Dyno bCap 1 delivery: Cell-type resolved characterization of CNS transduction by intravenously administered AAV capsids in non-human primates

Daniel Bloodgood, Mugdha Deshpande, Aashu Vihani, Barbara Diaz-Rohrer, Lindsey Campion, Sam Chen, Sarah Hilton, Dyno Therapeutics Team, Sam Sinai, Kathy Lin, Jamie Kwasnieski, Patrick McDonel, Adrian Veres, Eric Kelsic

Digital Poster

The Leading Edge of CNS IV Gene Delivery

Engineered by Dyno's AI platform to cross the blood-brain barrier

```
Dyno bCap 1  575 ESYGVVAINHQSAQAQAIVGALQSQGALP 603
      AAV9   575 ESYGQVAINHQSAQAQAQTGWVQNQGILP 603
```

- The Dyno bCap 1 capsid transduces 5-20% of neurons across the CNS after a low-dose IV injection of 1e13 vg/kg in Cyno NHPs.

Field-leading performance for CNS IV delivery

- **100X** brain transduction vs AAV9
- **10X** liver detargeting vs AAV9
- **1X** production vs AAV9

Thoroughly validated in multiple NHP species

- Dyno bCap 1 delivery efficiently crosses the blood-brain barrier in both African Green Monkey (*Chlorocebus sabaeus*) and cynomolgus macaque (*Macaca fascicularis*)

Superiority in head-to-head comparisons

- The Dyno bCap 1 capsid transduces Cyno NHPs more consistently and produces more efficiently than an external engineered capsid tested side-by-side

Inquire about licensing the Dyno bCap 1 capsid for your gene therapy program at bd@dynotx.com

AI-Powered AAV Capsids for Improved NHP Brain Transduction

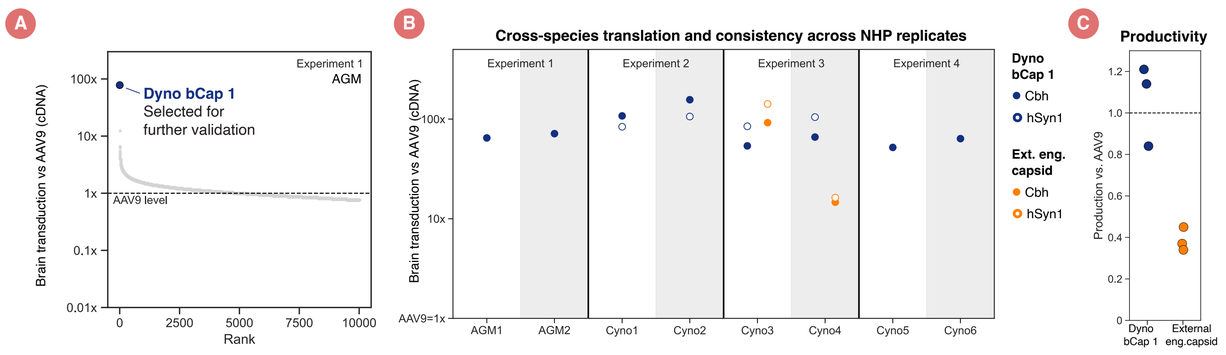

Figure 1. The Dyno bCap 1 capsid was engineered to efficiently cross the BBB and transduce the primate CNS following IV injection.

(A) The Dyno bCap 1 capsid was the top-performer among a library of AI-designed AAV9 variants. (B) Dyno bCap 1 delivery is consistently improved vs AAV9 across African Green Monkey (AGM) and Cynomolgus macaque (Cyno) NHPs. Experiment 3 included a head-to-head comparison to an external engineered capsid (orange) which showed inconsistent delivery performance. (C) In replicate single-capsid productions, Dyno bCap 1 capsid showed production efficiency similar to wild-type AAV9, compared to external capsid with ~40% AAV9 production efficiency.

