

The background of the slide is a scenic landscape. In the center, a large, snow-capped mountain peak rises above a valley. The valley is filled with a winding river and lush green fields. The foreground is dominated by a dense forest of evergreen trees. The sky is a clear, light blue. The overall scene is bright and vibrant.

Applying Artificial Intelligence to Multi-Property Optimization of AAV Capsids for Neuronal Gene Delivery

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Dyno Therapeutics

ASGCT 2024

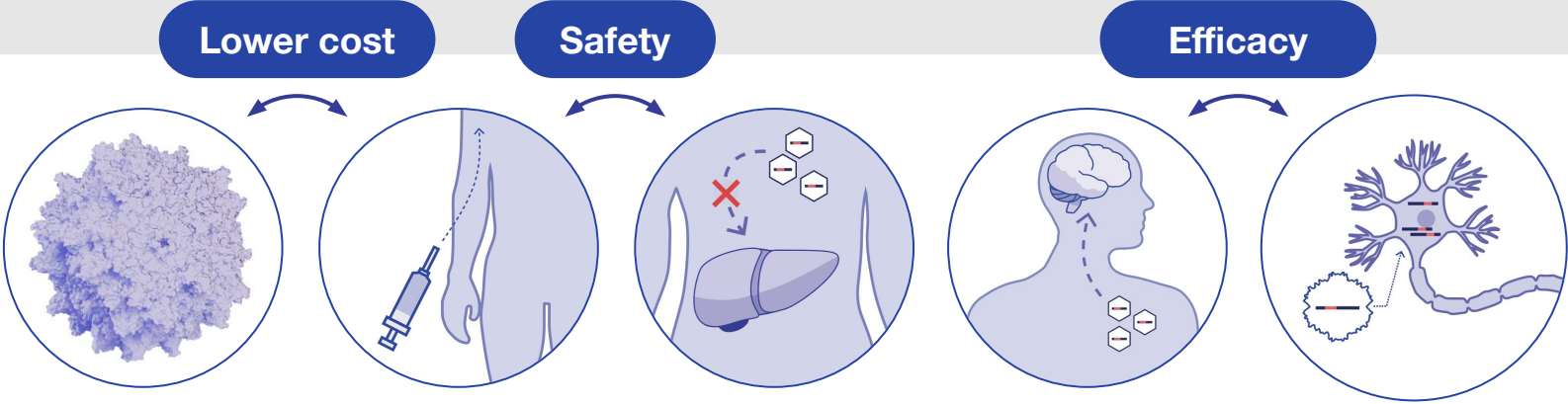
Disclosures

I receive salary and equity from Dyno Therapeutics.

MUCOPOLYSACCHARIDOSES PARKINSON'S DISEASE AMYOTROPHIC LAT
ERAL SCLEROSIS SCHWANNOMATOSIS ANGELMAN SYNDROME FRIEDRE
ICH'S ATAXIA HUNTINGTON'S DISEASE TAY-SACHS DISEASE ASPARTOAG
YLASE DEFICIENCY CANAVAN DISEASE RETT SYNDROME DRAVET SYN
DROME FRAGILE X SYNDROME SPINOCEREBELLAR ATAXIAS GAUCHE
DISEASE SPINAL MUSCULAR ATROPHY BATTEN DISEASE CHARCOT-MA
RIE-TOOTH DISEASE X-LINKED ADRENOLEUKODYSTROPHY PHELAN-MCDE
MID SYNDROME ALZHEIMER'S DISEASE ADRENOMYELONEUROPATHY
FRONTOTEMPORAL DEMENTIA KRABBE DISEASE METACHROMATIC LEUKO
DYSTROPHY CHANNELOPATHIES ADULT POLYGLUCOSAN BODY DISEAS
NEUROFIBROMATOSIS AUTOSOMAL DOMINANT LEUKODYSTROPHY WITI
AUTONOMIC DISEASE PROGRESSIVE SUPRANUCLEAR PALSY GIAN
AXONAL NEUROPATHY AICARDI-GOUTIERES SYNDROME NEURODEGENER



Better delivery means....



Efficient production

Low dose and non-invasive administration

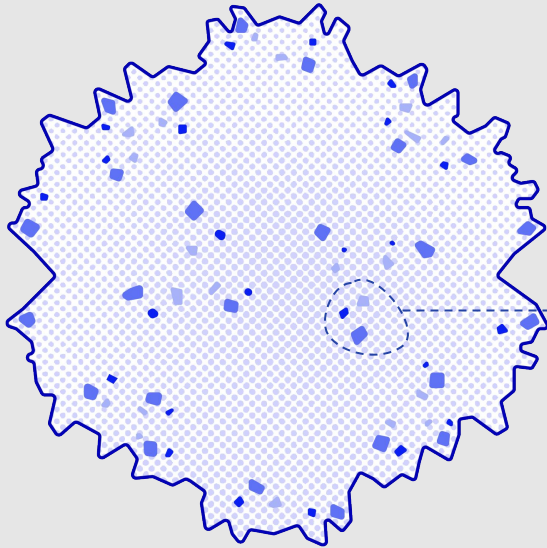
Detargeted from liver

Efficient BBB crossing

Broad neuronal transduction



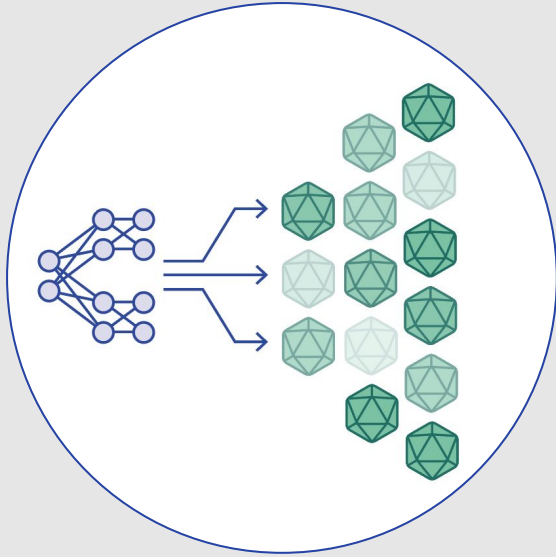
AAV capsid: a ~735 letter search problem



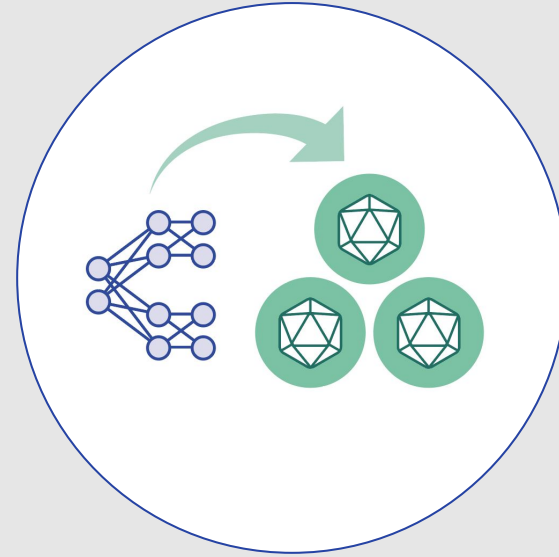
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AI helps us solve this problem faster



