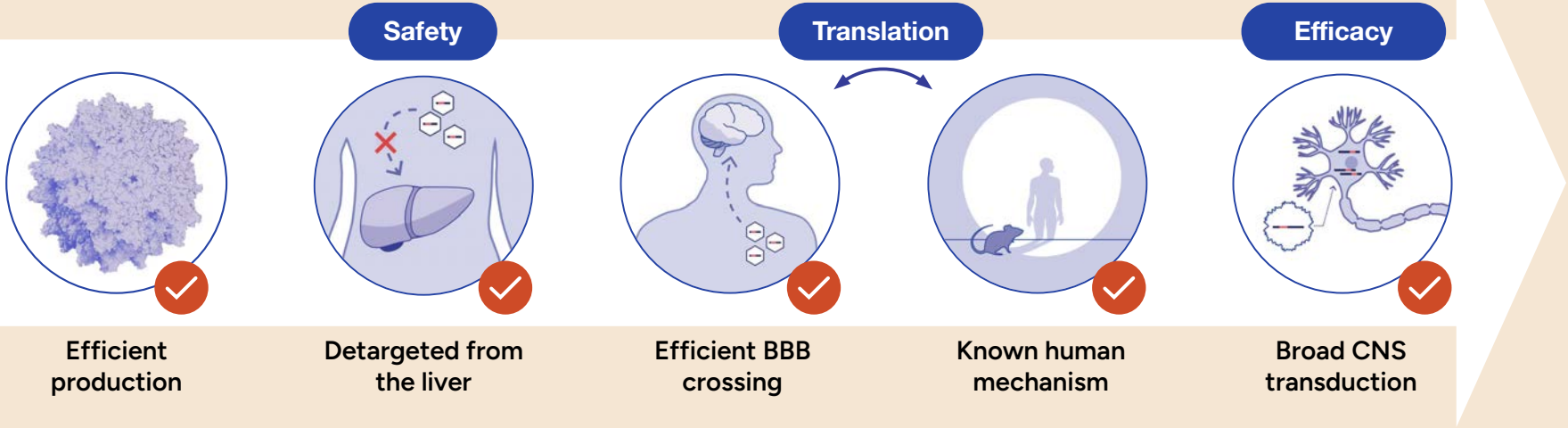
Dyno-yp2: A leading hTfR1-targeted capsid enabling robust brain transduction and liver detargeting

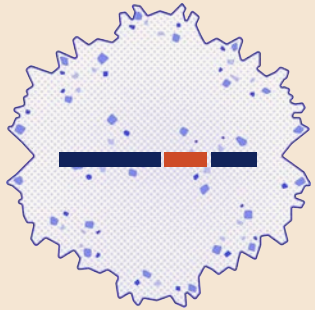
Dyno-yp2 transduces 94% of neurons in humanized TfR1 mice



Dyno-yp2 broadly and efficiently transduces the CNS through a human TfR1-mediated mechanism



We compared Dyno-yp2 head-to-head in humanized TfR1 mice with the published capsid BI-hTFR1



AAV capsid packaging
CAG-H3F3-HA genome
with ssAAV ITRs

Confirm engineered
binding to hTfR1

Wildtype (C57BL/6J)

Humanized (Hum.) TfR1
(Substitution of TfR1 extracellular domain)

- Dyno-yp2
- BI-hTFR1*
- AAV9

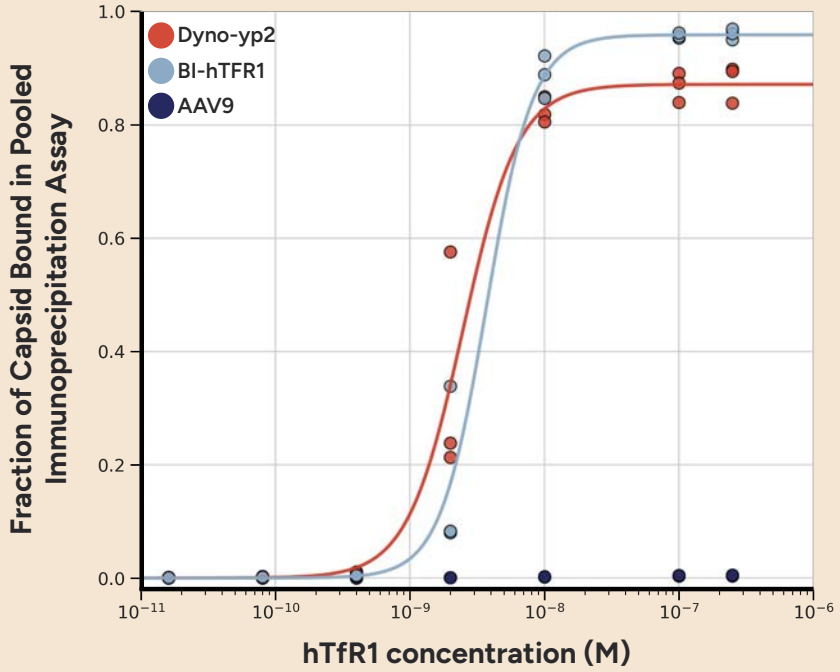
×

2e12 vg/kg
2e13 vg/kg
21 days in life
n=3 per group

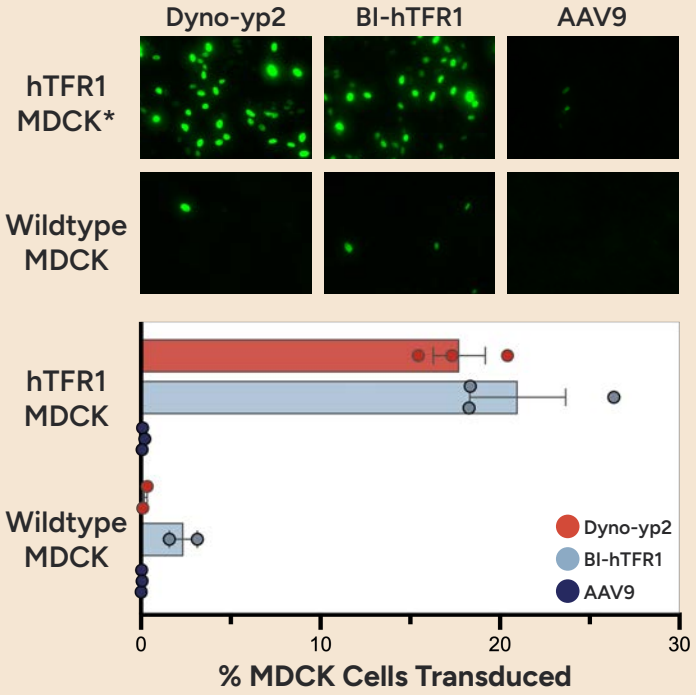
*BI-hTFR1, Huang et al. 2024. *Science*

Dyno-yp2 binds the human TfR1 receptor, increasing confidence in successful translation to humans

