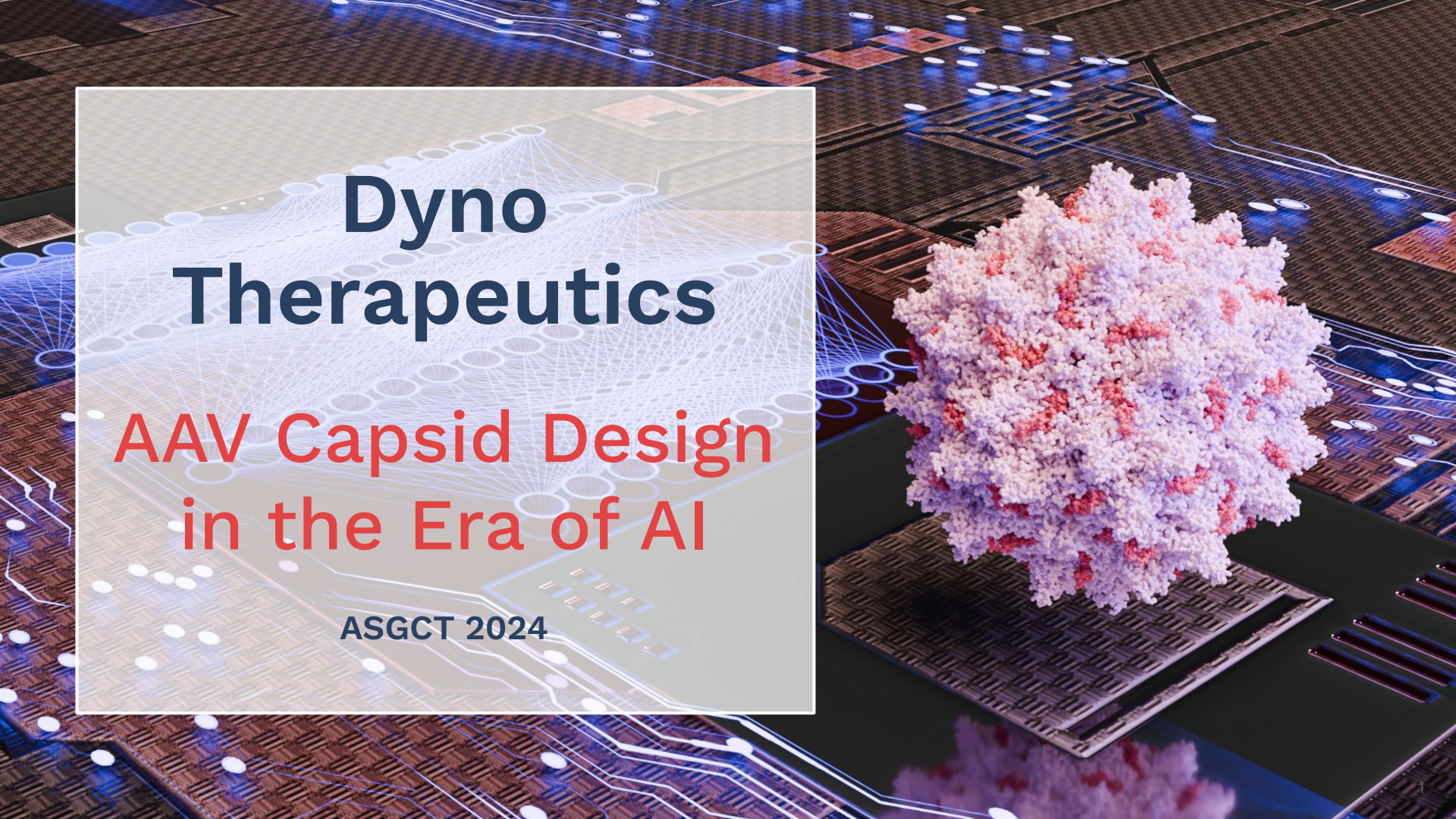
Dyno Therapeutics

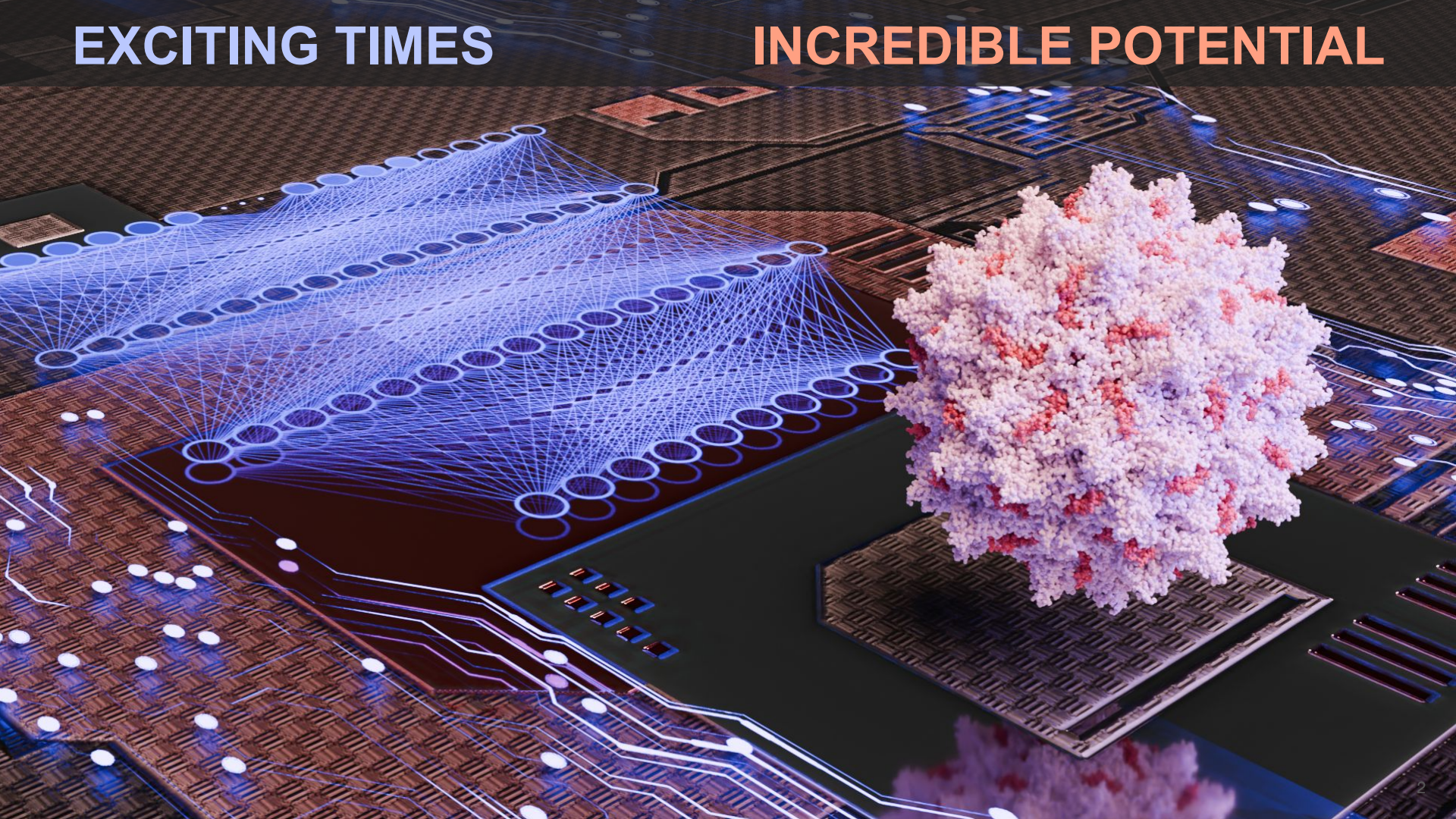
AAV Capsid Design in the Era of AI

ASGCT 2024



EXCITING TIMES

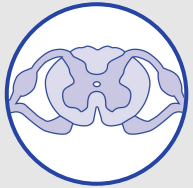
INCREDIBLE POTENTIAL



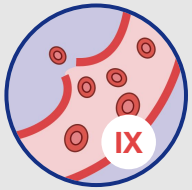
Progress worth celebrating

LUXTURNA
December 2017

ZOLGENSMA
May 2019

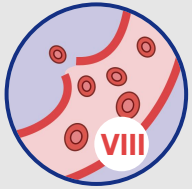


HEMGENIX
November 2022

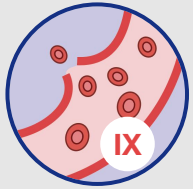


ELEVIDYS
June 2023

ROCTAVIAN
June 2023



BEQVEZ
April 2024

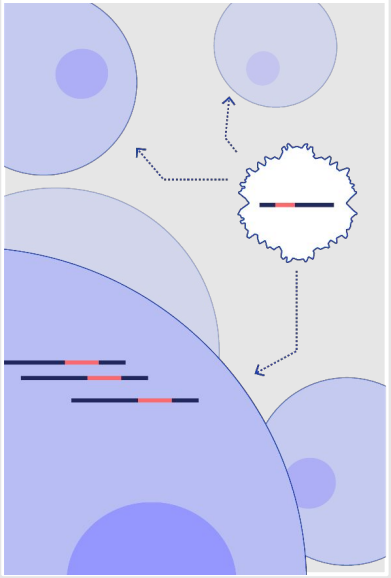