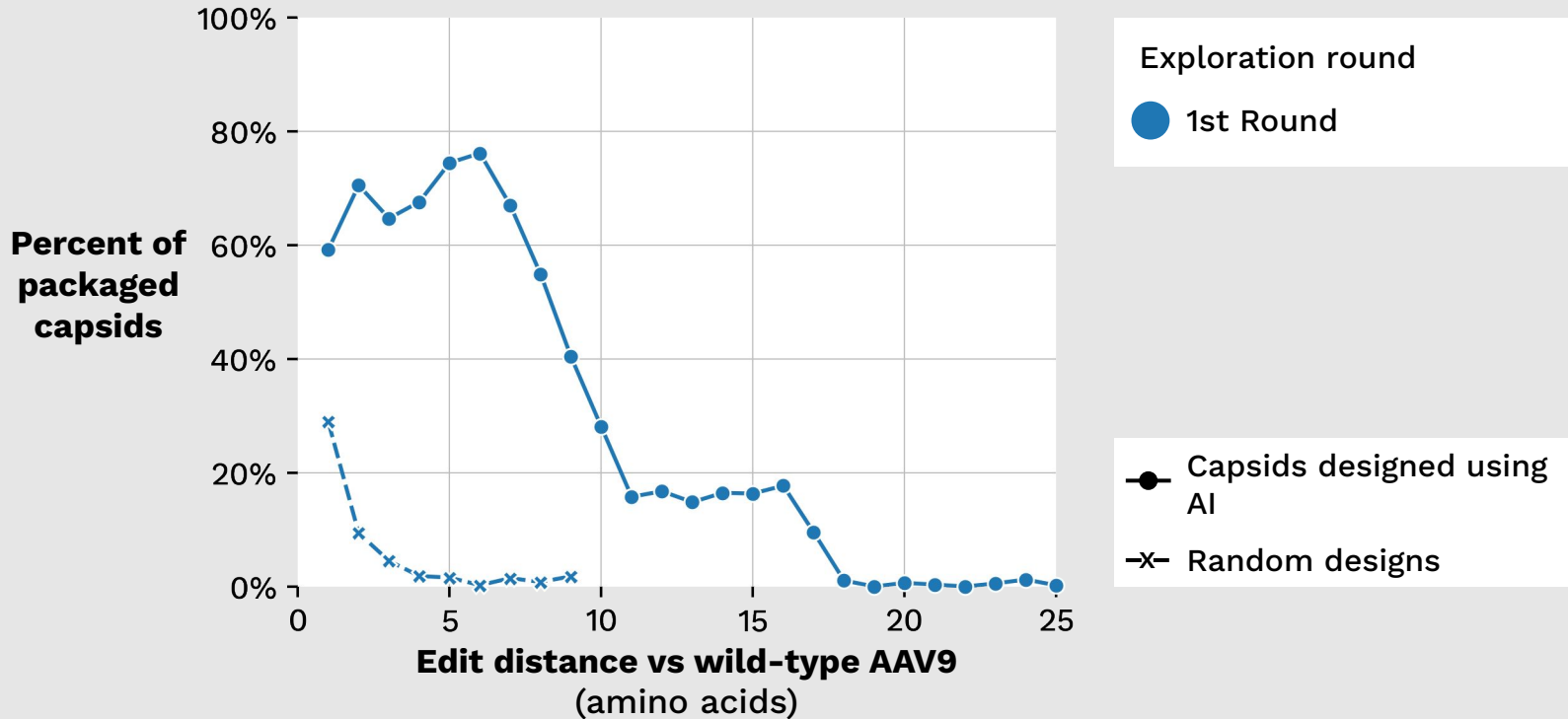
Powering Exploration rounds



LEAPSM Technology



Using AI design, we preserve capsid packaging during deep exploration of the AAV sequence space



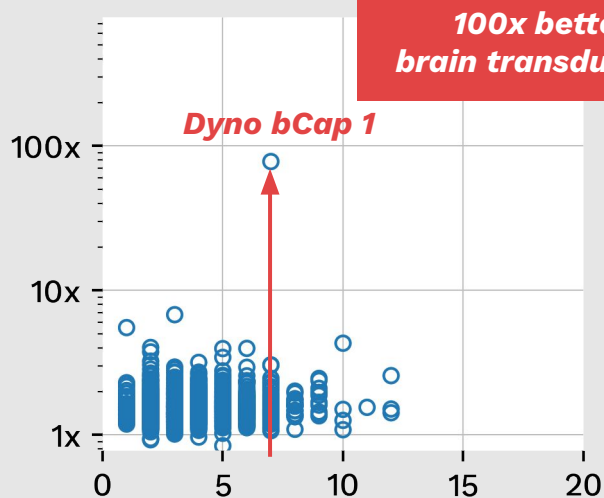
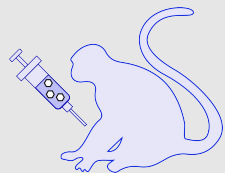
AI design simultaneously improves NHP brain transduction and liver detargeting

1st Round

○ Top 100

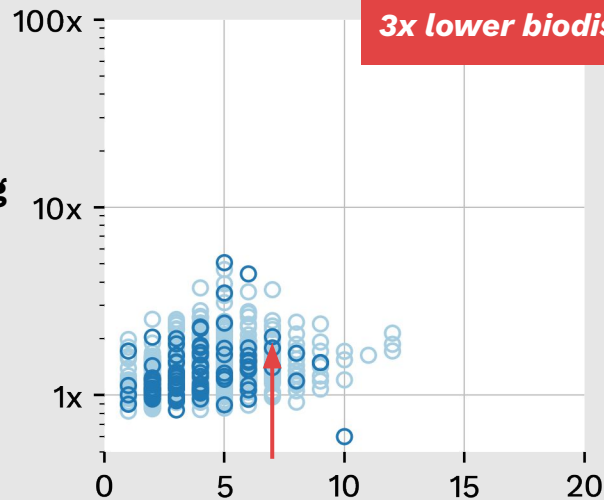
○ Top 1000

Brain
transduction
vs AAV9



Round includes >100k
capsids, top are shown

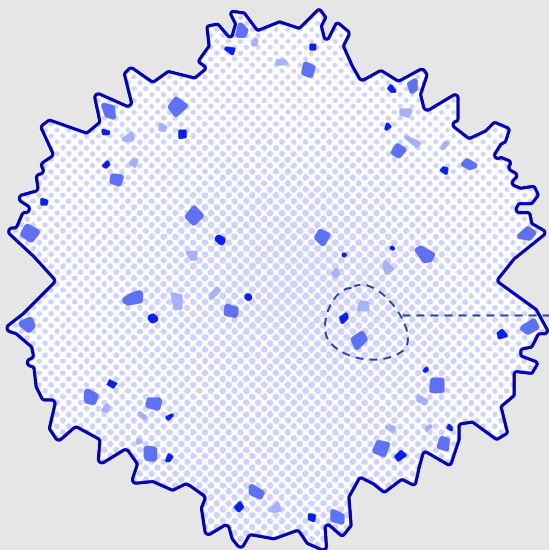
Liver
detargeting
vs AAV9



Edit distance vs AAV9
(# of changed amino acids)