Dyno-yp2 binds to human TfR1

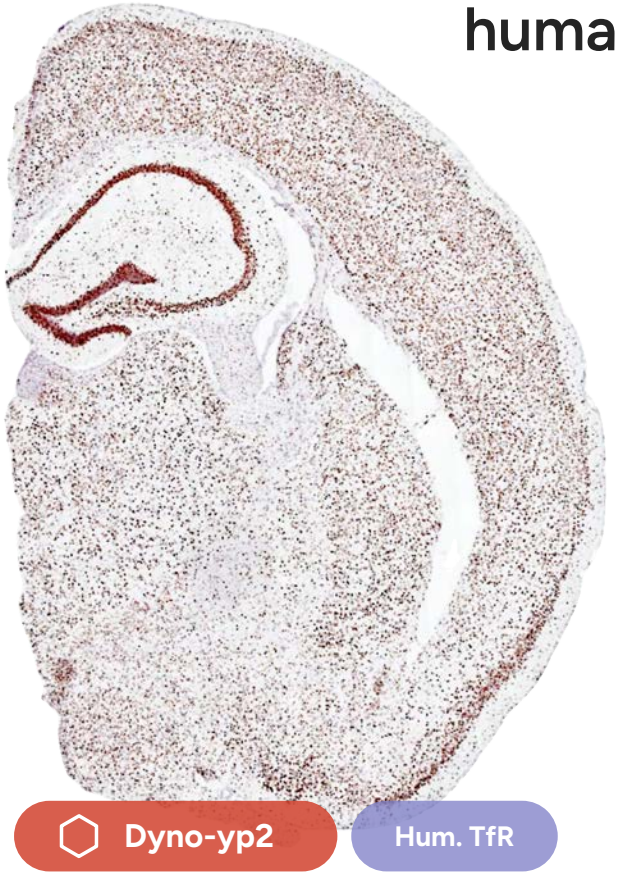


Dyno-yp2 specifically transduces cells expressing human TfR1



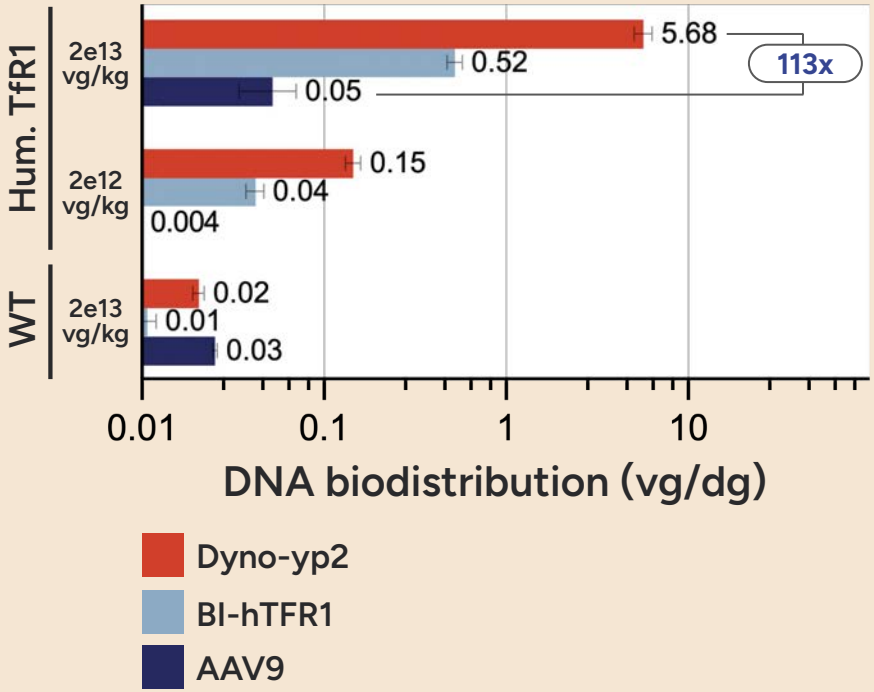
*Madin-Darby Canine Kidney cells

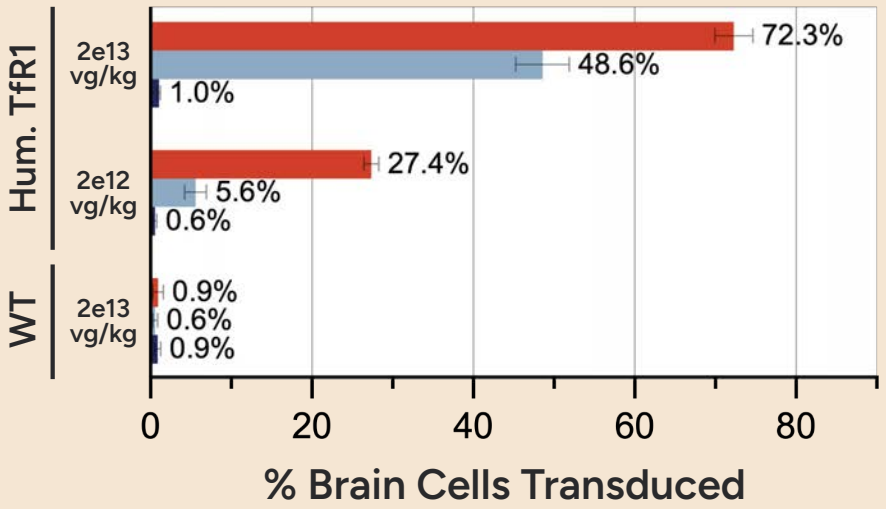
Dyno-yp2 transduction in the CNS is dependent on human TfR1 expression



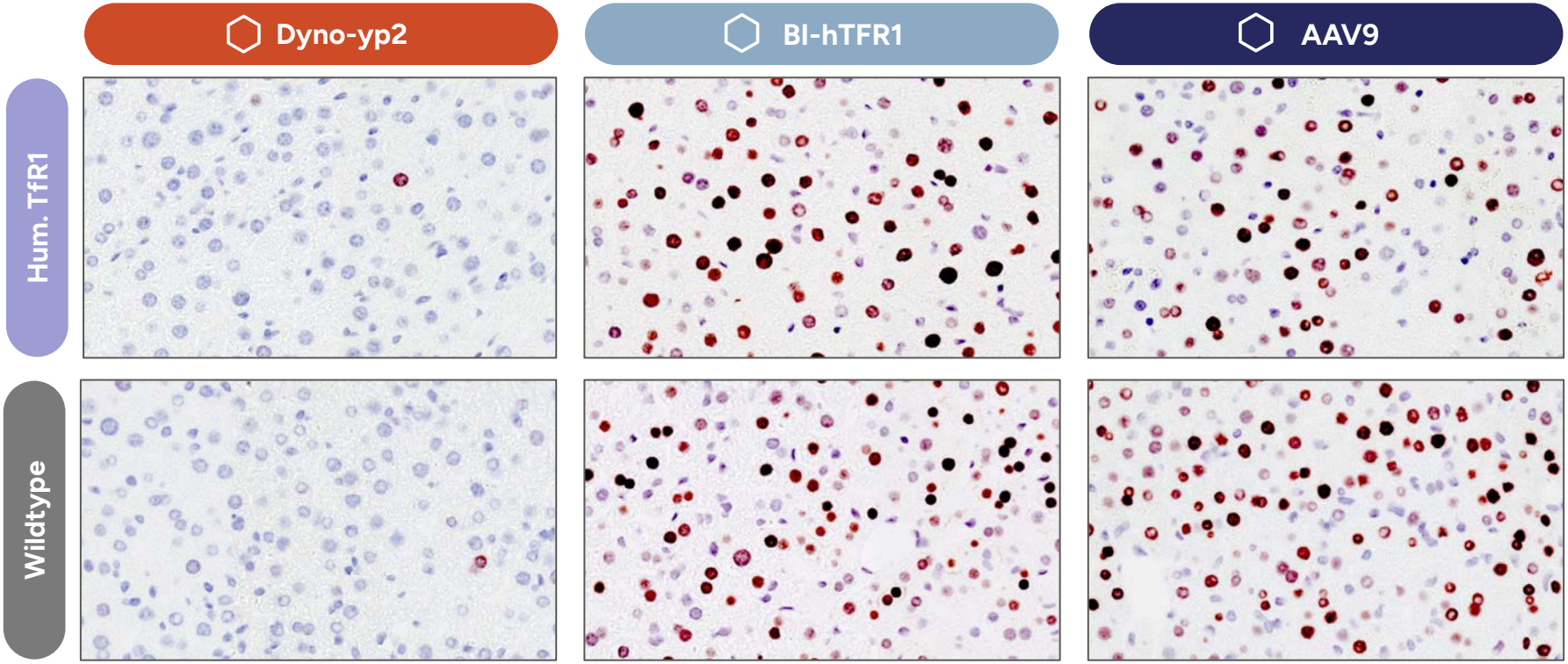
2e13 vg/kg dose

Dyno-yp2 brain biodistribution is 113x higher than AAV9 at 2e13 vg/kg in humanized TfR1 mice