Broad, Pan-brain delivery using Dyno bCap1 capsid

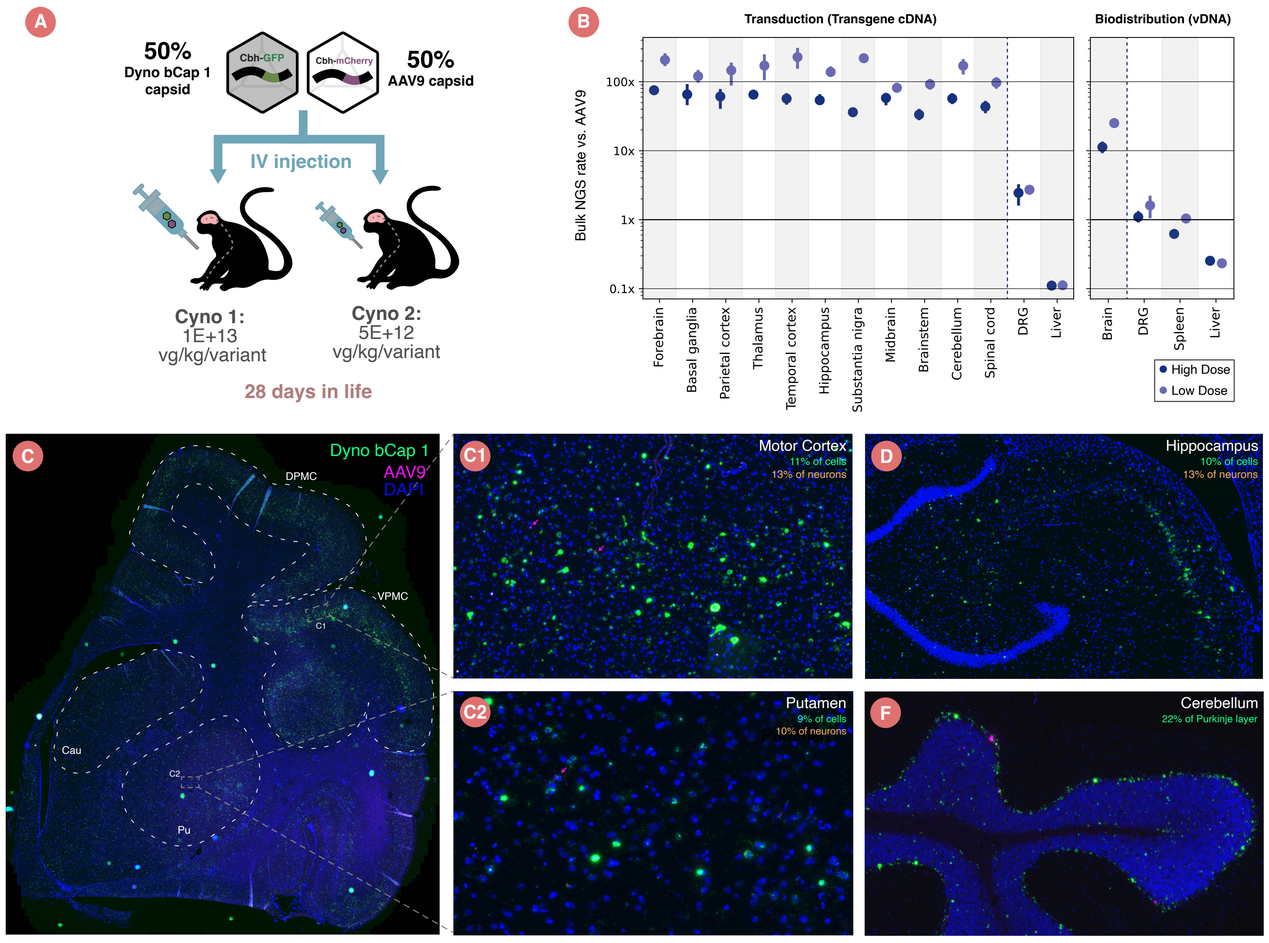

Figure 2. Two-capsid validation study confirms greatly improved transduction with Dyno bCap 1 delivery vs AAV9 in Cyno NHPs.

(A) Two Cynos were dosed intravenously at 1E13 vg/kg per variant (2E13 vg/kg total) or 5E12 vg/kg per variant (1E13 vg/kg total) with a pooled test article containing an equal mixture of Dyno bCap 1 and AAV9. (B) NGS-based measurement shows consistent 100x improvement for Dyno bCap 1 vs AAV9 across CNS regions, including deep brain and spinal cord. Dyno bCap 1 delivery is 10x detargeted from liver vs AAV9, and shows comparable delivery to DRG. (C-G) At a dose of 1E13 vg/kg, Dyno bCap 1 transduces 5-14% of all cells and 5-20% of neurons (Fox3+) across therapeutically-relevant brain regions. (H) Pan-brain transduction quantified from RNAscope. (I) Pan-brain neuronal (Fox3+) transduction quantification from RNAscope.