DELIVERY

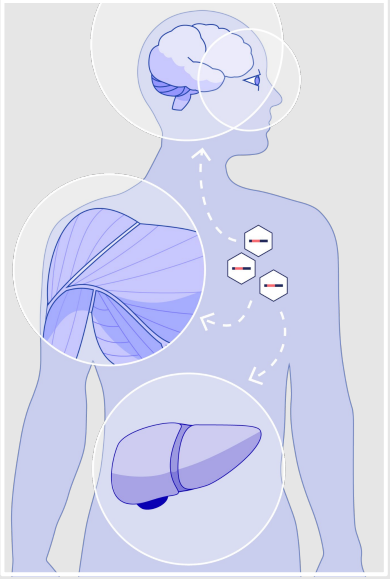
our shared challenge

Dyno’s goal is solving in vivo gene delivery

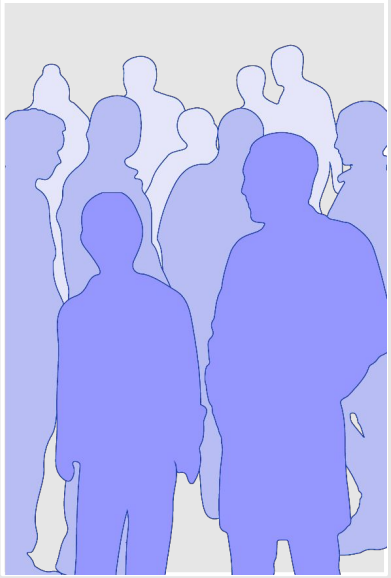
Every cell



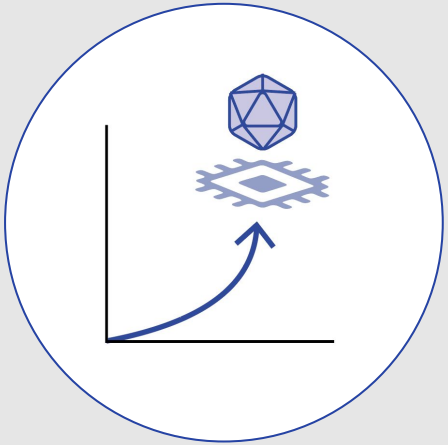
Every organ



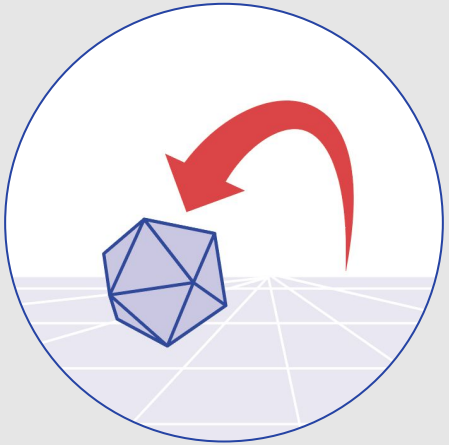
Every patient



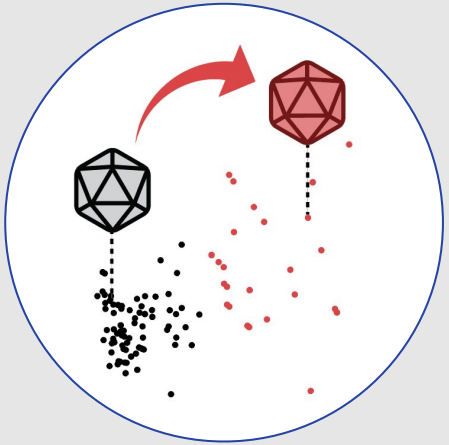
How AI can help



Exponential change

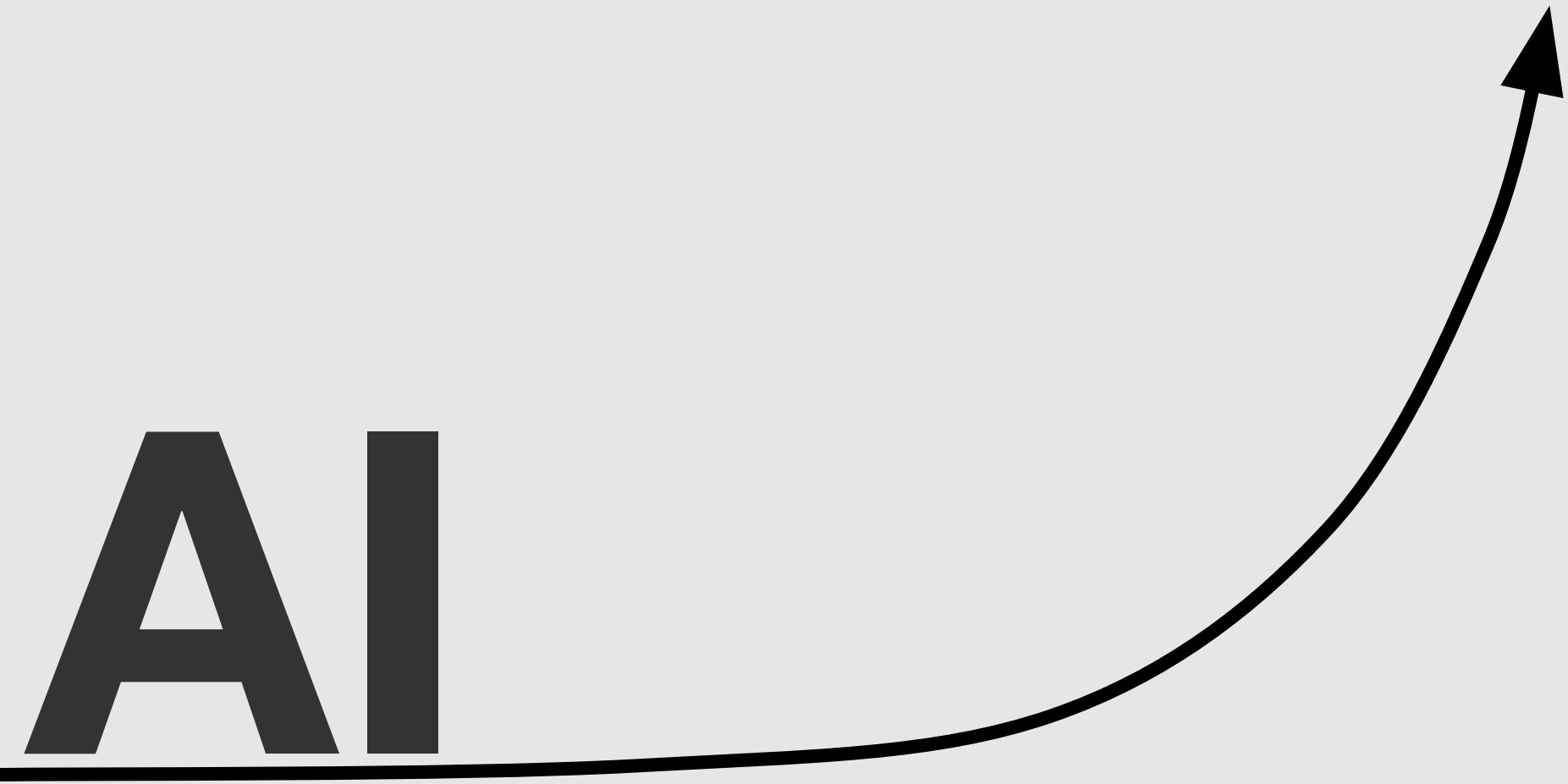


LEAP^{SM} Technology

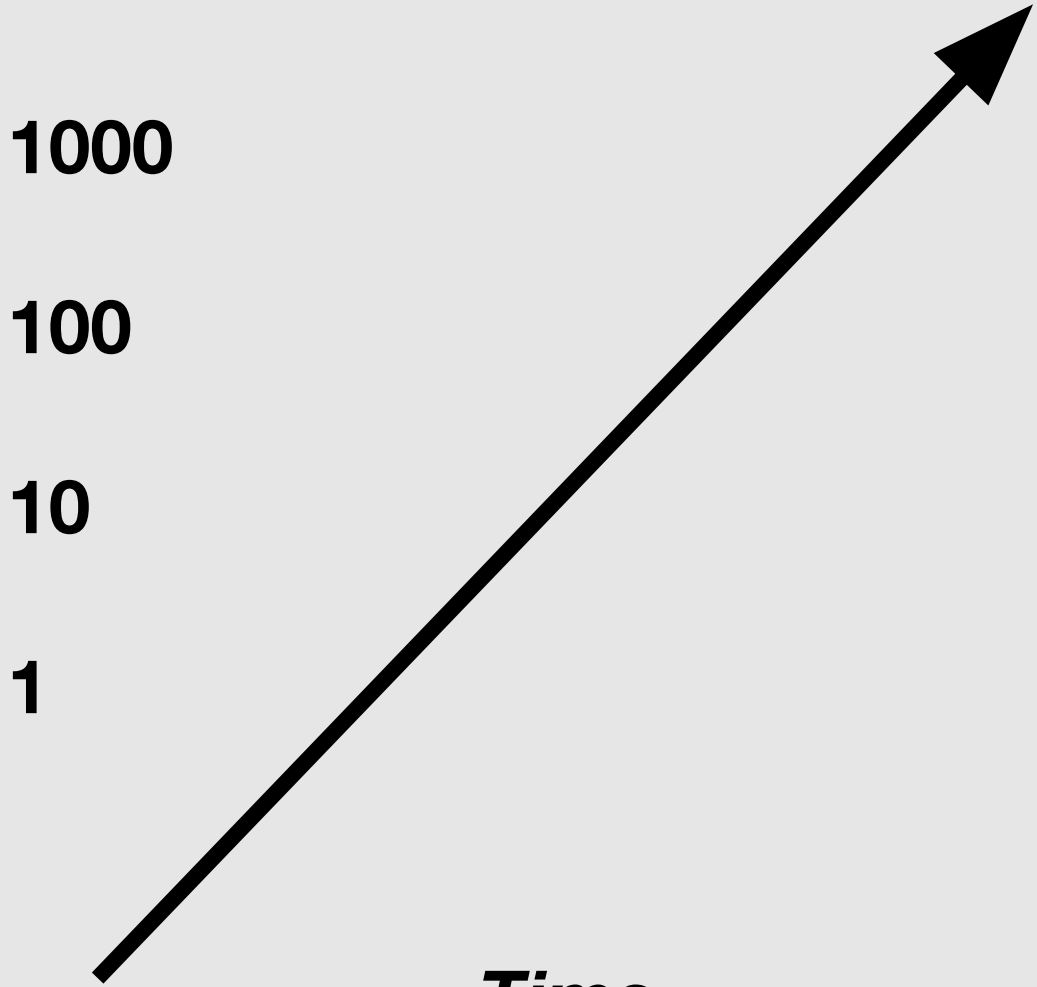


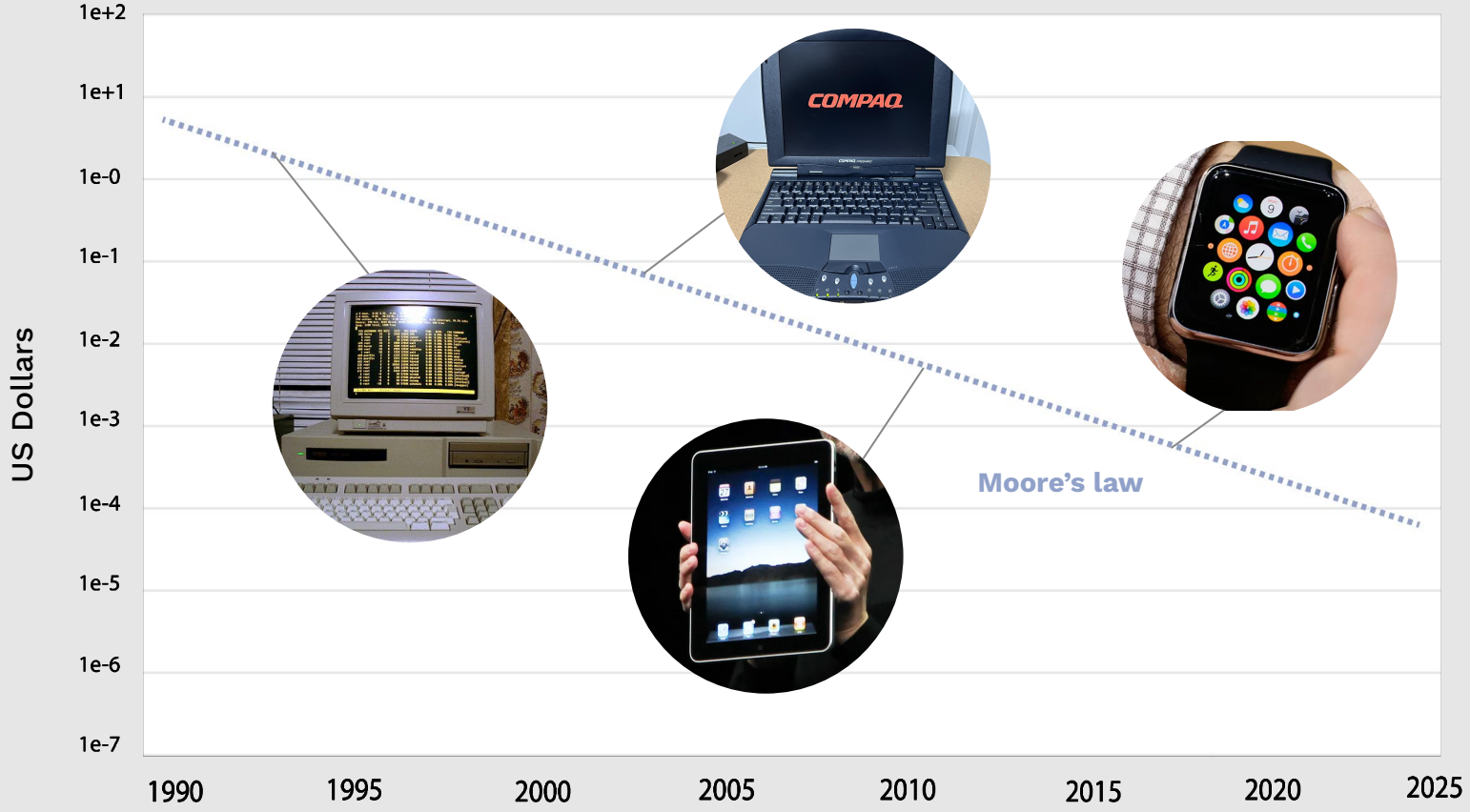
Synthetic Serotypes