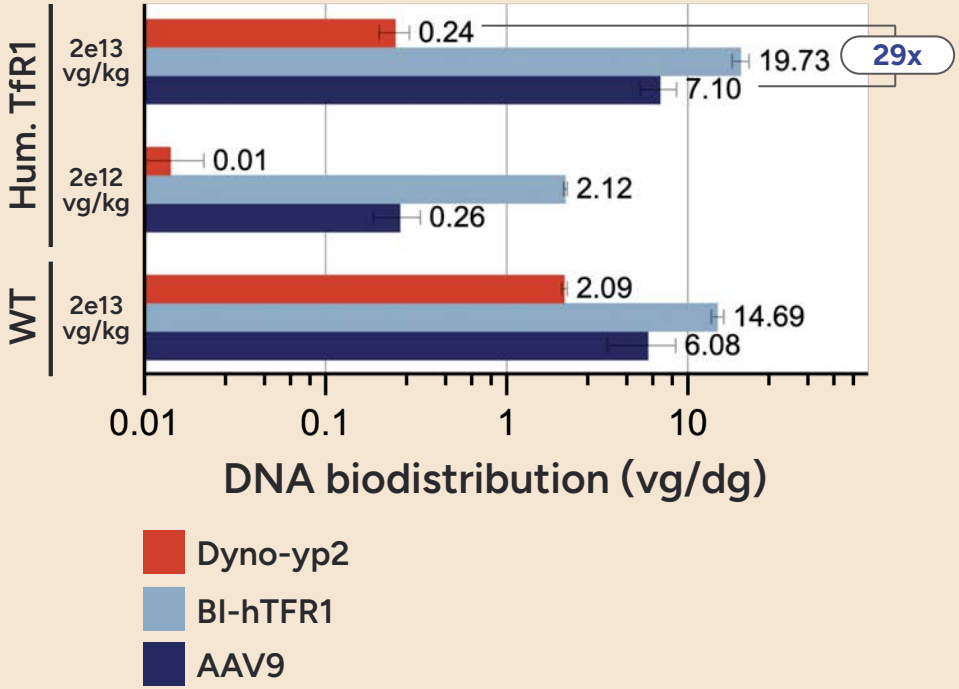


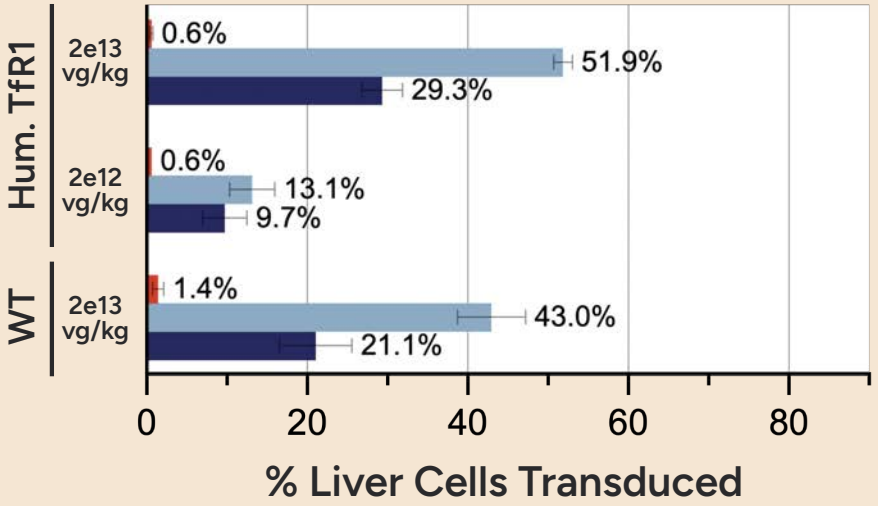
Dyno-yp2 combines CNS tropism with excellent liver detargeting



2e13 vg/kg dose

Dyno-yp2 detargets the liver with 29x lower biodistribution compared to AAV9 at 2e13 vg/kg in humanized TfR1 mice





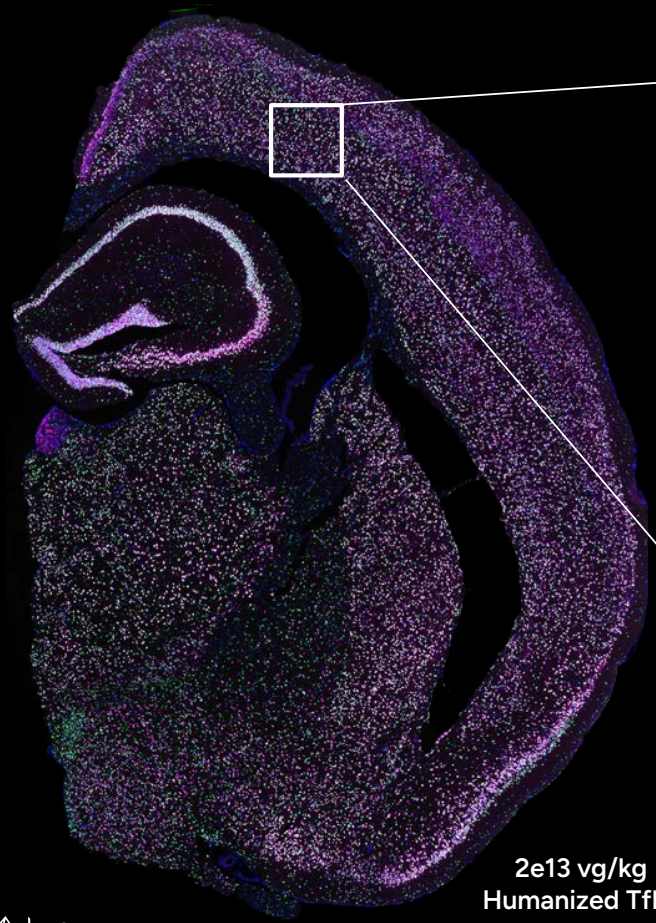
Dyno-yp2 liver detargeting is conserved across species

Liver detargeting in a pooled library (fold change over AAV9)		
	Dyno-yp2	**BI-hTFR1**
Humanized TfR1 mice	12 x	1.3 x*
Wildtype mice	7 x	1.3 x
Cynomolgus macaque	6.1 x	1.6 x

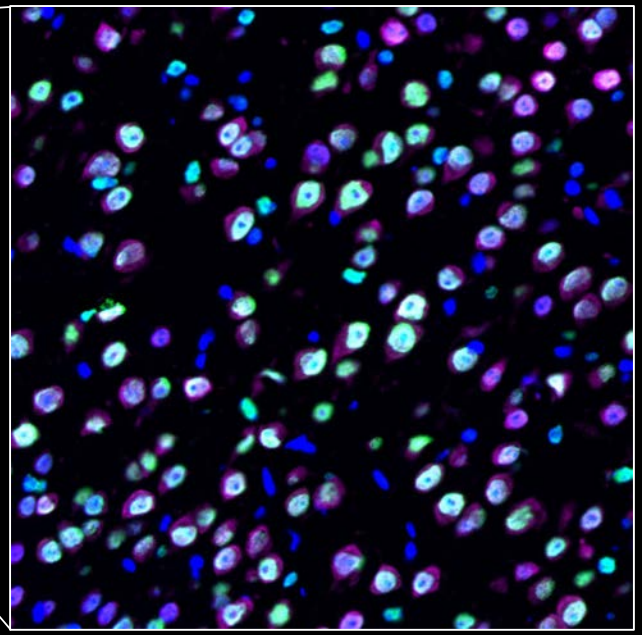
*Lack of liver detargeting for BI-hTFR1 was recapitulated in single capsid study.

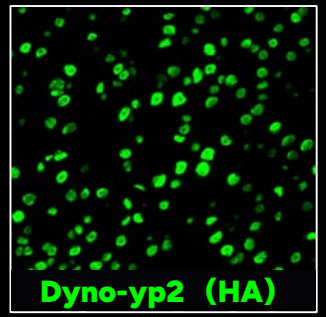
- In a pooled capsid library, Dyno-yp2 de-targets the liver in **humanized TfR1** and **wildtype** mice as well as **cynomolgus macaques**.
- Although Dyno-yp2 does not bind to the cynomolgus macaque TfR1 receptor, **liver detargeting is conserved in both NHPs and mice** as measured in a pooled assay.
- These findings support that Dyno-yp2's excellent liver detargeting may be **translatable to humans**, improving the safety profile of this capsid compared to others.