IV-Delivered Dyno bCap 1 Efficiently Transduces Therapeutically Relevant Neuronal Subpopulations

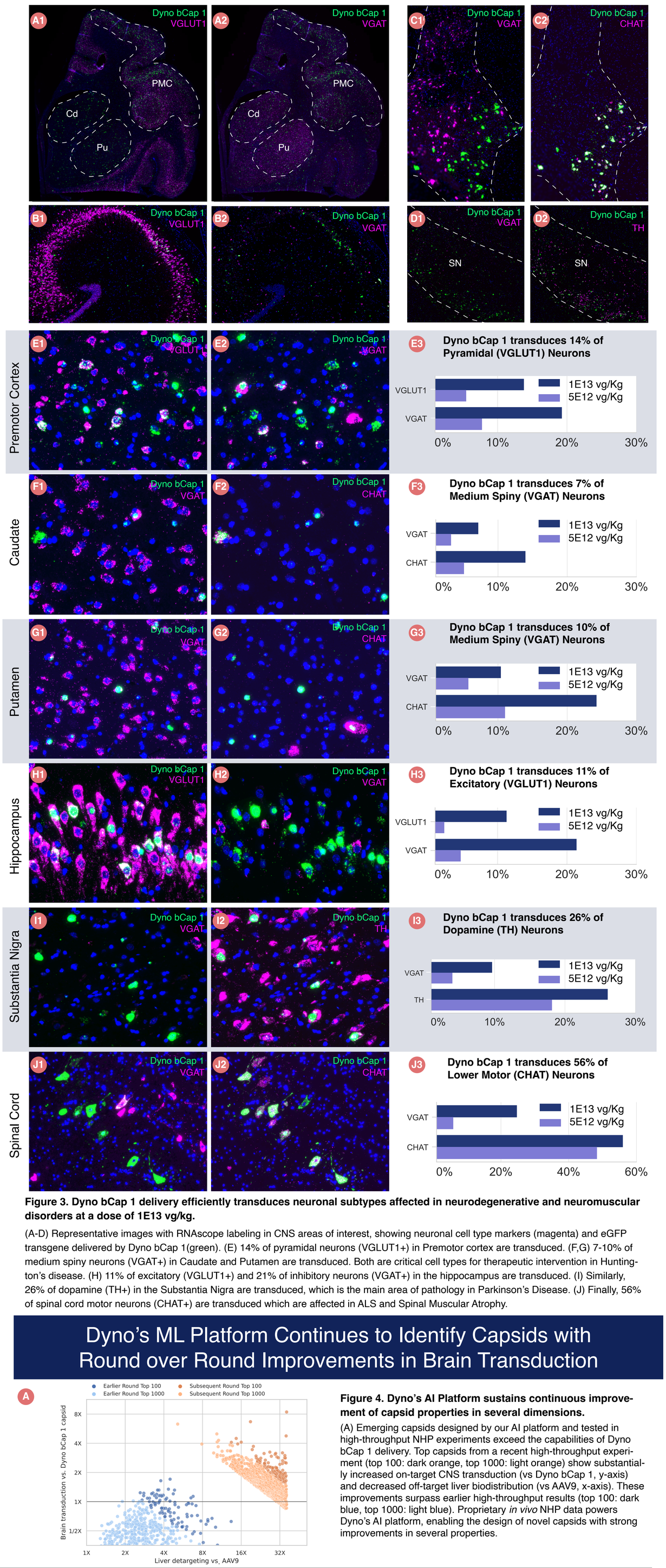

Figure 3. Dyno bCap 1 delivery efficiently transduces neuronal subtypes affected in neurodegenerative and neuromuscular disorders at a dose of 1E13 vg/kg.

(A-D) Representative images with RNAscope labeling in CNS areas of interest, showing neuronal cell type markers (magenta) and eGFP transgene delivered by Dyno bCap 1(green). (E) 14% of pyramidal neurons (VGLUT1+) in Premotor cortex are transduced. (F,G) 7-10% of medium spiny neurons (VGAT+) in Caudate and Putamen are transduced. Both are critical cell types for therapeutic intervention in Huntington's disease. (H) 11% of excitatory (VGLUT1+) and 21% of inhibitory neurons (VGAT+) in the hippocampus are transduced. (I) Similarly, 26% of dopamine (TH+) in the Substantia Nigra are transduced, which is the main area of pathology in Parkinson's Disease. (J) Finally, 56% of spinal cord motor neurons (CHAT+) are transduced which are affected in ALS and Spinal Muscular Atrophy.

Dyno's ML Platform Continues to Identify Capsids with Round over Round Improvements in Brain Transduction

Figure 4. Dyno's AI Platform sustains continuous improvement of capsid properties in several dimensions.

(A) Emerging capsids designed by our AI platform and tested in high-throughput NHP experiments exceed the capabilities of Dyno bCap 1 delivery. Top capsids from a recent high-throughput experiment (top 100: dark orange, top 1000: light orange) show substantially increased on-target CNS transduction (vs Dyno bCap 1, y-axis) and decreased off-target liver biodistribution (vs AAV9, x-axis). These improvements surpass earlier high-throughput results (top 100: dark blue, top 1000: light blue). Proprietary *in vivo* NHP data powers Dyno's AI platform, enabling the design of novel capsids with strong improvements in several properties.

Dyno Therapeutics, Inc. Watertown, Massachusetts USA www.dynotx.com bd@dynotx.com