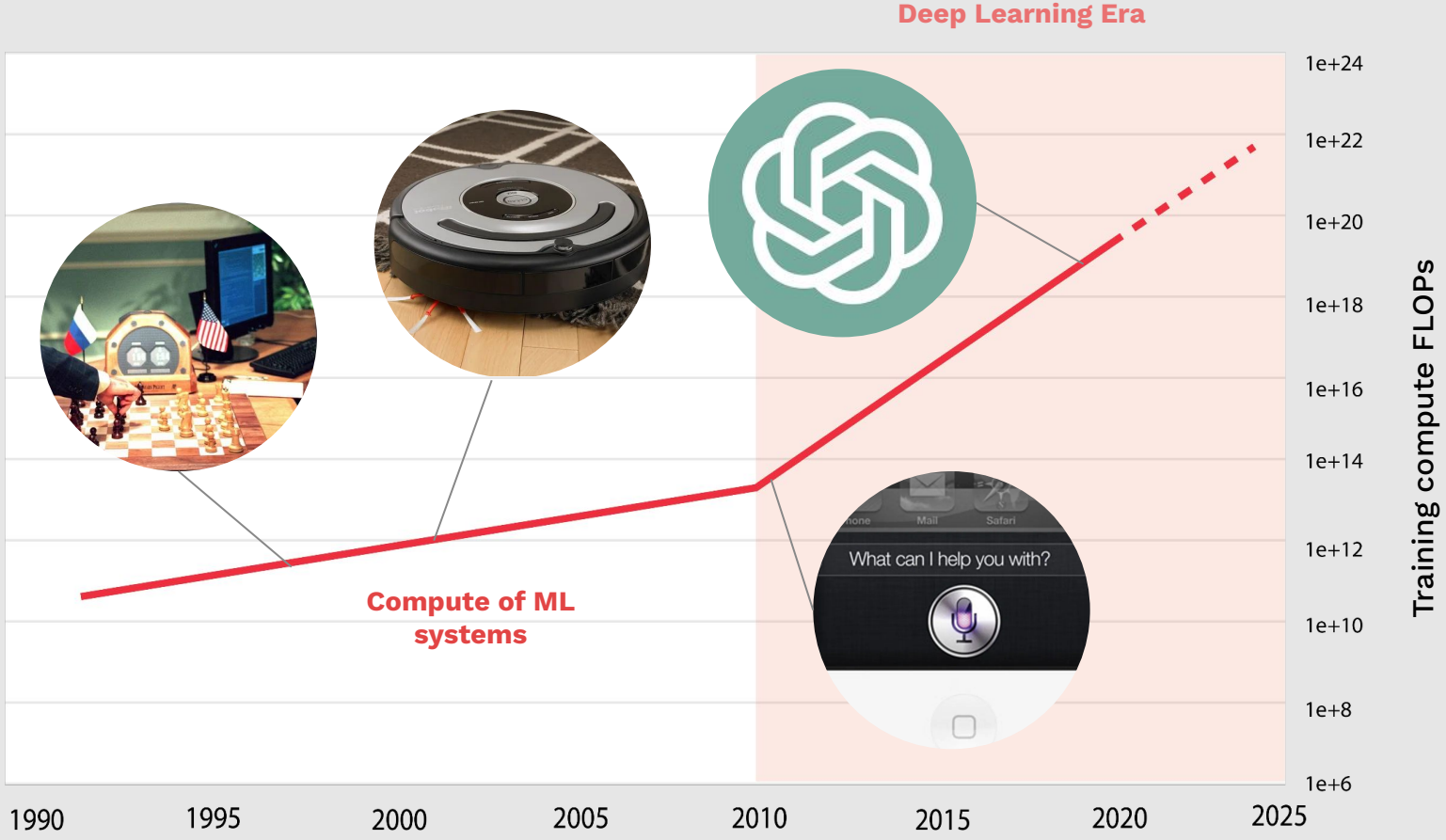
AI



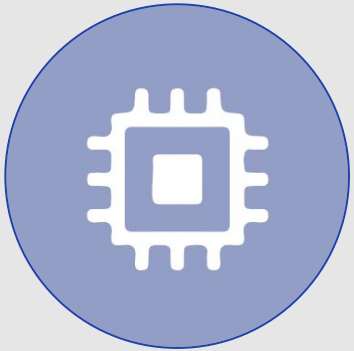
that exponential feeling


1000
100
10
1
Time →


1e+2
1e+1
1e-0
1e-1
1e-2
1e-3
1e-4
1e-5
1e-6
1e-7
US Dollars
1990
1995
2000
2005
2010
2015
2020
2025
COMPAQ
Moore's law

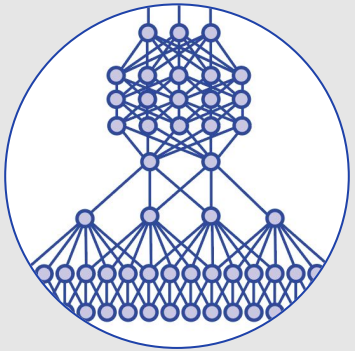

Deep Learning Era
1e+24
1e+22
1e+20
1e+18
1e+16
1e+14
1e+12
1e+10
1e+8
1e+6
Training compute FLOPs
1990
1995
2000
2005
2010
2015
2020
2025
Compute of ML systems
Mail
Safari
What can I help you with?

What sparked the AI revolution?