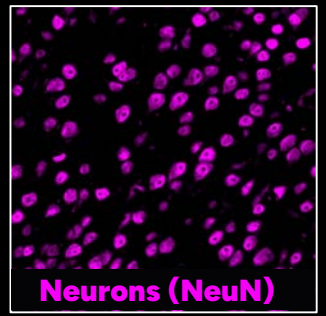
Dyno-yp2 transduces 98% of NeuN+ neurons in the cortex

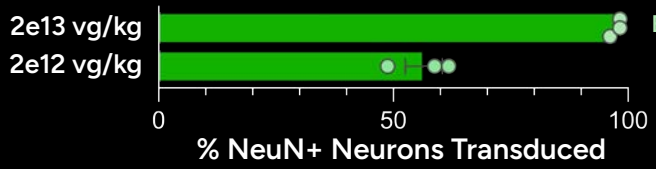


2e13 vg/kg
Humanized TfR1



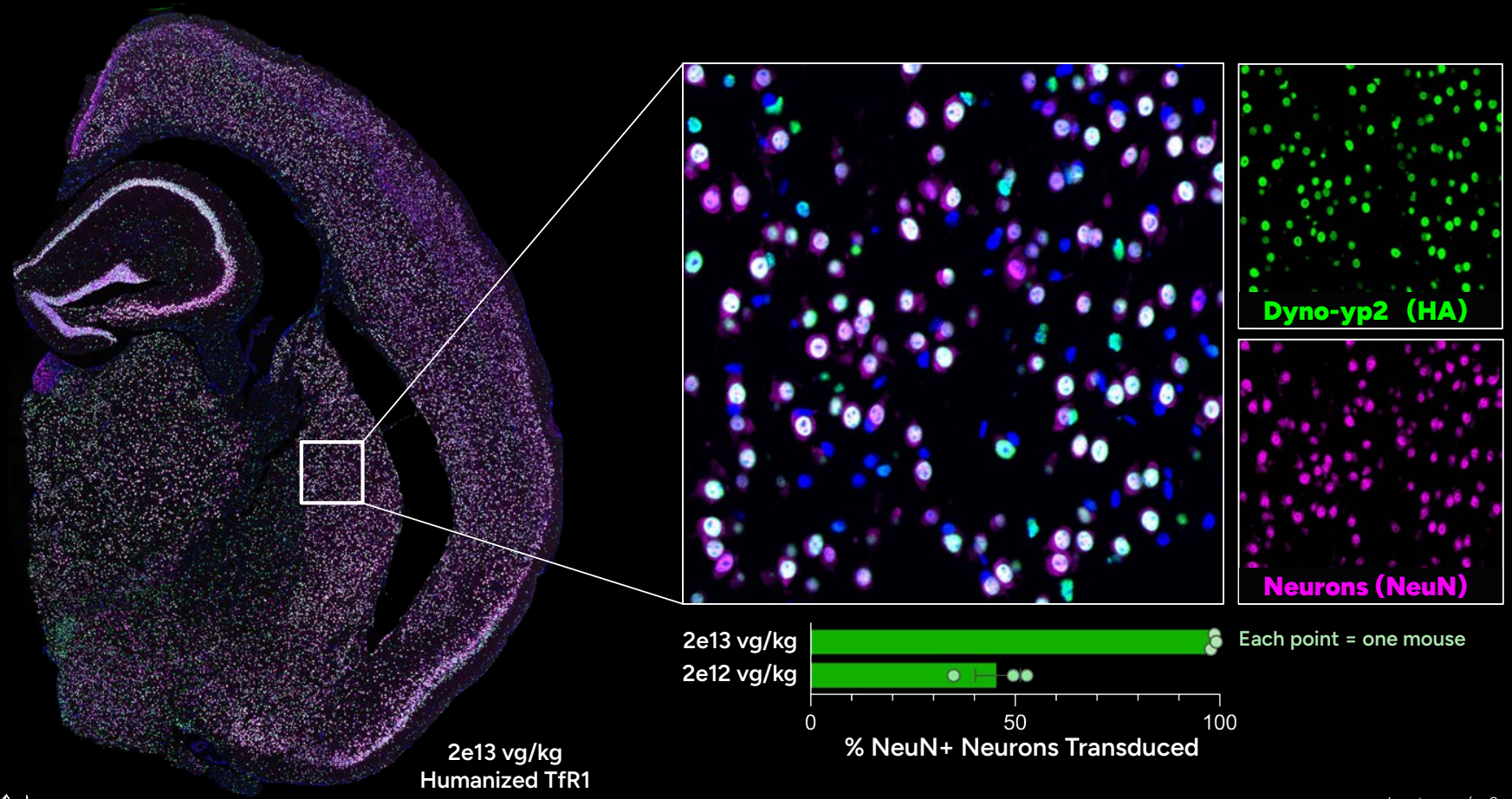




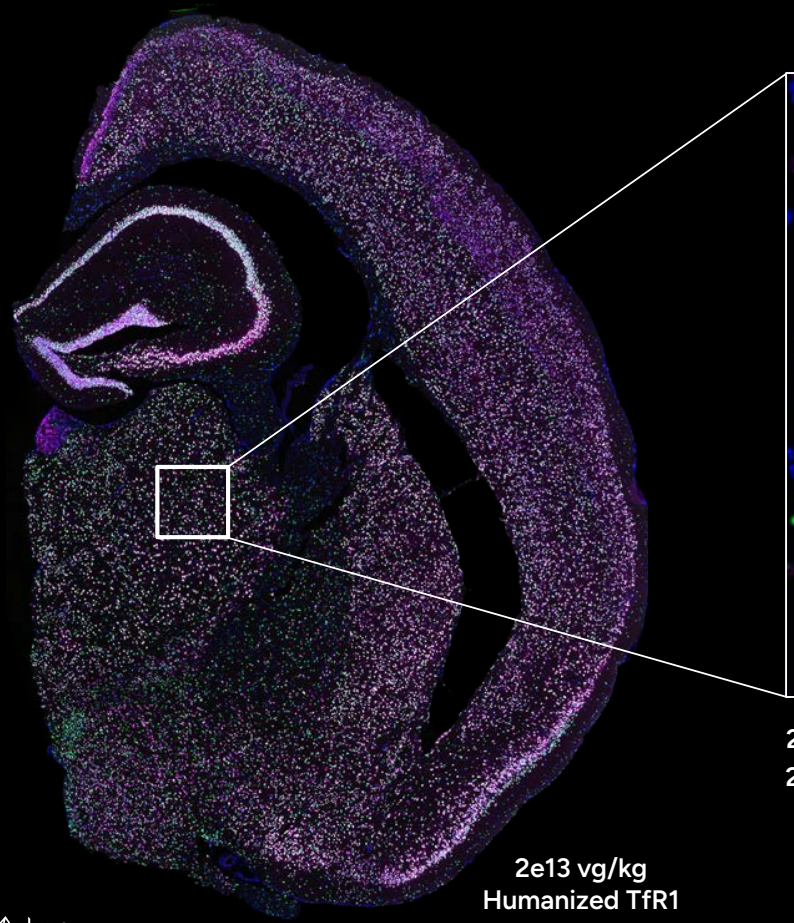


Each point = one mouse

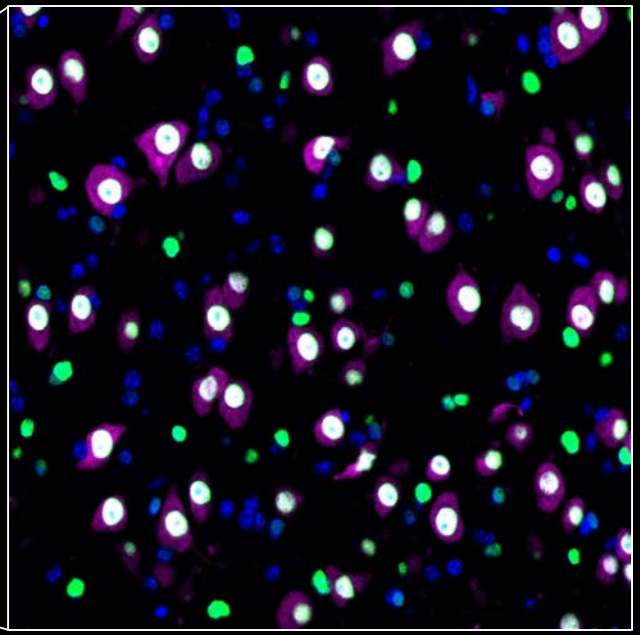
Dyno-yp2 transduces 99% of NeuN+ neurons in the striatum