Same capsids shown
for both properties

AI design allows exploration and optimization across the full AAV Cap sequence

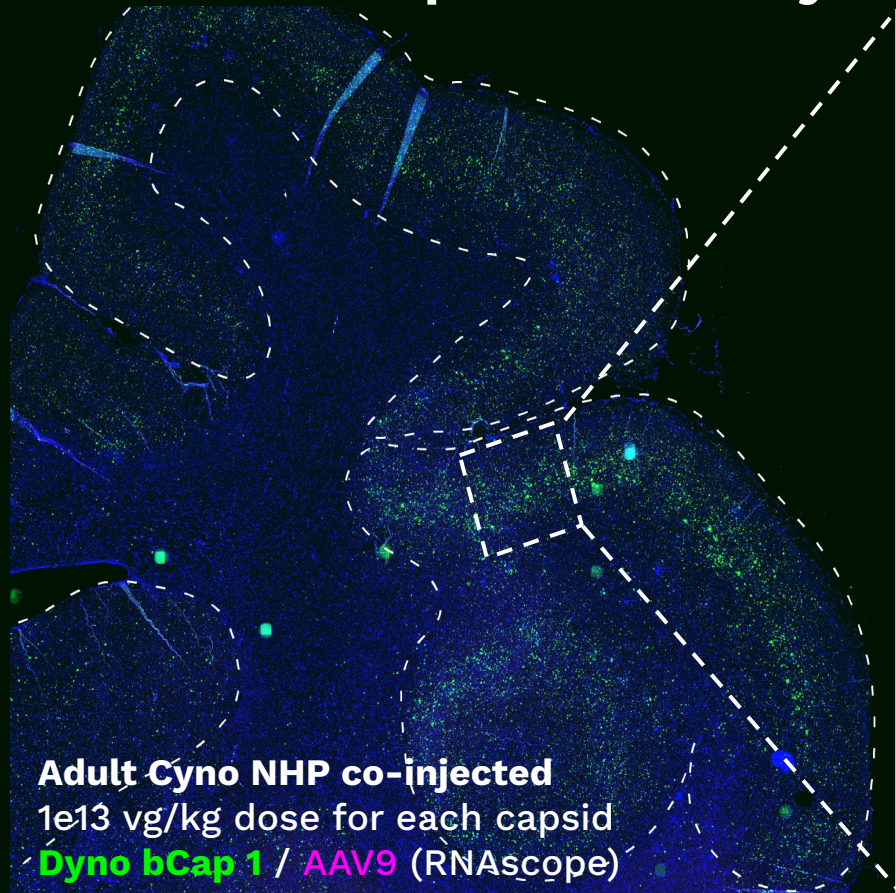


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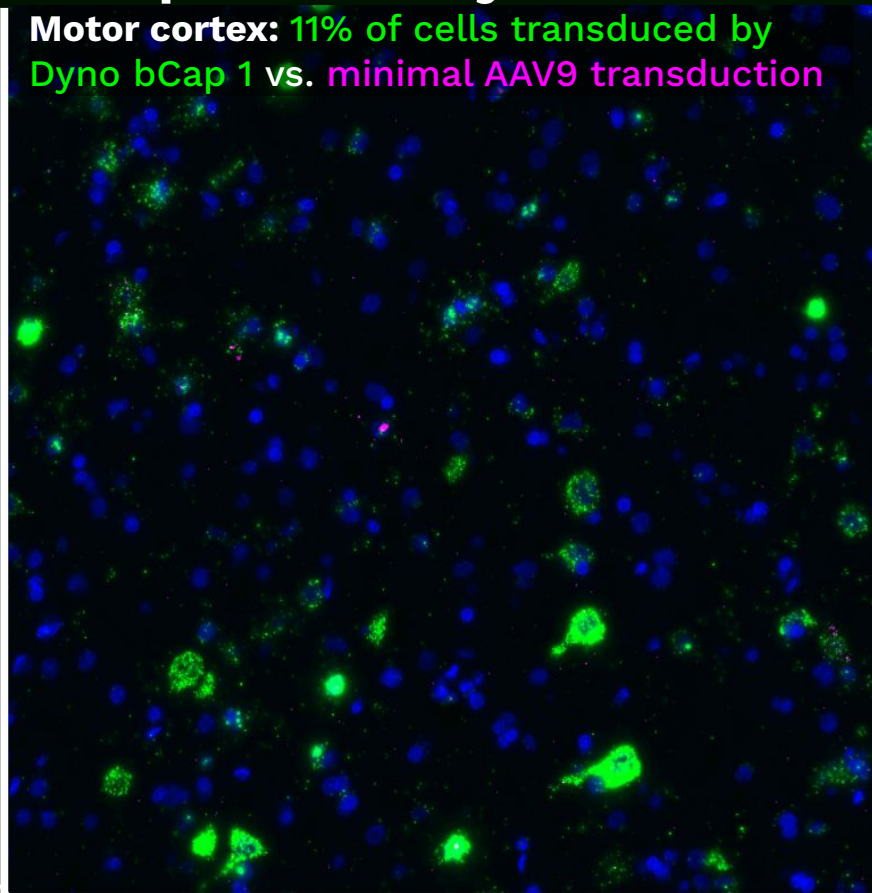
Dyno bCap 1 sequence



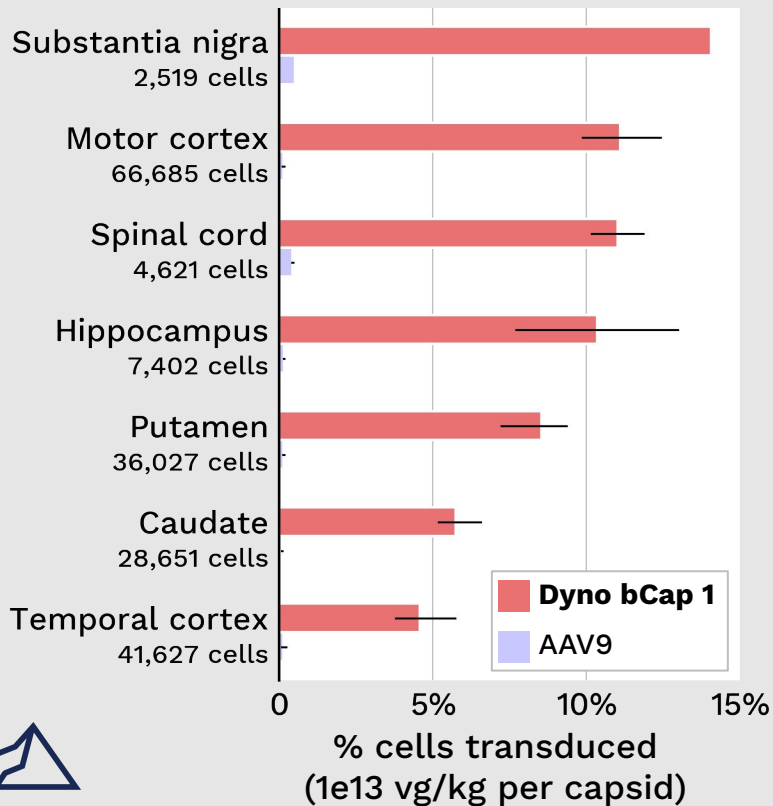
In two-capsid validation study, histology confirms pan-brain Dyno bCap 1 delivery



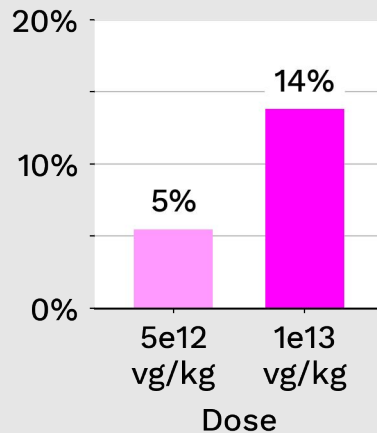
Motor cortex: 11% of cells transduced by
Dyno bCap 1 vs. minimal AAV9 transduction



Dyno bCap 1 delivery is pan-brain and reaches clinically relevant neuronal populations

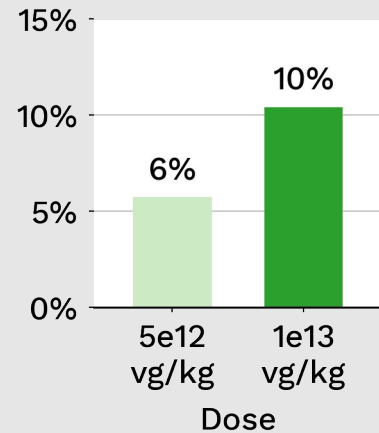


% transduced upper motor neurons (VGLUT1+)