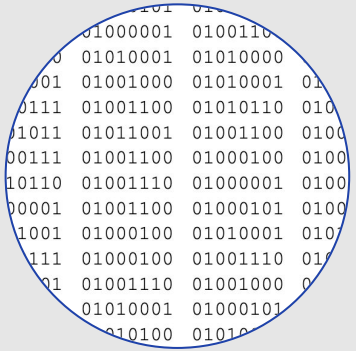


Compute

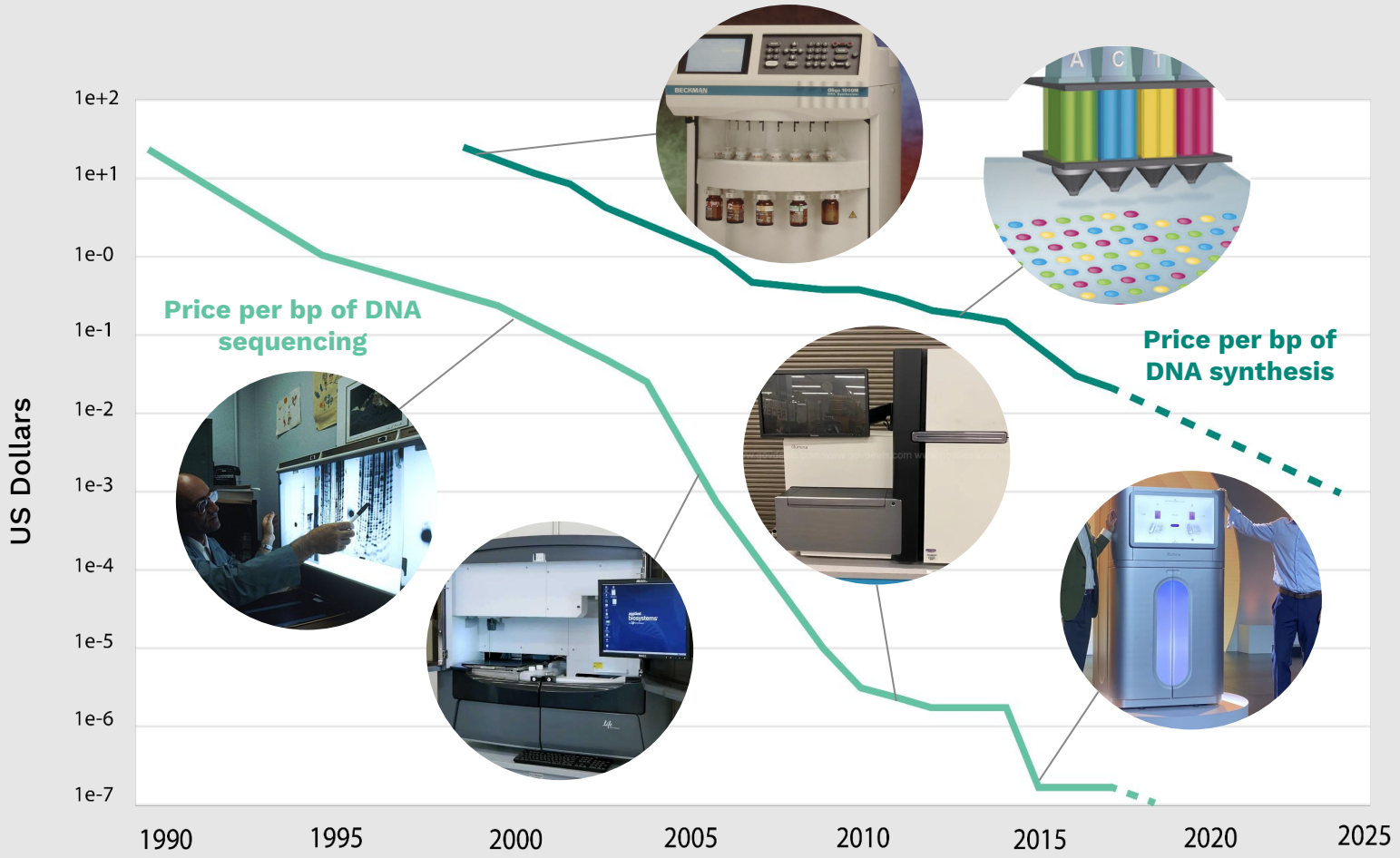
Infrastructure



Algorithms



Data


US Dollars
1e+2
1e+1
1e-0
1e-1
1e-2
1e-3
1e-4
1e-5
1e-6
1e-7
1990
1995
2000
2005
2010
2015
2020
2025
Price per bp of DNA sequencing
Price per bp of DNA synthesis
BECKMAN
A C T

Dyno:

(noun) in climbing, a powerful jump across a rock face to reach a hold

Dyno Therapeutics

Engineering the world's best AAV capsids

so our partners can work

at the leading edge of gene delivery

Our team of AAViators

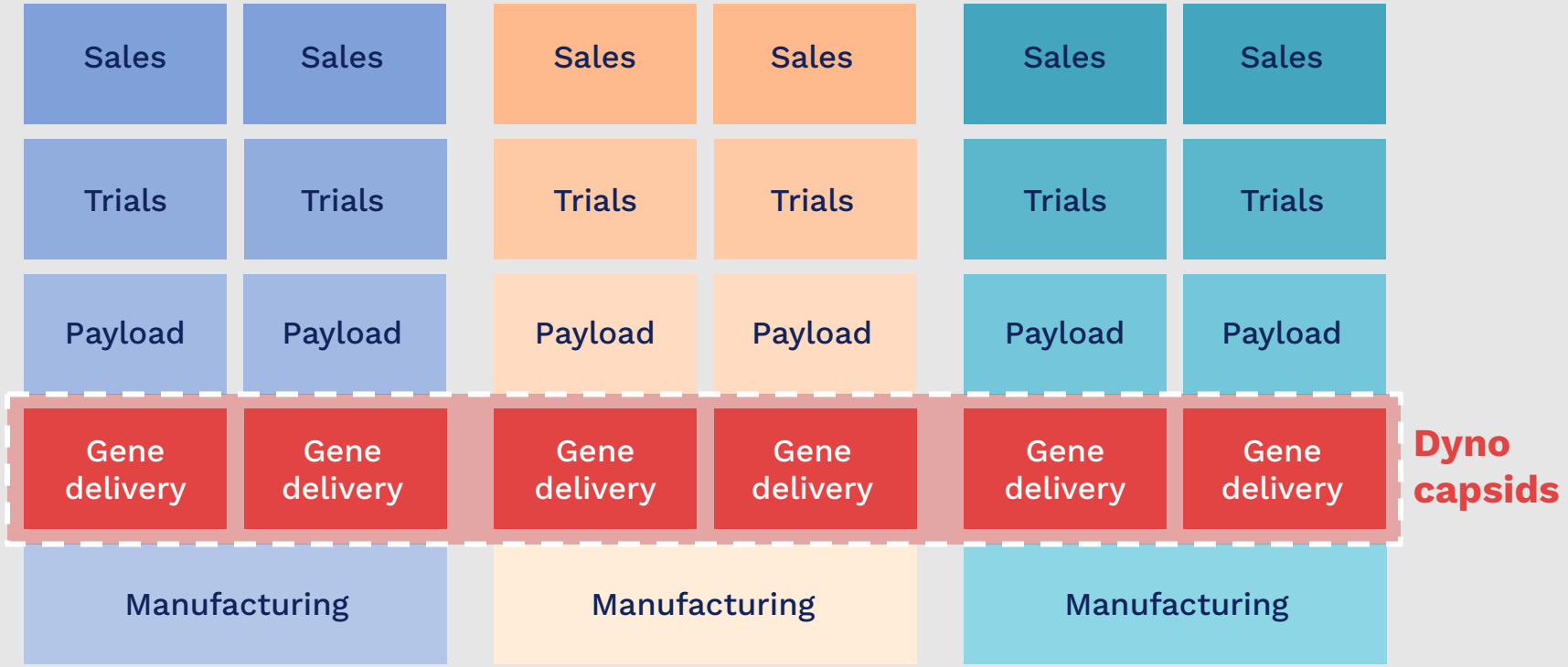
Why partner with Dyno?

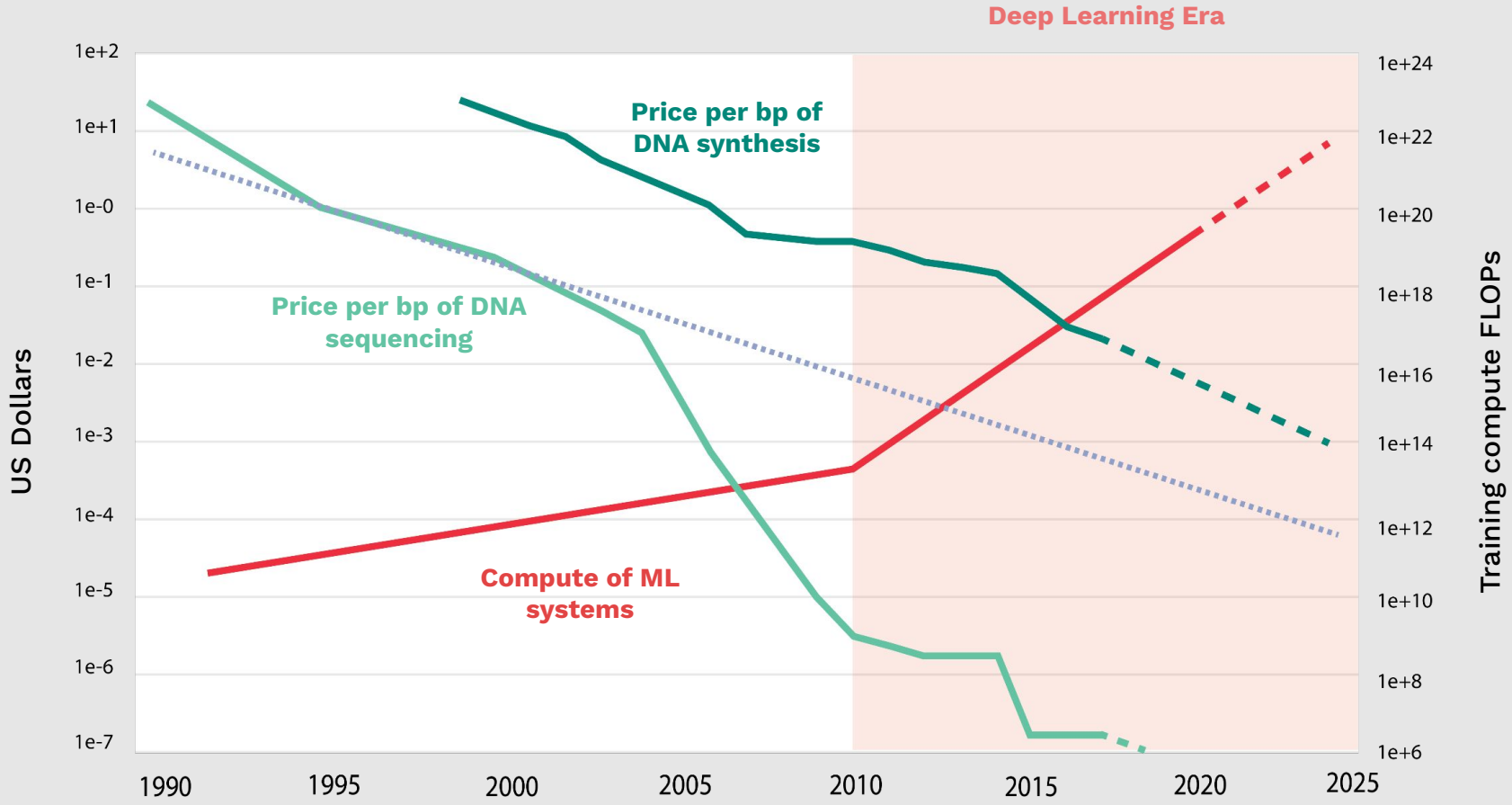
100% focused on capsid engineering

Partnership-centric business model = 100% alignment

Dyno's partnerships to date...