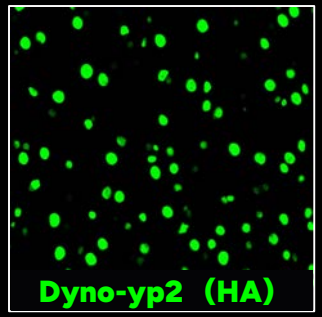


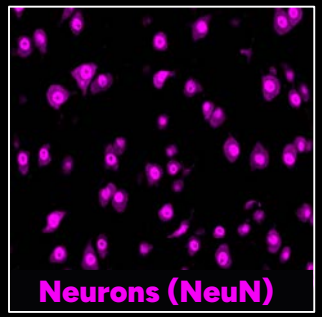
Dyno-yp2 transduces 98% of NeuN+ neurons in the thalamus

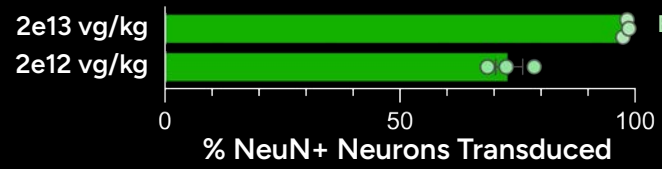


2e13 vg/kg
Humanized TfR1



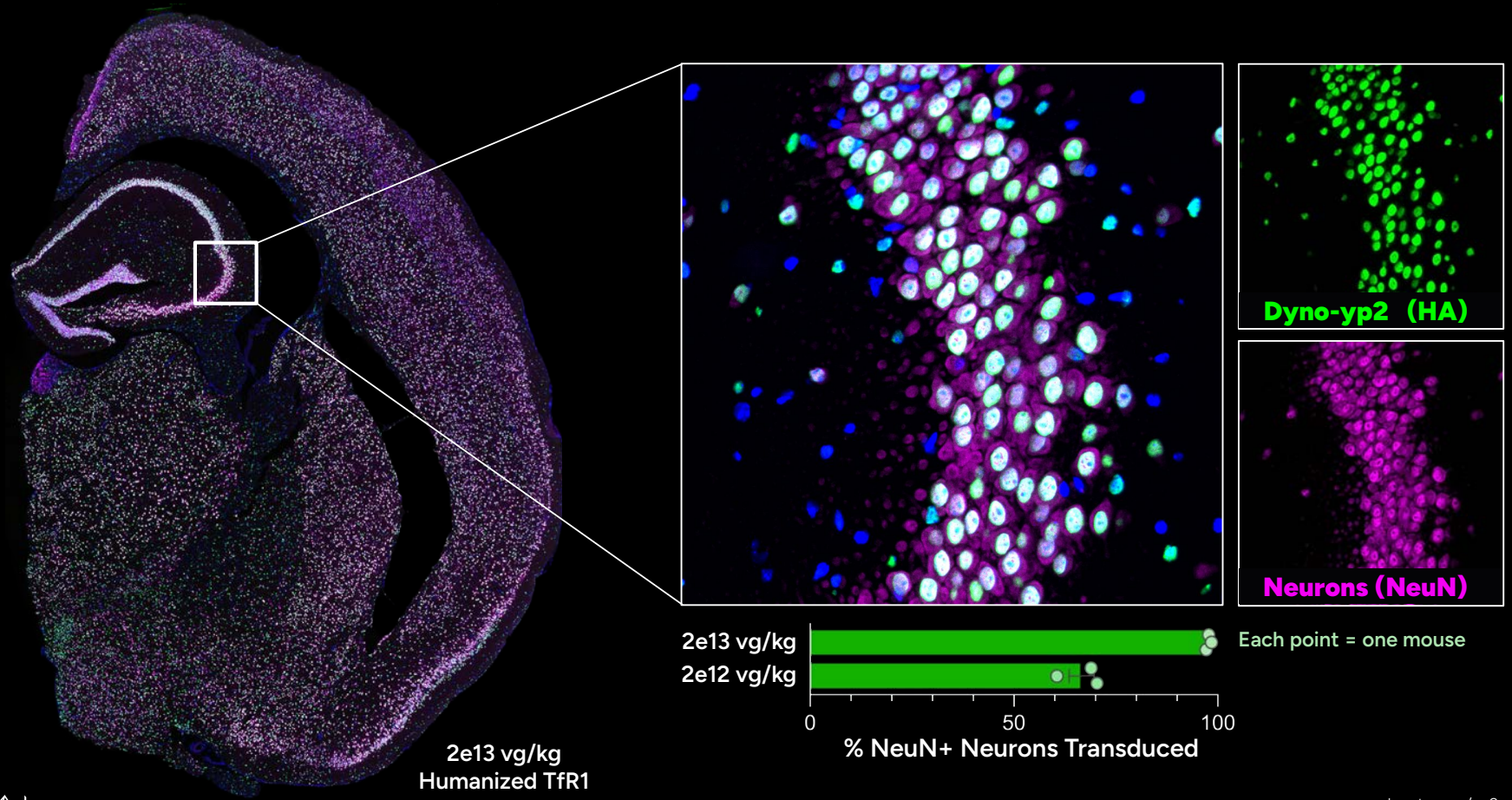