24551 43560
Total counted VGLUT1+ cells

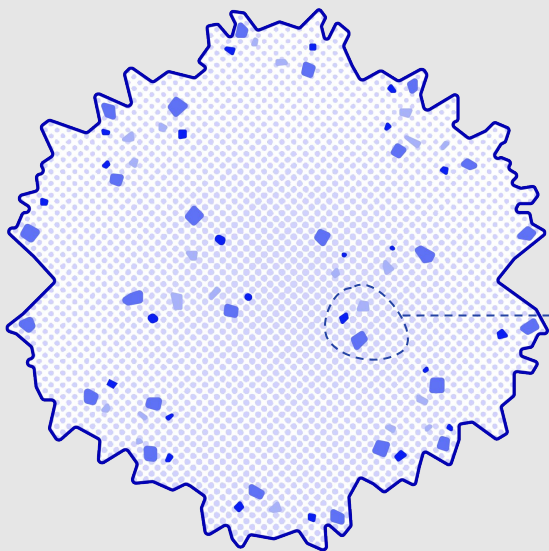
% transduced medium spiny neurons, putamen (VGAT+)



21957 30255
Total counted VGAT+ cells



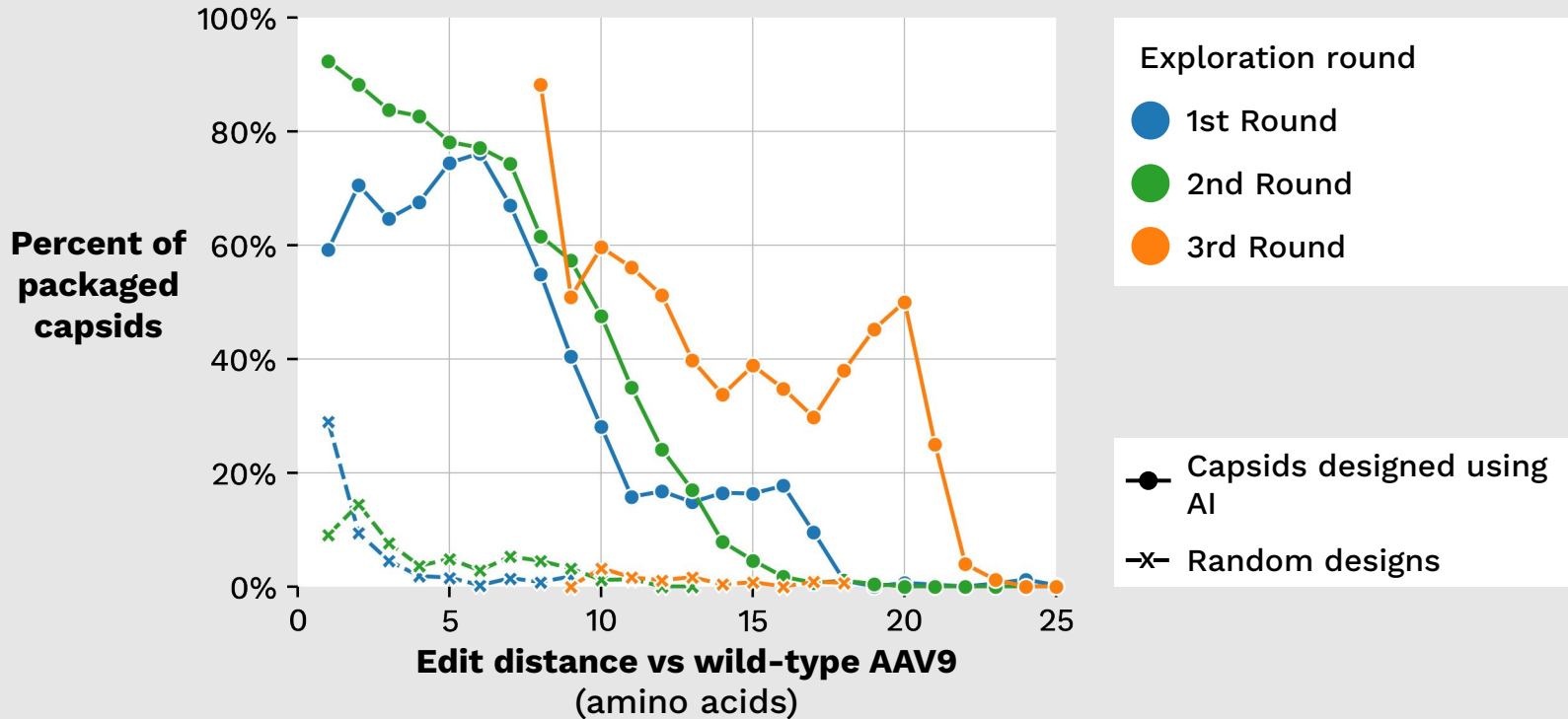
We built on what we learned from our Dyno bCap 1 capsid in subsequent Exploration rounds



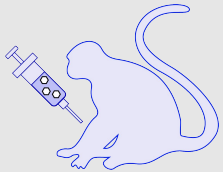
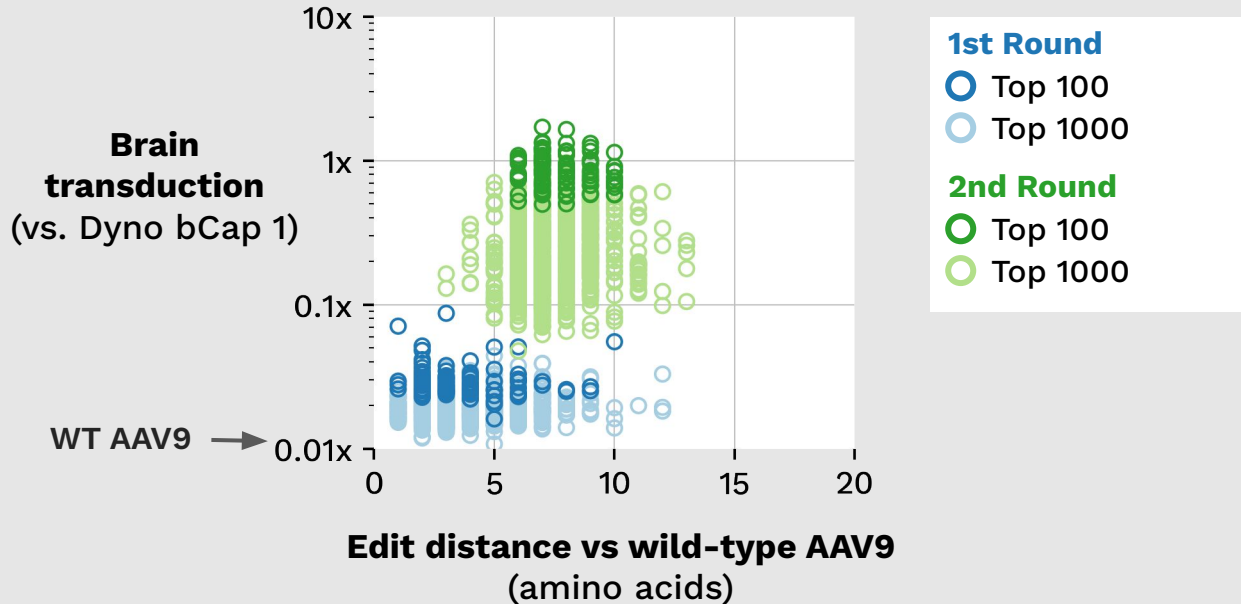
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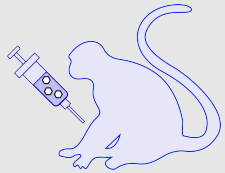
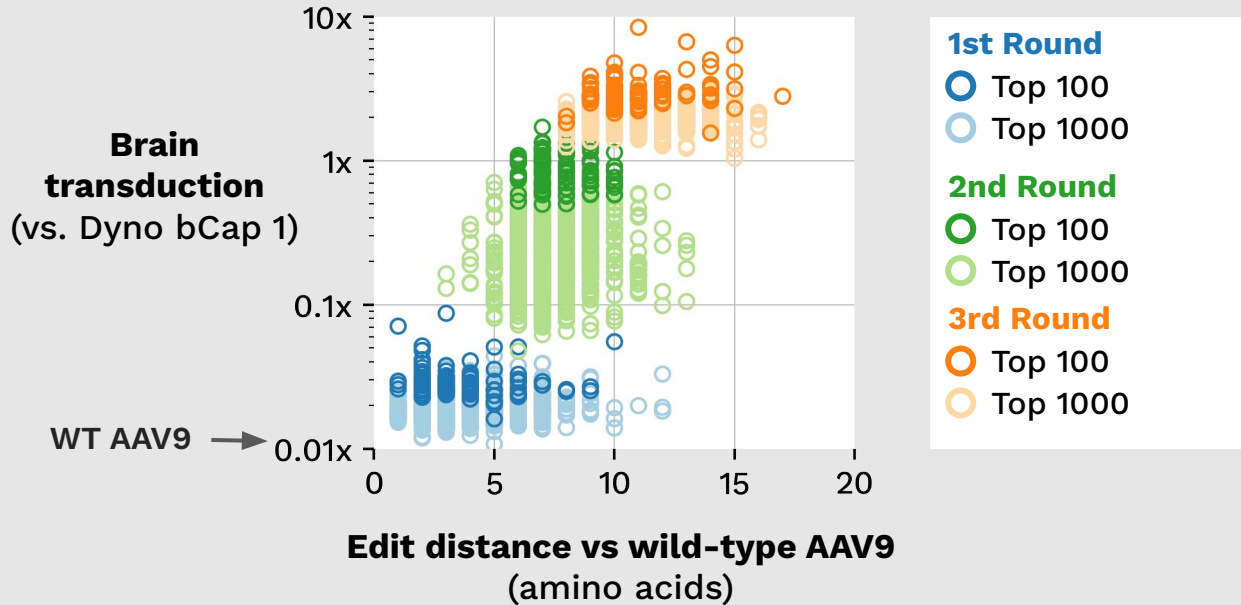
We achieved >40% packaging rates even while changing 20 amino acid positions