Our ambition is solving delivery generally and broadly

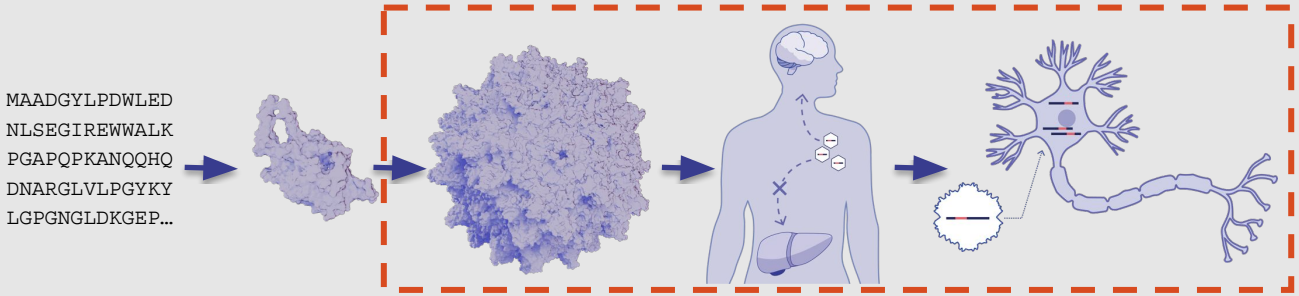



Deep Learning Era
Price per bp of DNA synthesis
Price per bp of DNA sequencing
Compute of ML systems
US Dollars
Training compute FLOPs
1e+2
1e+1
1e-0
1e-1
1e-2
1e-3
1e-4
1e-5
1e-6
1e-7
1e+24
1e+22
1e+20
1e+18
1e+16
1e+14
1e+12
1e+10
1e+8
1e+6
1990
1995
2000
2005
2010
2015
2020
2025

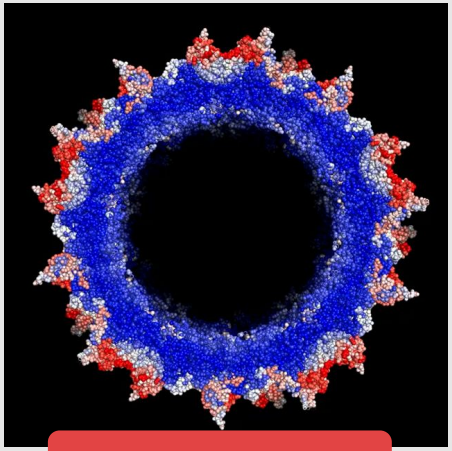
Dyno’s platform

Data excellence

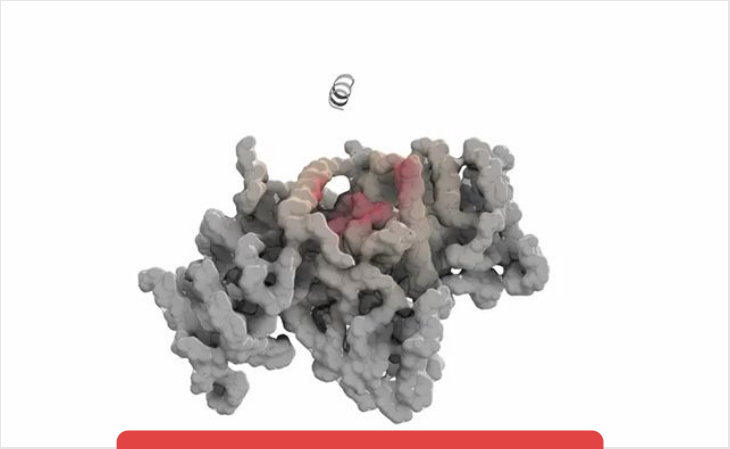
Dyno: An AI-powered in vivo capsid engineering platform