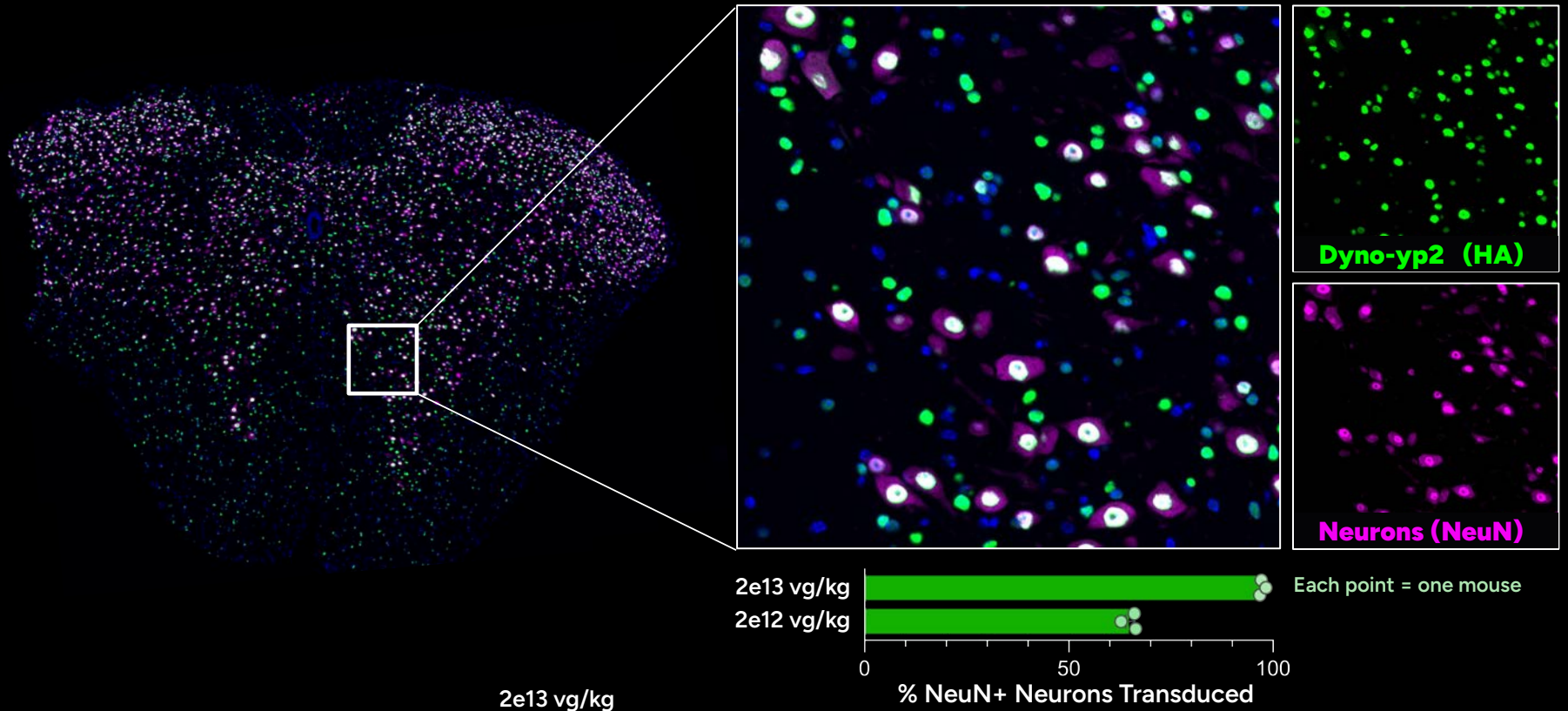


Each point = one mouse

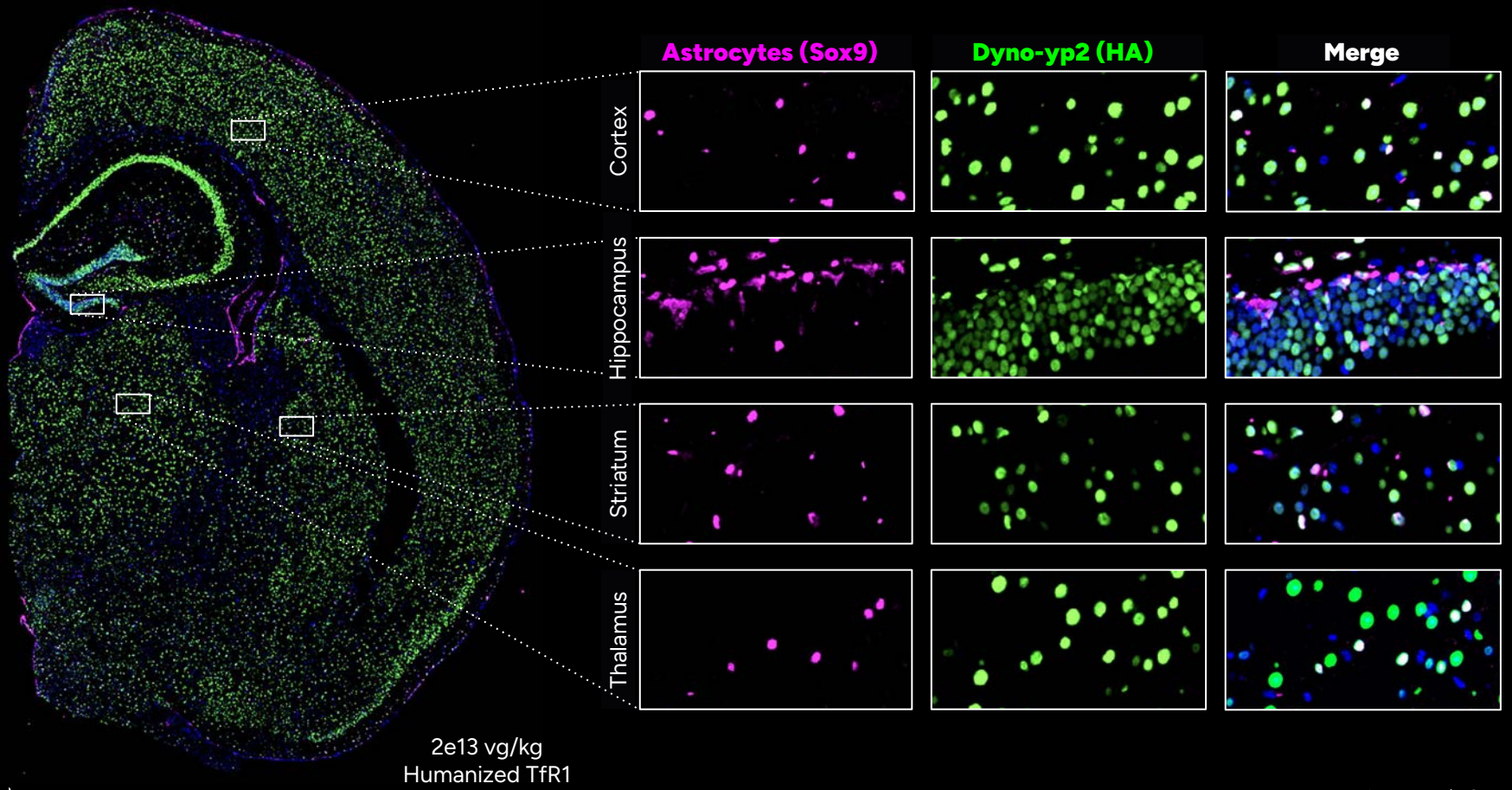
Dyno-yp2 transduces 98% of NeuN+ neurons in the hippocampus



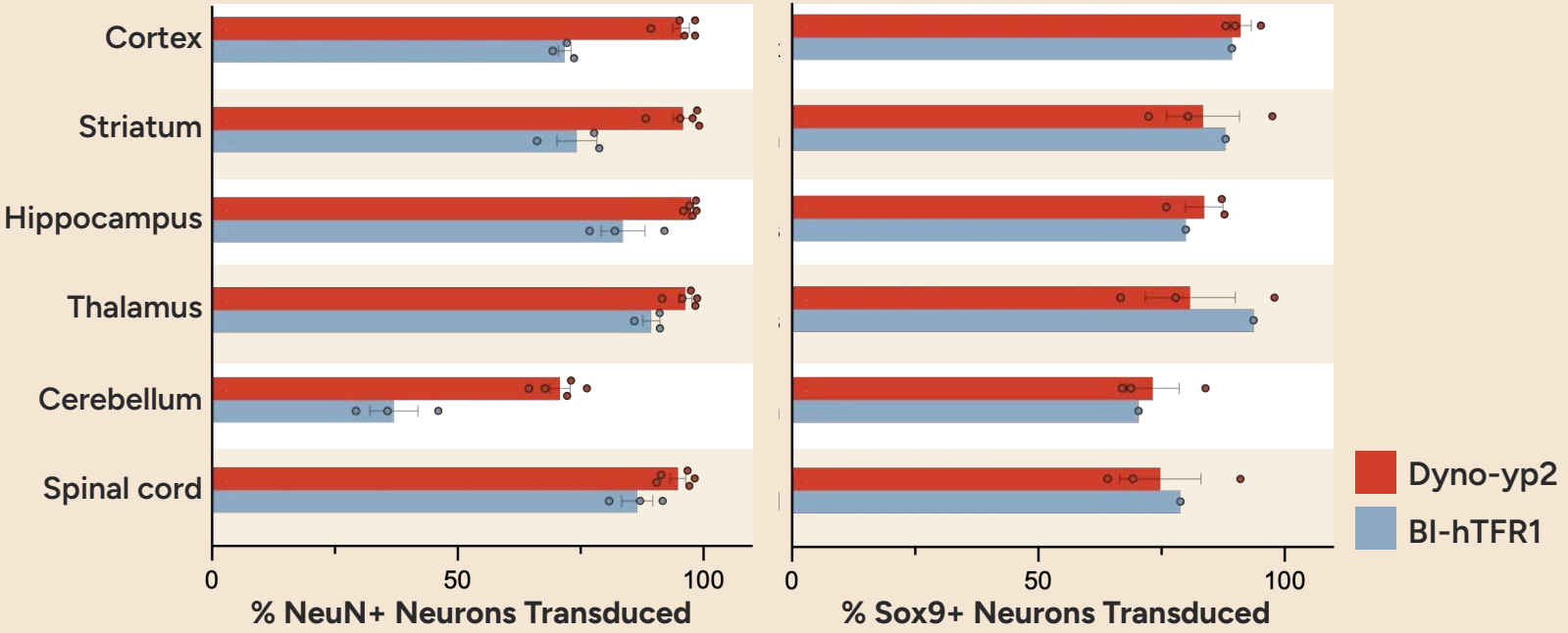
Dyno-yp2 transduces 97% of NeuN+ neurons in the spinal cord