Using AI design in successive rounds, we further improved brain transduction through deeper exploration of the sequence space

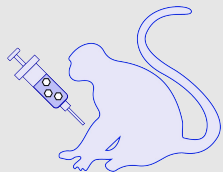
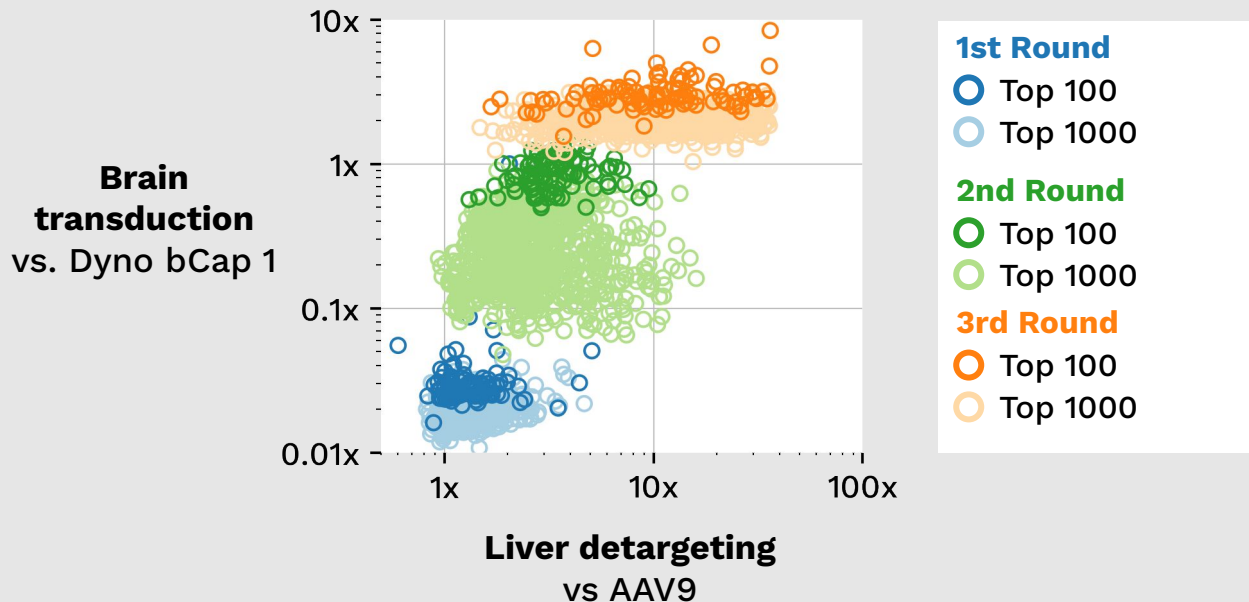


Using AI design in successive rounds, we further improved brain transduction through deeper exploration of the sequence space

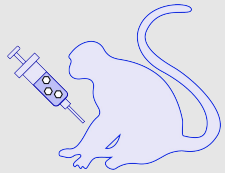
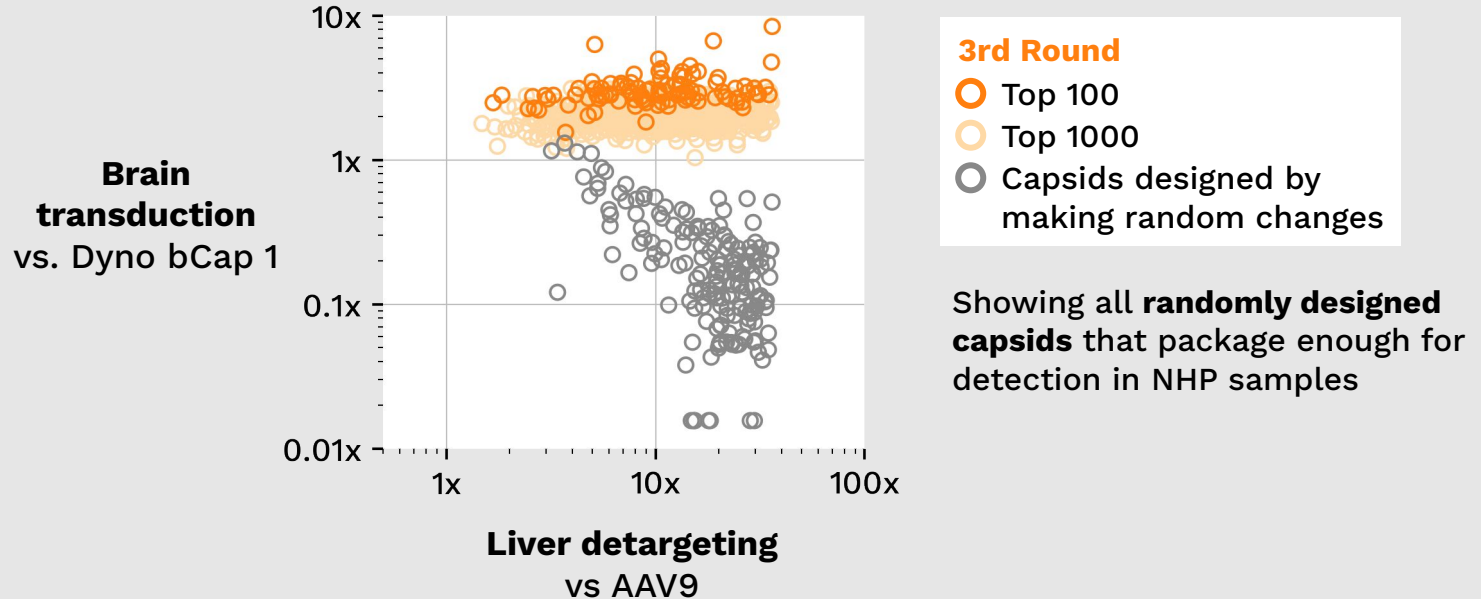