Experimental data required to enable AI-powered design

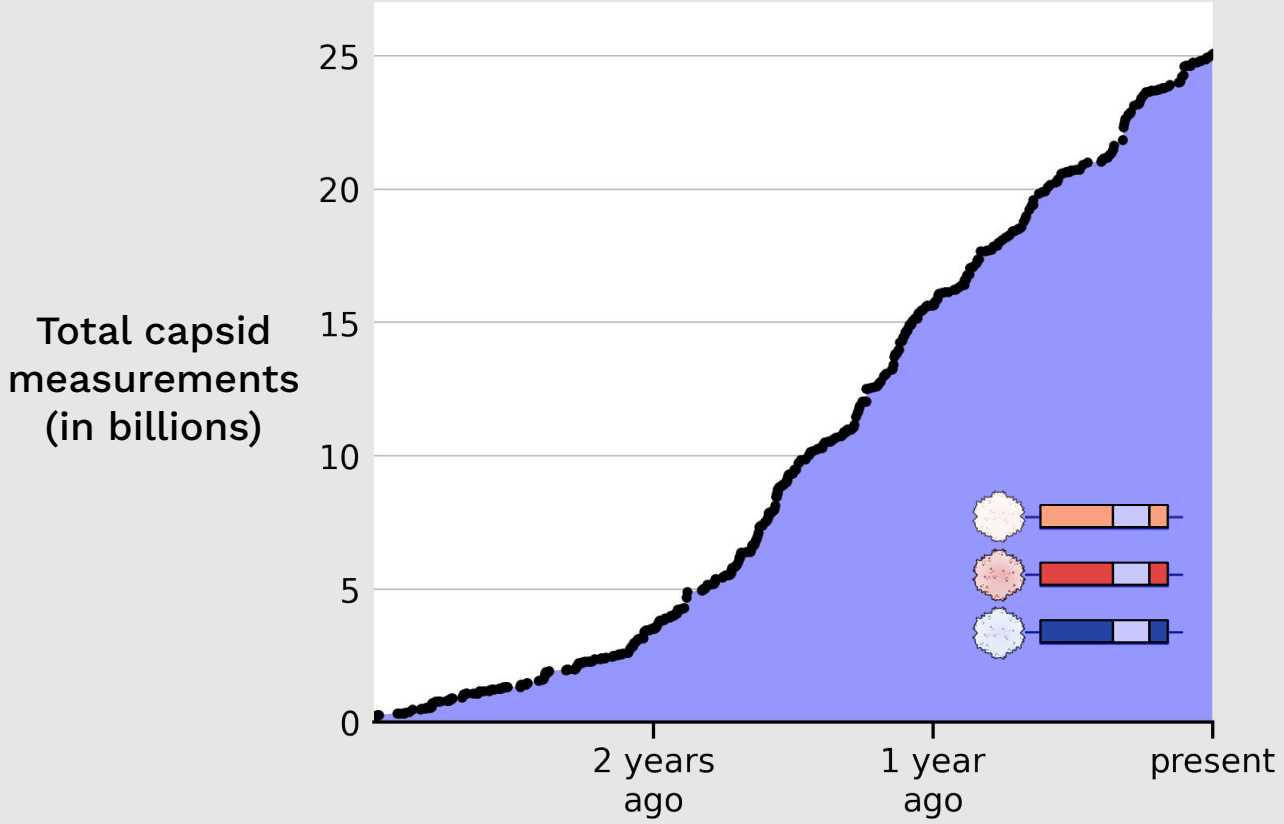


Production

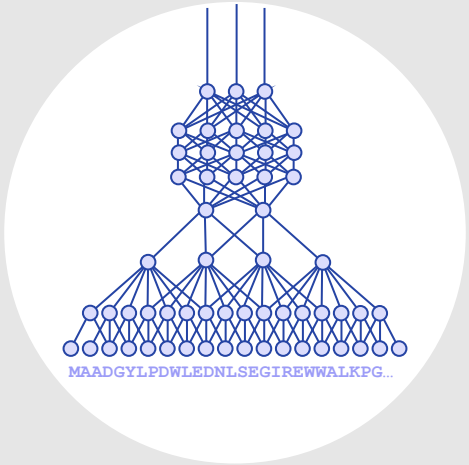


Receptor docking

We make billions of measurements every month



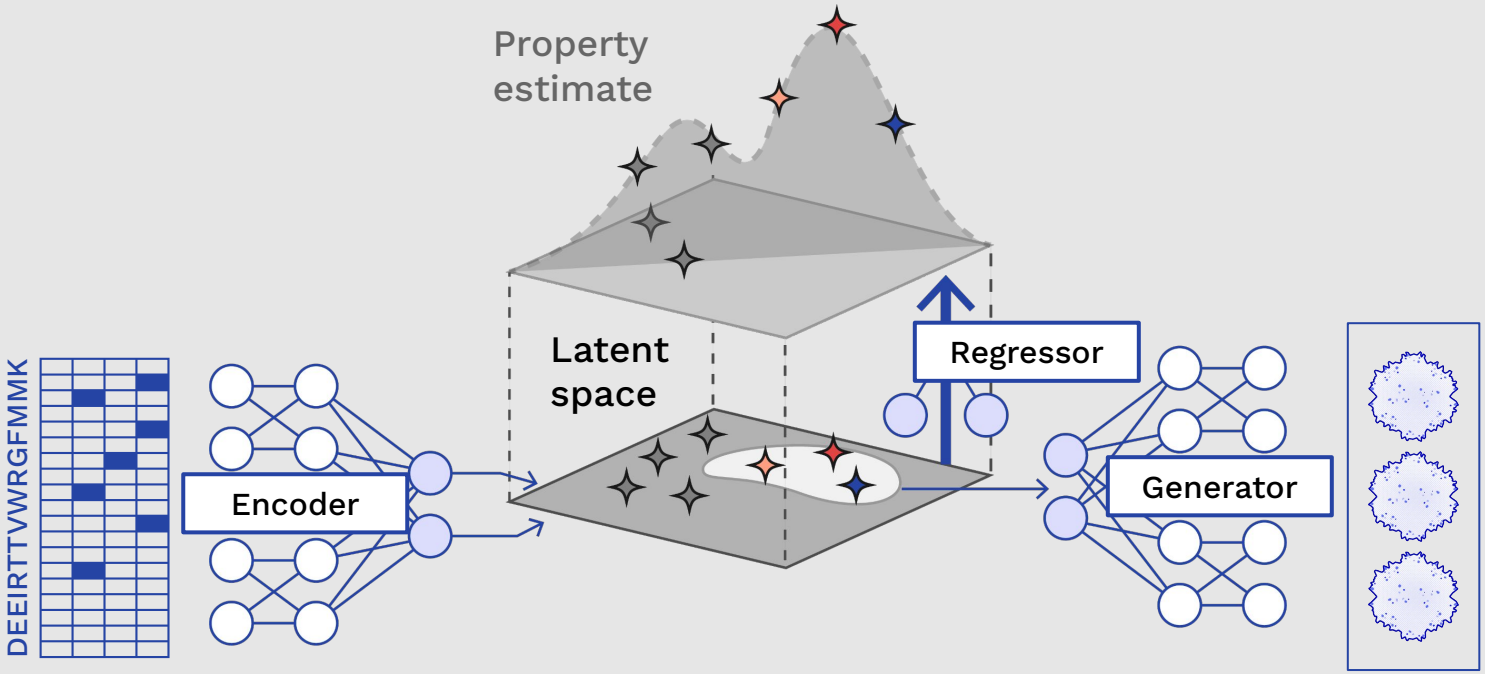
Dyno’s platform



Data excellence

AI excellence

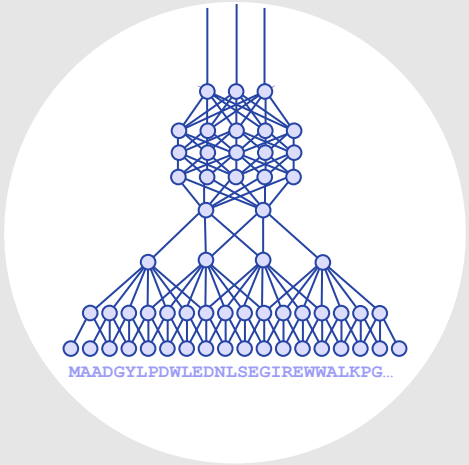
We program AI to generate optimized capsid sequences



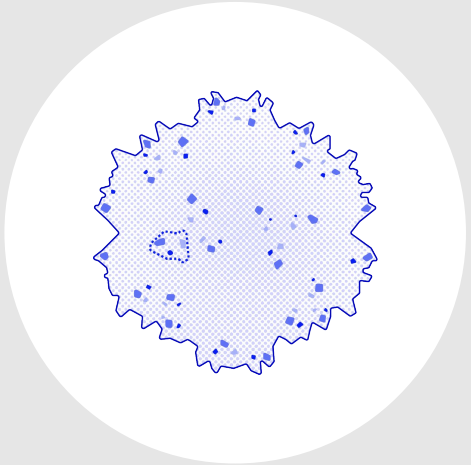
Sinai et al. arxiv 2017, Sinai et al. Biorxiv 2021

Dyno’s platform

Data excellence

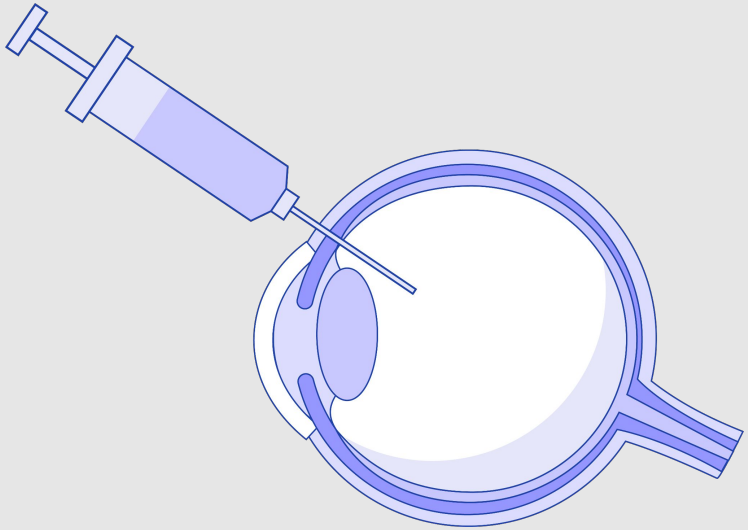


AI excellence



Better capsids

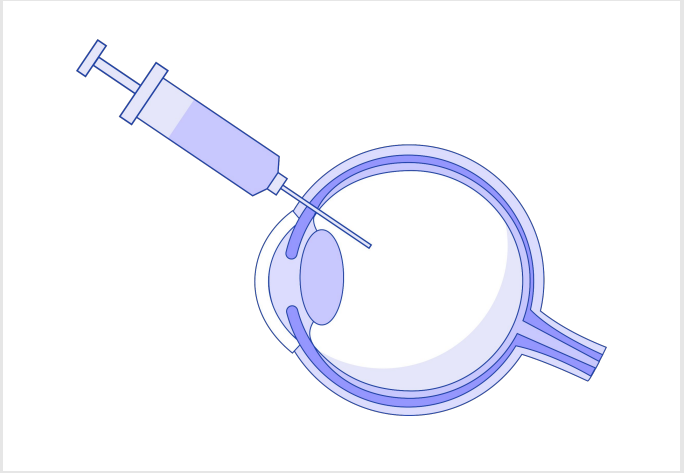
Solving the challenge of ocular gene delivery via intravitreal (IVT) injection

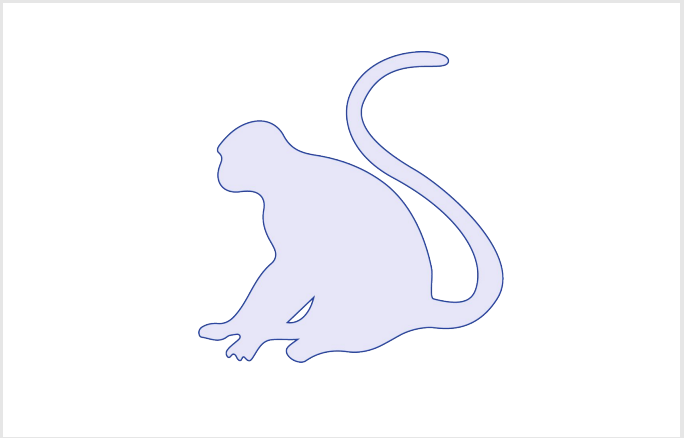


Safe, non-surgical method for ocular gene therapy delivery

Minimal transduction using AAV2 intravitreal delivery

Dyno eCap™ 1 delivery





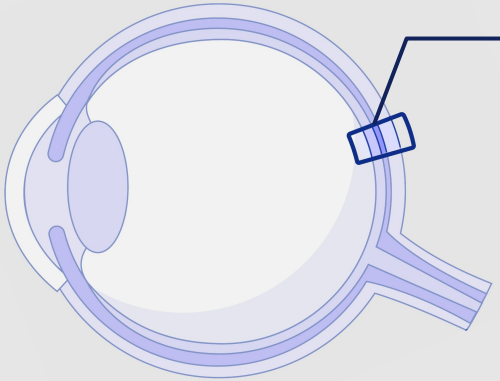
Designed for **IVT eye delivery**

1x production vs AAV2

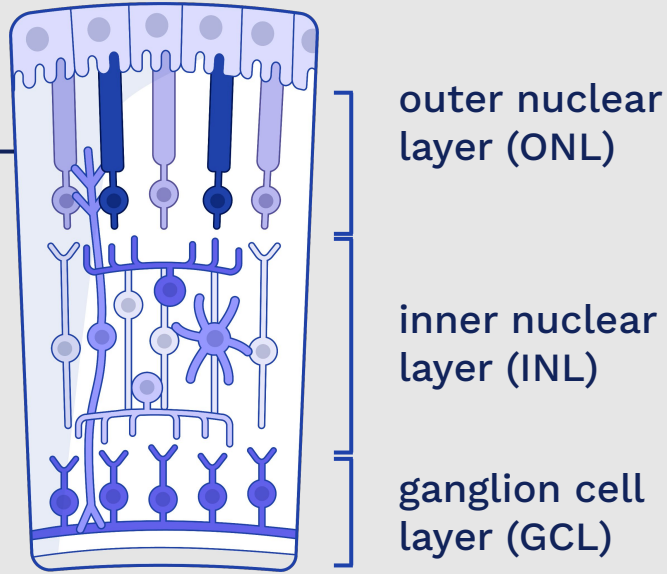
80x retina transduction vs AAV2
in Cyno monkeys