Dyno-yp2 transduces 89% of Sox9+ astrocytes in the brain

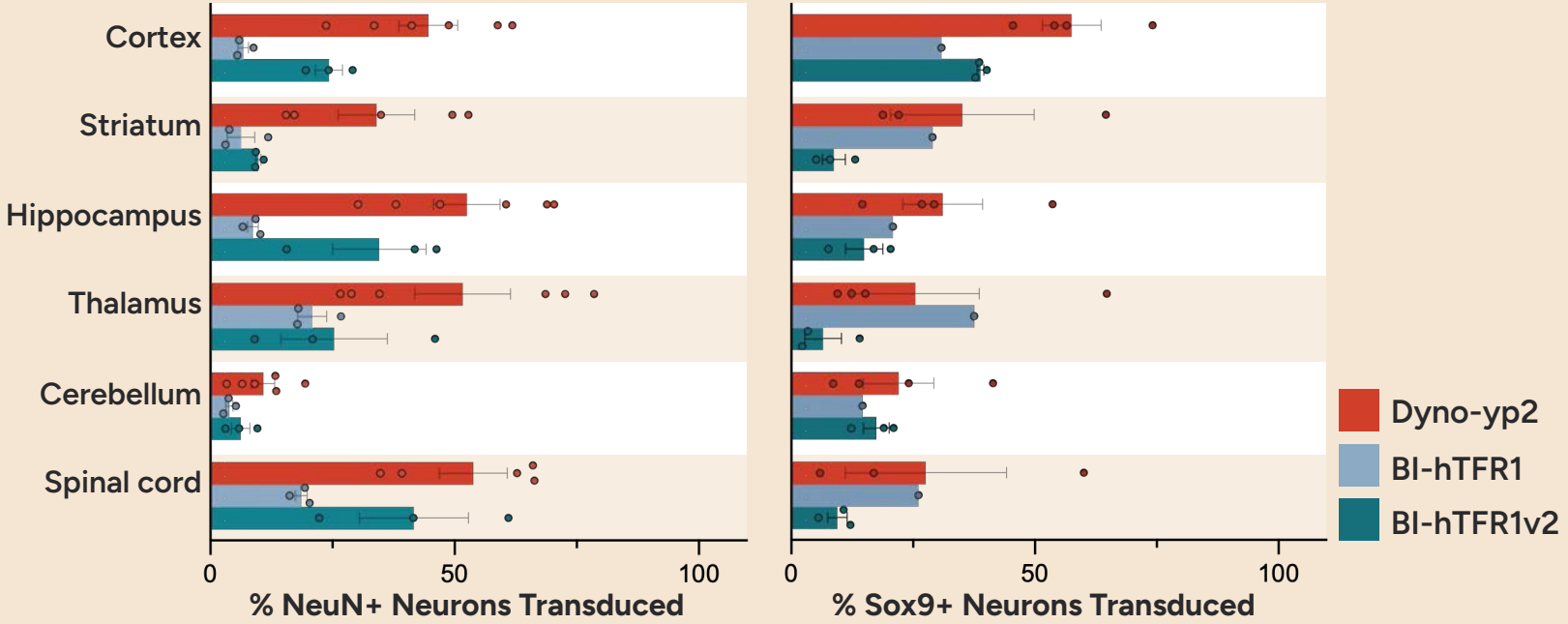


Dyno-yp2 achieves exceptional pan-brain neuronal and astrocyte transduction in humanized TfR1 mice at 2e13 vg/kg