We achieved round-over-round improvement in multiple *in vivo* NHP properties

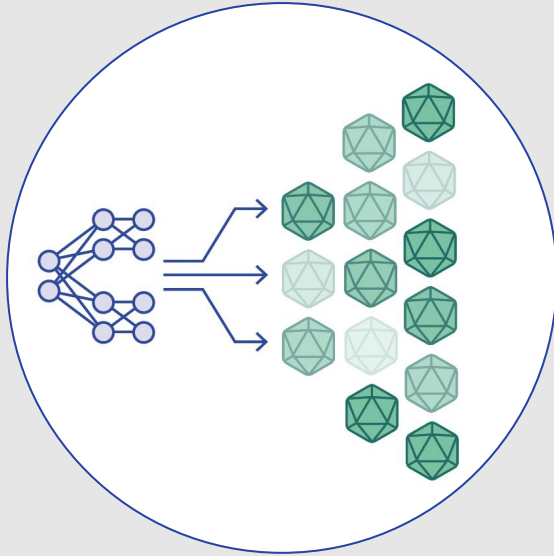
Up to 8x higher brain transduction vs Dyno bCap 1
with 30x liver detargeting vs AAV9



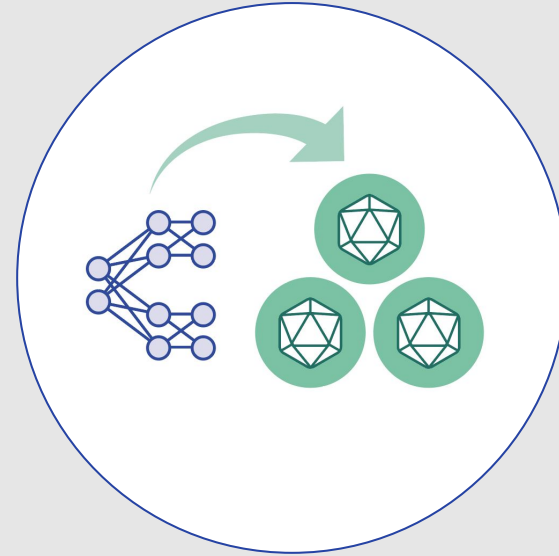
Improving brain transduction requires intentional design, making random changes is not enough



AI helps us go even faster with LEAP



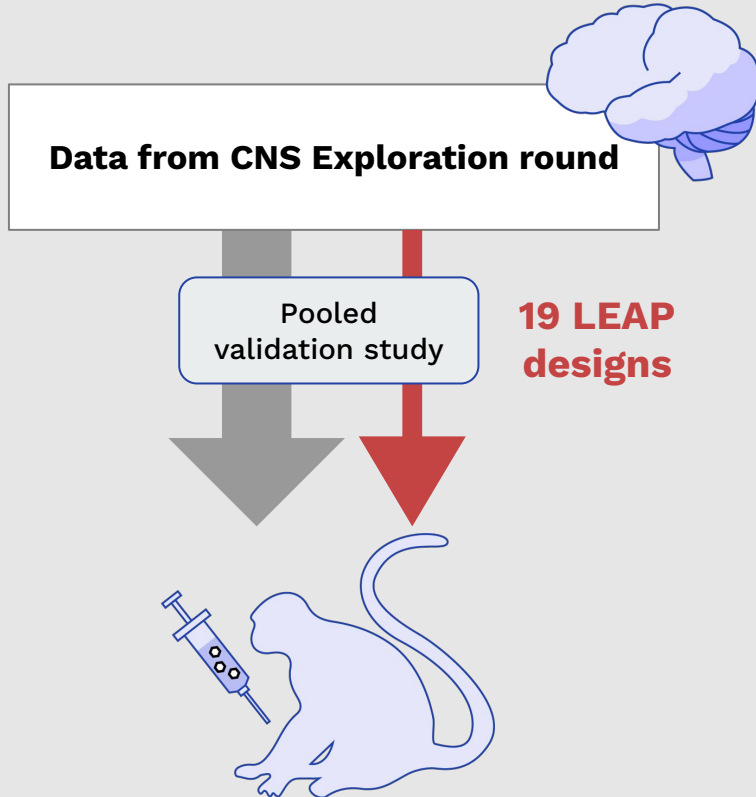
Powering Exploration rounds



LEAP Technology



Low-shot Efficient Accelerated Performance (LEAP)



Head-to-head comparison

- Top Exploration round capsids
- New capsids, rationally designed using Exploration round
- **New capsids, designed using LEAP trained on Exploration round**

Pooled validation design

- IV co-injection
- 2 adult Cyno NHPs
- 28 day in-life period
- 1.5e13 vg/kg dose for total pool

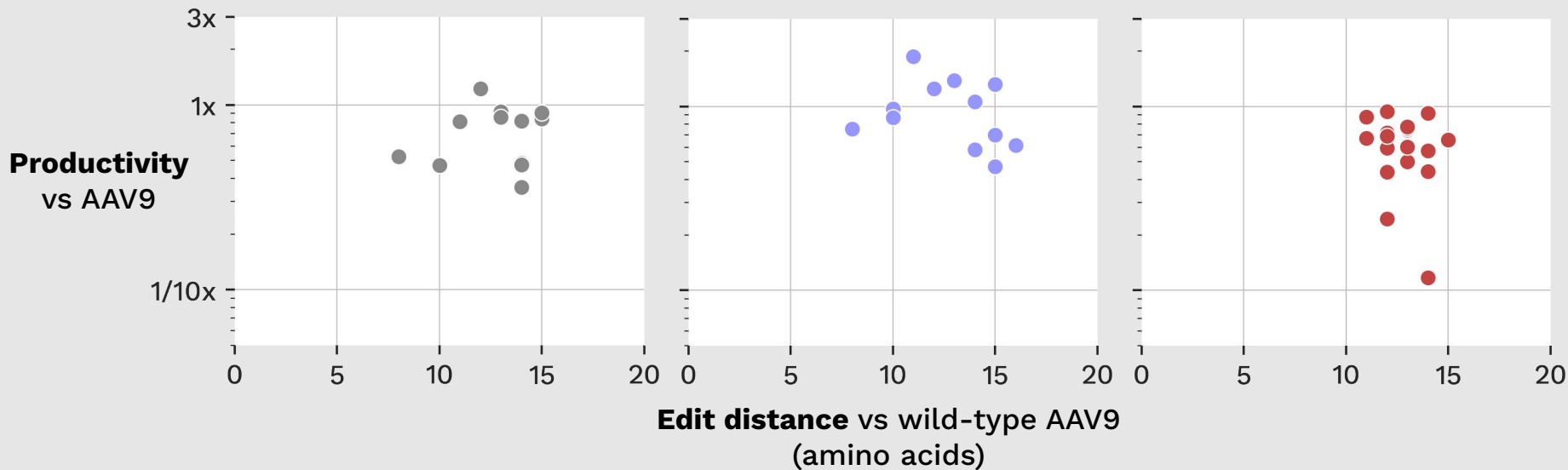


>90% of capsids designed using LEAP successfully package, even with 10-15 edits compared to WT AAV9

Capsids designed previously,
selected from Exploration
round data

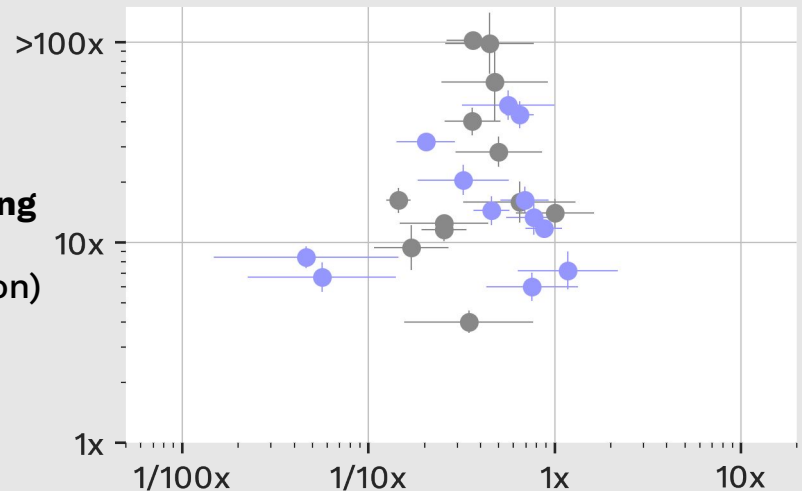
New capsids,
rationally designed using
Exploration round data