NHP Validation studies

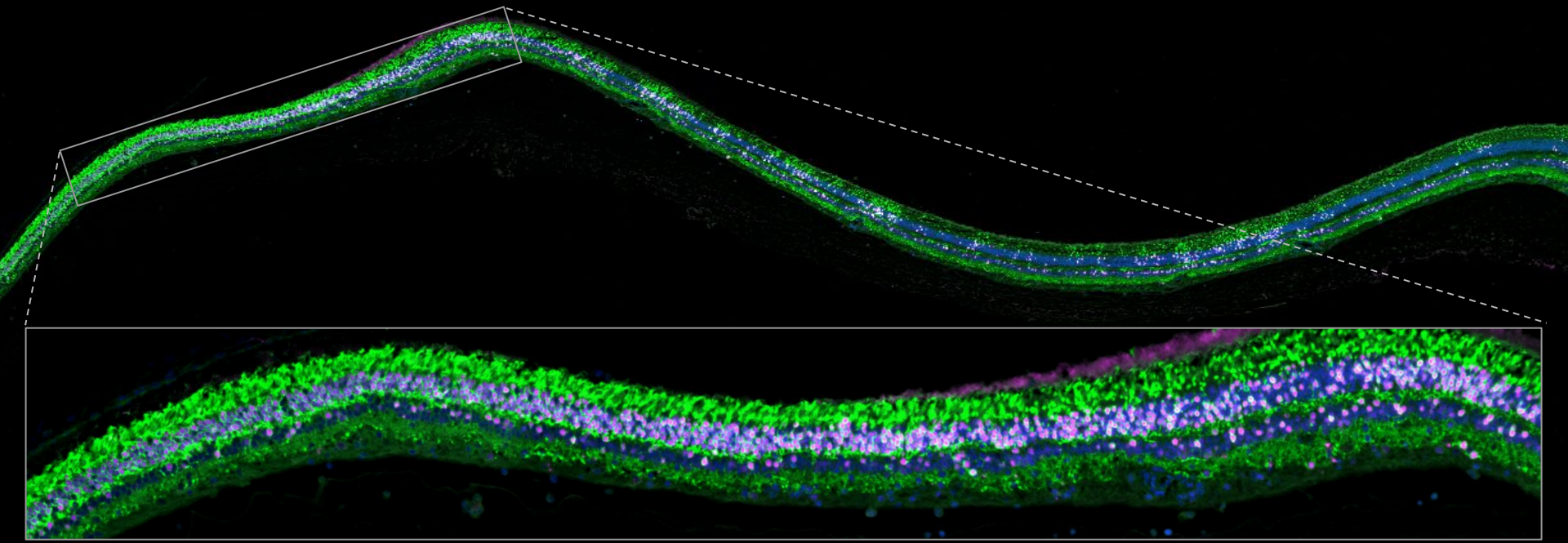
Where along the retina?



Which retinal layers?



Dyno eCap 1 efficiently transduces more retinal cells after low dose IVT injection than external capsids

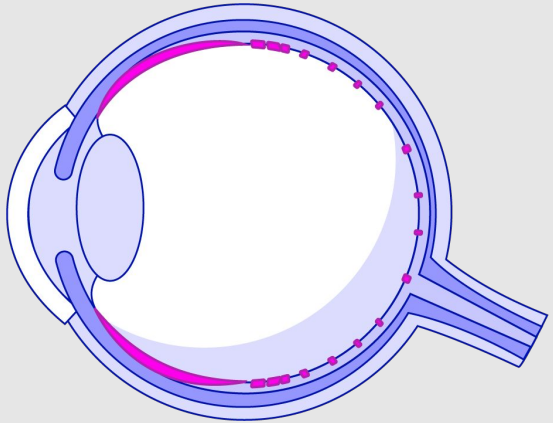


USE CASE 1

Secreted therapeutic biofactory

Delivery challenge:

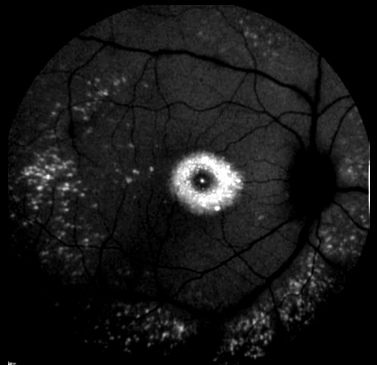
Safe and easy-to-administer delivery across retina, **reaching enough cells** for secreted proteins to achieve a therapeutic dose



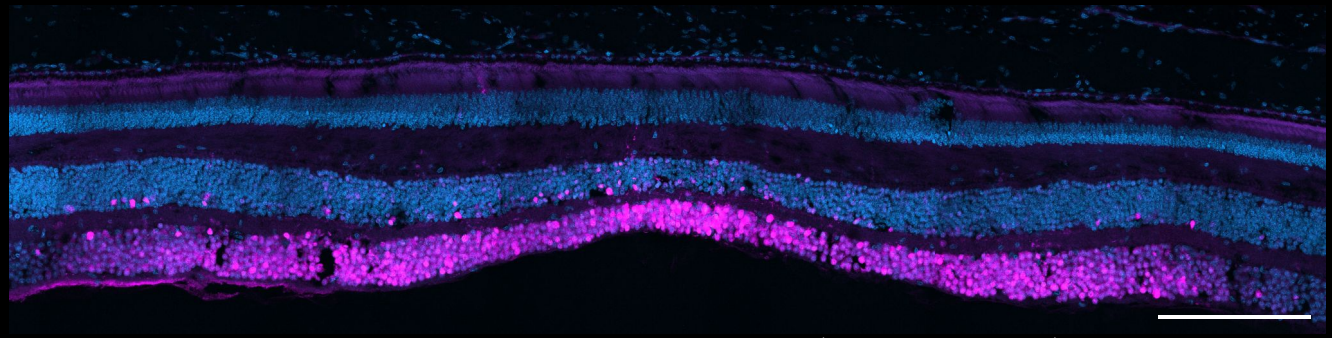
Patient unmet need:

Age-related Macular Degeneration (AMD)
Dry AMD with Geographic atrophy (GA)
Diabetic Macular Edema (DME)

Dyno eCap 1 achieves highly efficient transduction of RGCs in macular



cSLO imaging
(8.1e10 vg IVT)



Cyno macula with Dyno eCap 1 (1.4e11 vg IVT)

200 µm

USE CASE 2

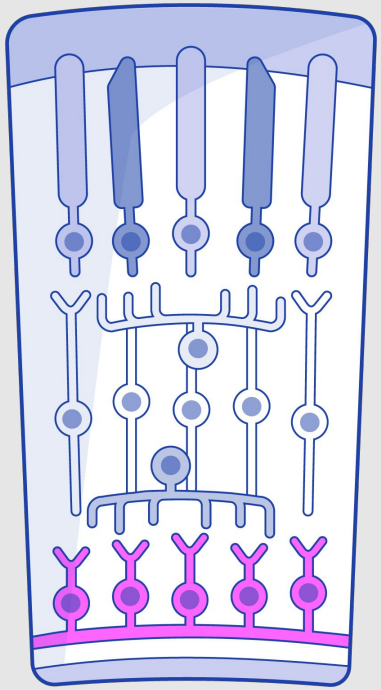
Glaucoma

Delivery challenge:

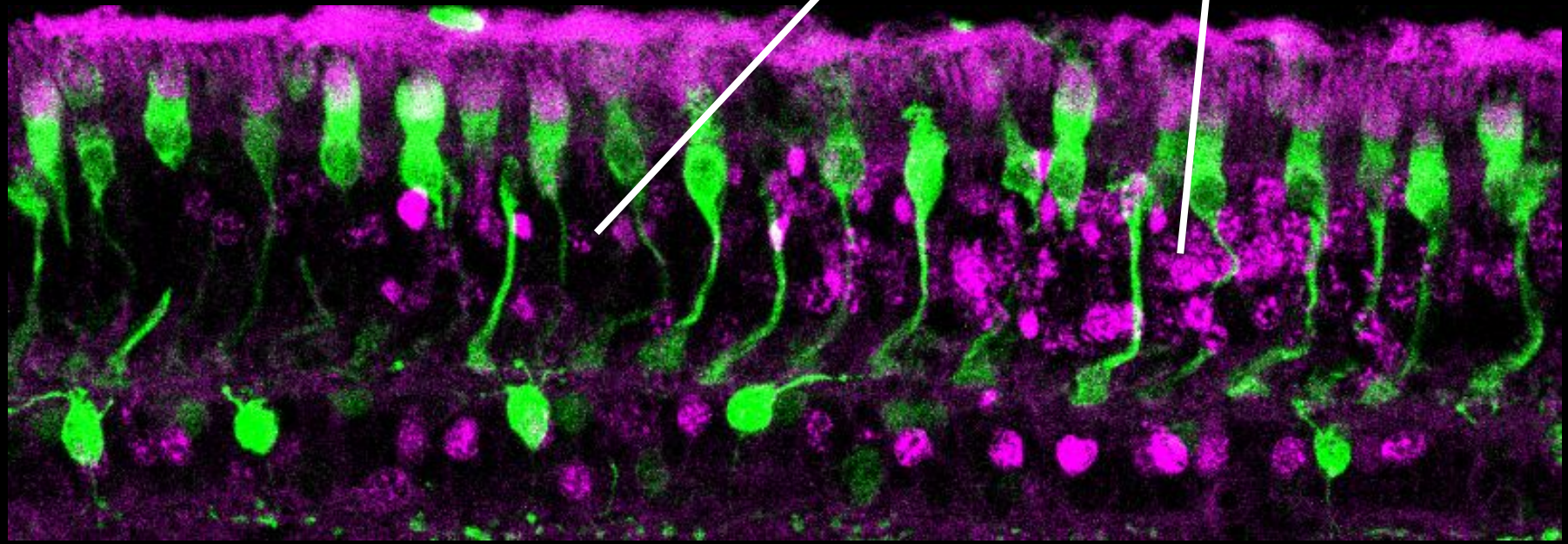
Safe and easy-to-administer delivery to **RGCs** responsible for central vision in the **macula**

Patient unmet need:

Degeneration of retinal ganglion cells (RGCs) in macula leading to central vision loss