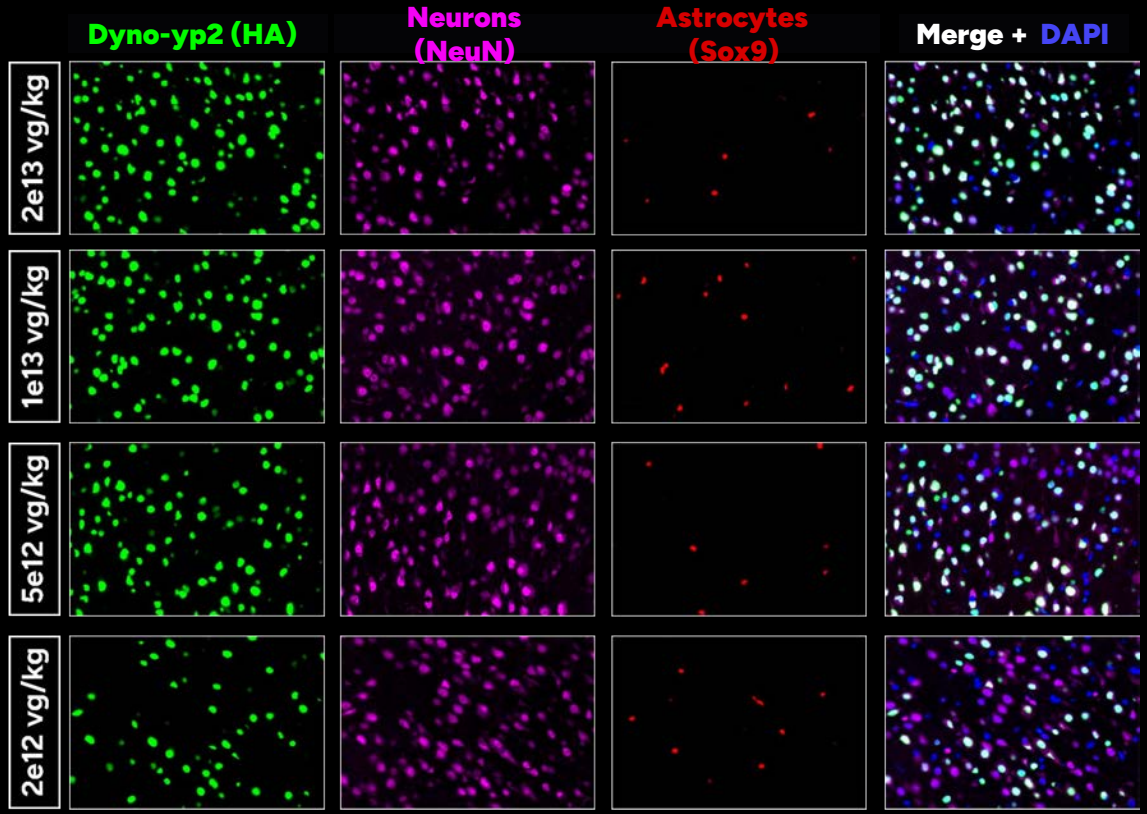


Dyno-yp2 outperforms BI-hTfR1 in every brain region

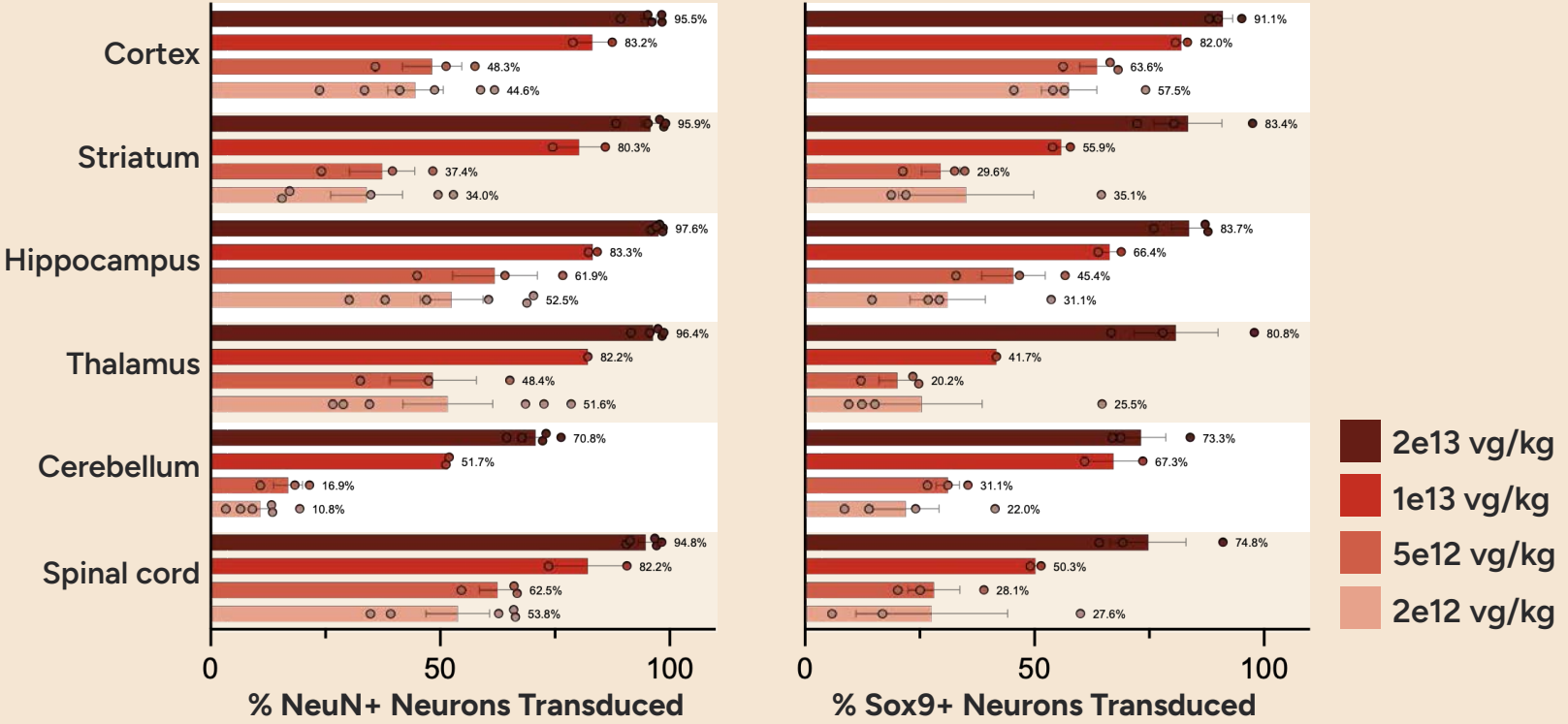
Dyno-yp2 outperforms external capsids in percent cells transduced at 2e12 vg/kg



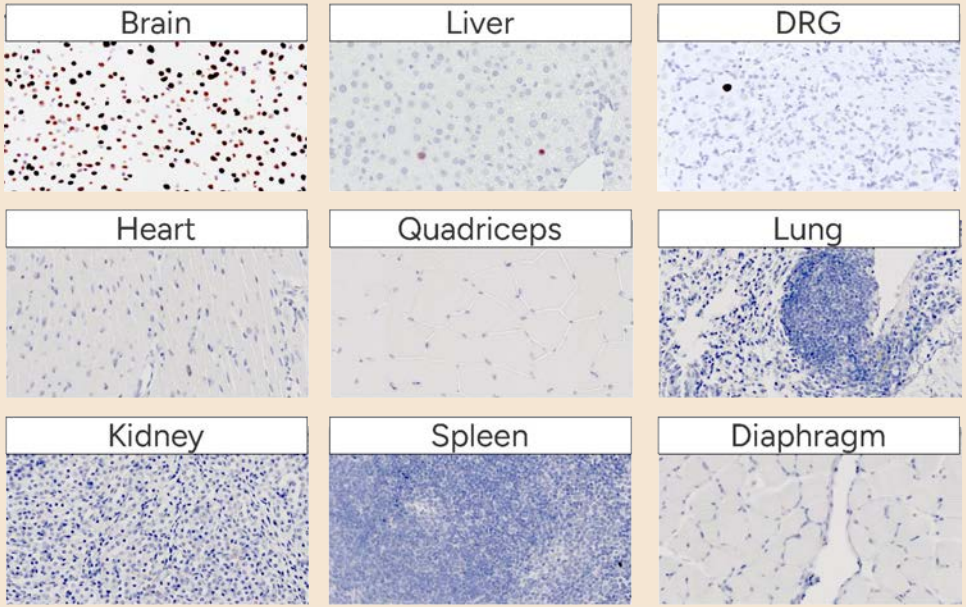
Dose-response of Dyno-yp2 transduction across mouse brain regions and cell types

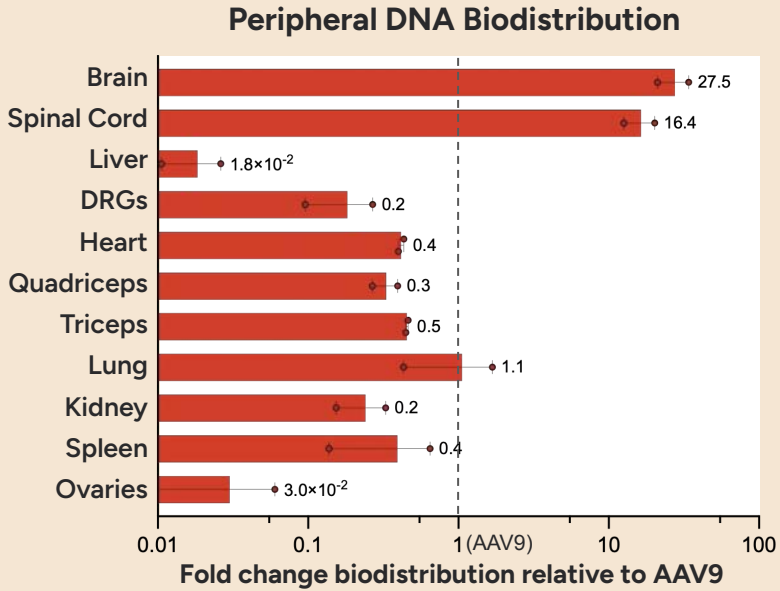


Dose-response of Dyno-yp2 transduction across mouse brain regions and cell types



Dyno-yp2 has minimal targeting to peripheral organs

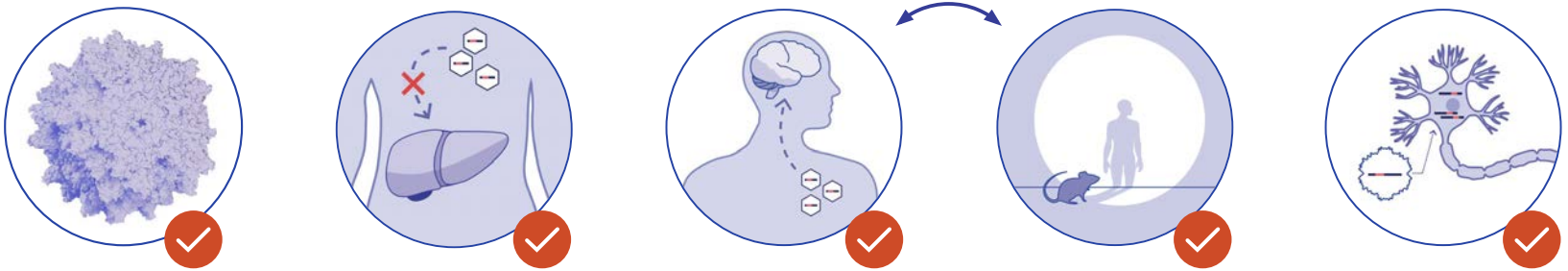




*n=1 animal per group

Dyno-yp2 broadly and efficiently transduces the CNS through a human TfR1-mediated mechanism

Safety | **Translation** | **Efficacy**



Efficient production	Detargeted from the liver	Efficient BBB crossing	Known human mechanism	Broad CNS transduction
Compatible with AAV9-based purification systems	29x liver detargeting compared to AAV9	Engineered for binding human TfR1; known mechanism translatable to humans		93% NeuN+ neurons 82% Sox9+ astrocytes

dyno

DYNO FRONTIERS NETWORK

Access Dyno capsids.

EASY.