New capsids,
designed using LEAP trained
on Exploration round data



Liver detargeting
vs AAV9
(1/biodistribution)

Transduction and
biodistribution measured by
counting barcodes with NGS

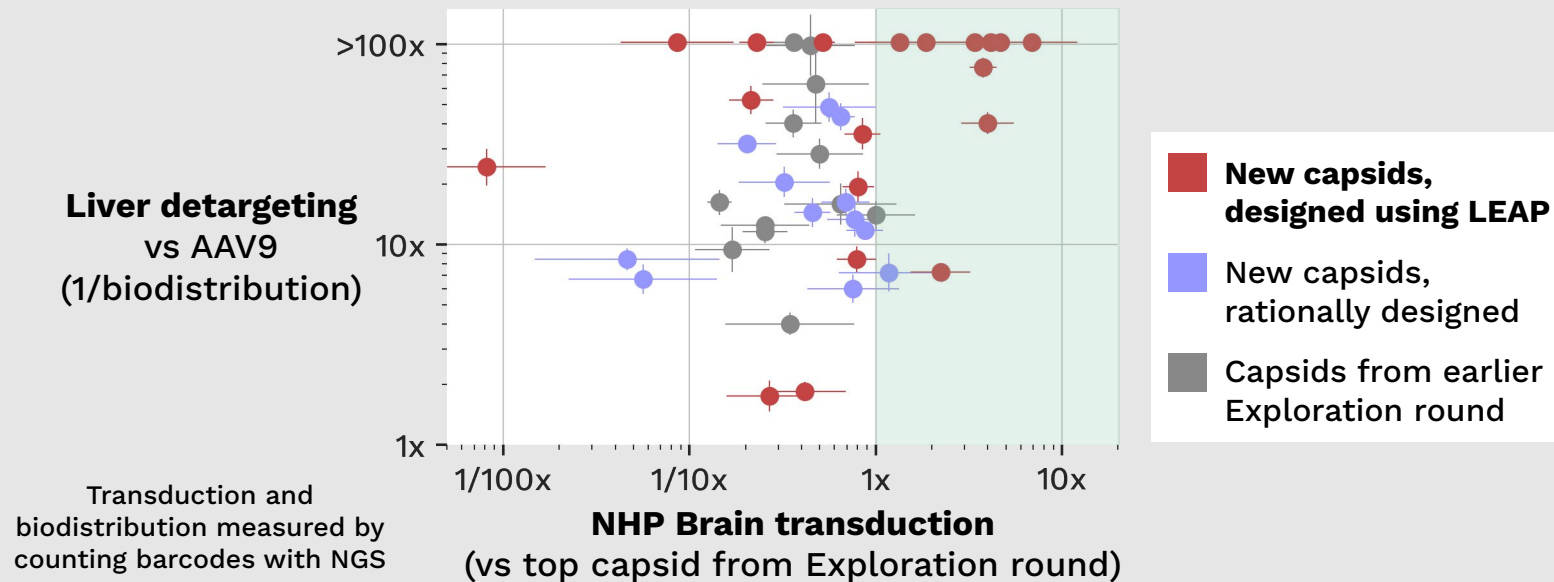


NHP Brain transduction
(vs top capsid from Exploration round)

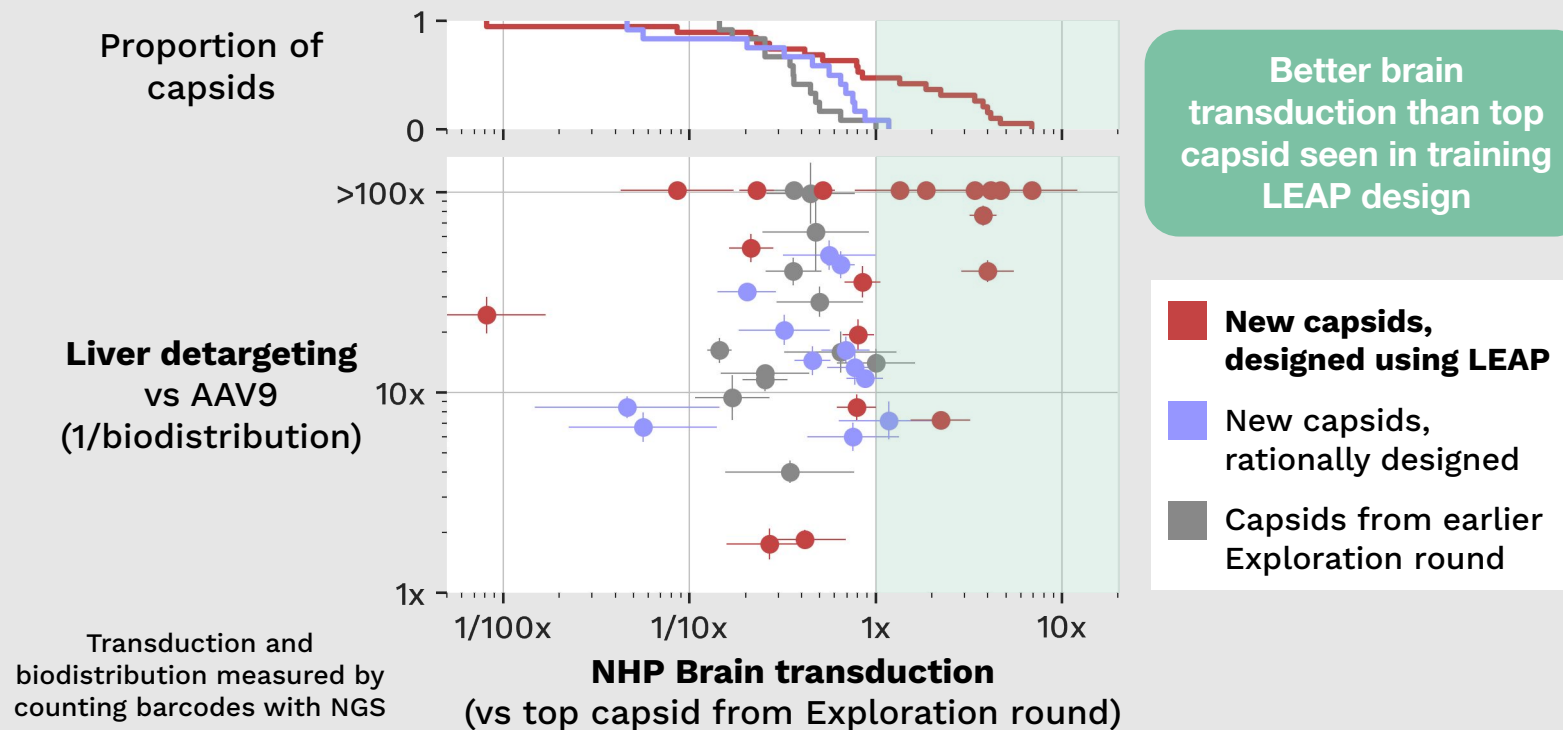
- New capsids, rationally designed
- Capsids from earlier Exploration round



50% of LEAP capsids transduce the NHP brain better than the best capsid from the earlier Exploration round

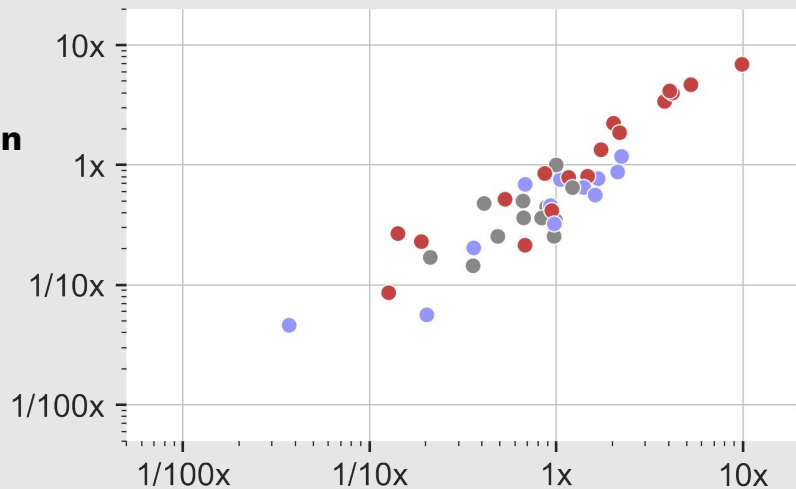


50% of LEAP capsids transduce the NHP brain better than the best capsid from the earlier Exploration round



Single-nuclei RNA sequencing confirms capsids designed using LEAP transduce neurons more effectively

**NHP neuronal transduction
measured by snRNA-seq**
(vs top capsid from
Exploration round)

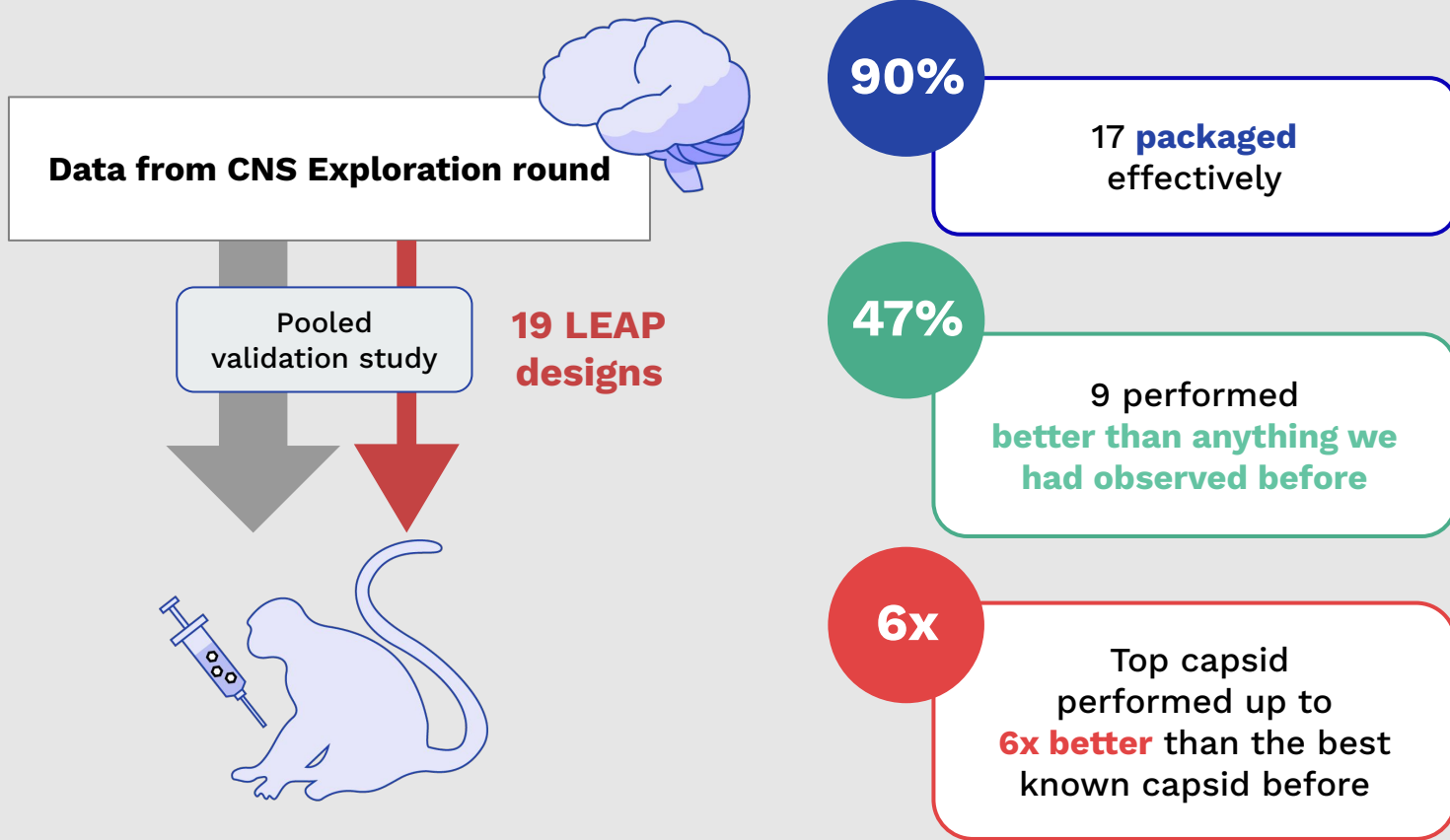


- New capsids, designed using LEAP
- New capsids, rationally designed
- Capsids from earlier Exploration round

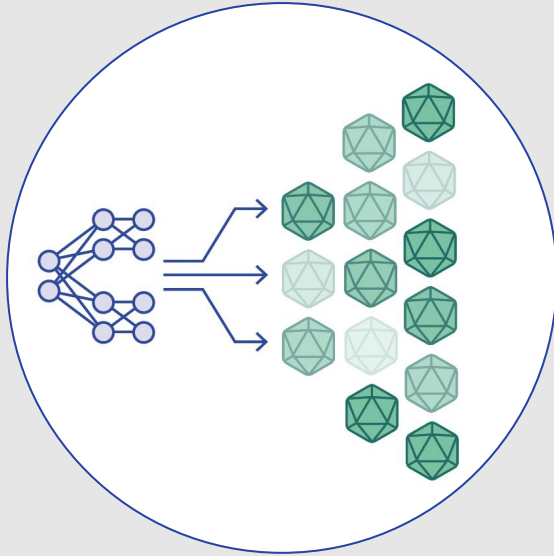


**NHP Brain transduction,
measured by bulk NGS**
(vs top capsid from Exploration round)

Low-shot Efficient Accelerated Performance (LEAP)

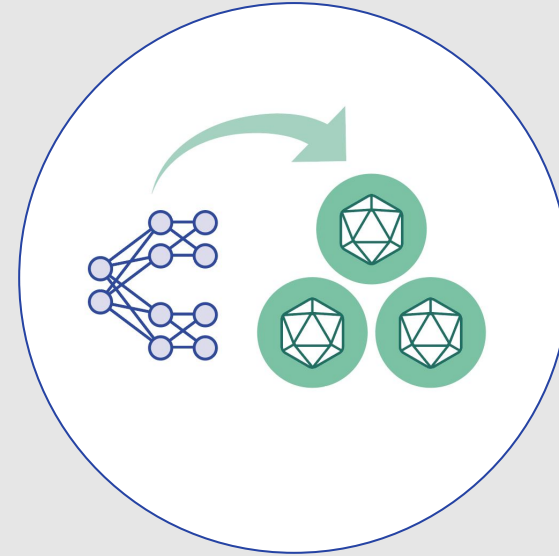


AI helps us make CNS delivery a reality sooner



Powering Exploration rounds

- Exploring the AAV sequence space
- Multi-property optimization
- Round-over-round improvement



LEAP Technology

- Design capsids directly for validation using Low-shot Efficient Accelerated Performance (LEAP) technology



Thank
you!