Dyno eCap 1 primarily transduces rod photoreceptors



Calbindin (cones) / **Dyno eCap 1**

USE CASE 3

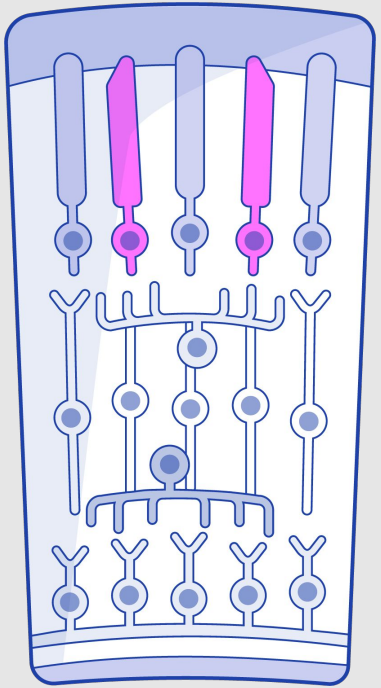
Inherited retinal diseases

Delivery challenge:

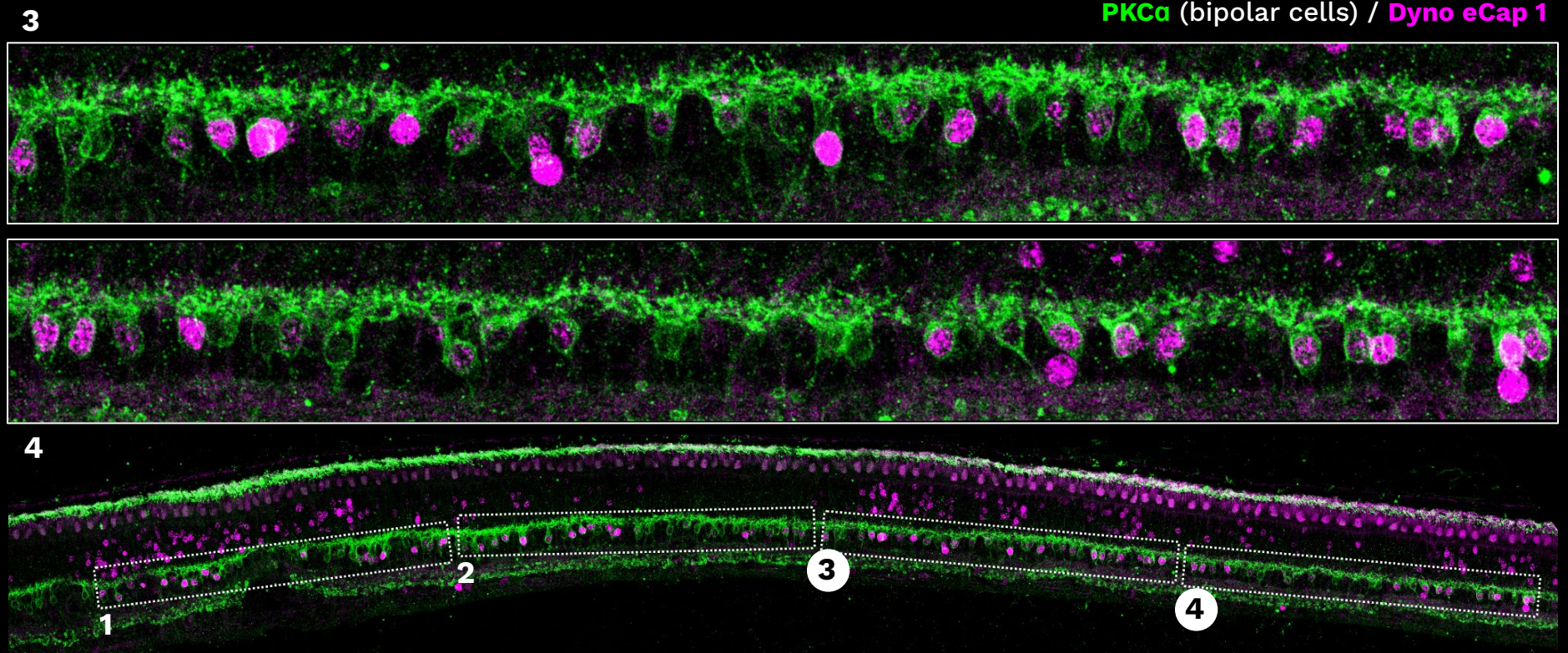
Reach enough photoreceptors to prevent their degeneration and modify disease progression

Patient unmet need:

Retinitis pigmentosa is the leading cause of progressive vision loss early in life



Highly efficient transduction of bipolar cells with Dyno eCap 1



USE CASE 4

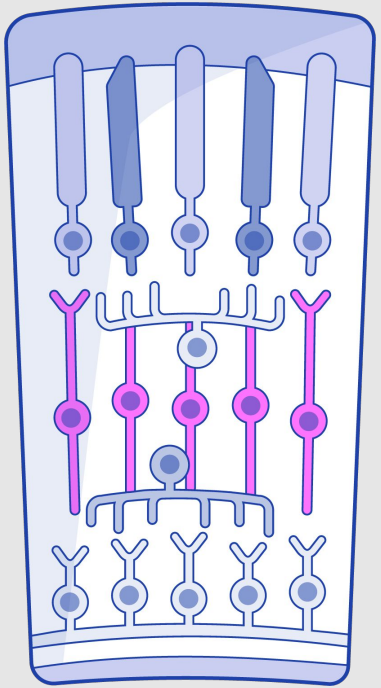
Optogenetic therapy

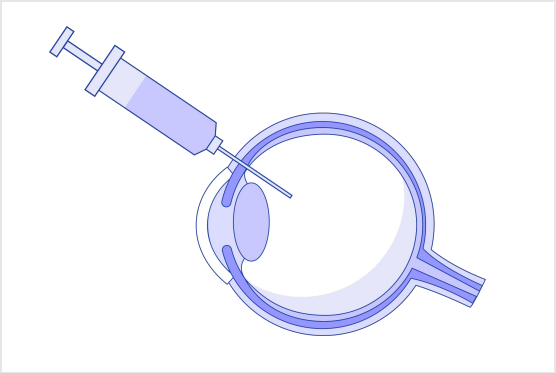
Delivery challenge:

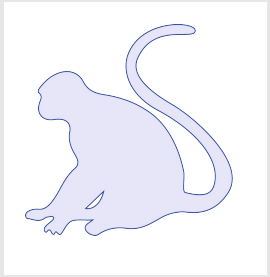
Reaching enough bipolar cells, to enable an optogenetic intervention to have an impact

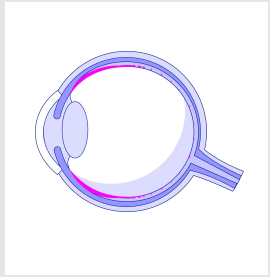
Patient unmet need:

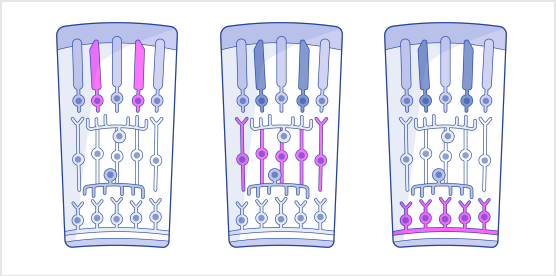
Total vision loss due to advanced retinal disease progression











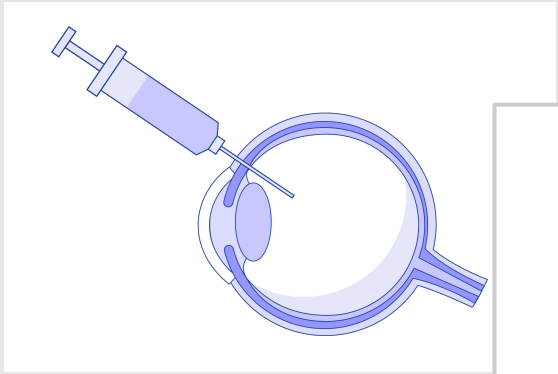
Dyno eCap 1 delivery

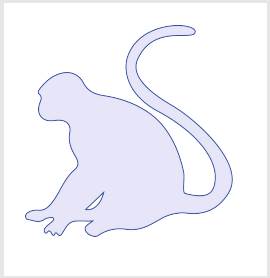
Designed for **IVT eye delivery**

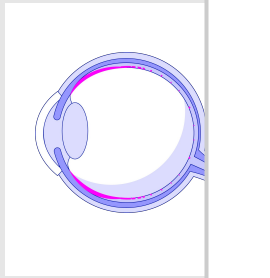
1x production vs AAV2
80x retina transduction vs AAV2

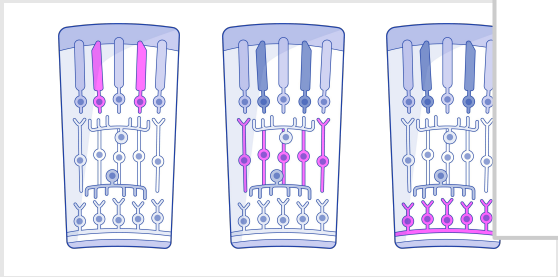
Transduces key **NHP retina** cell types including **retinal ganglion cells, bipolar cells & rod photoreceptors**

Ready for use in **biofactory, neuroprotection, optogenetic & photoreceptor targeted ocular gene therapies**









Dyno eCap 1 delivery

e delivery

AAV2

on vs AAV2

ina cell types

glion cells,

toreceptors

neuroprotection,

optogenetic & photoreceptor targeted

ocular gene therapies

Poster #516

Non-Human Primate Evaluation of an Engineered AAV Capsid for Retinal Cell-Specific and Biofactory-Based Ocular Gene Therapies

Heikki Turunen

May 8, 2024 12:00 PM EDT,
Exhibit Hall

Challenge: safe and effective gene delivery

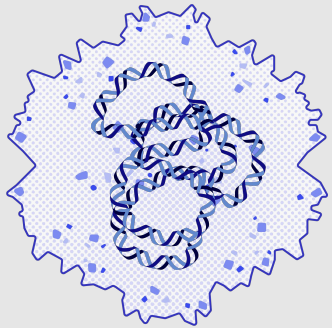
Intravenous (IV) injection

Easily **administered**

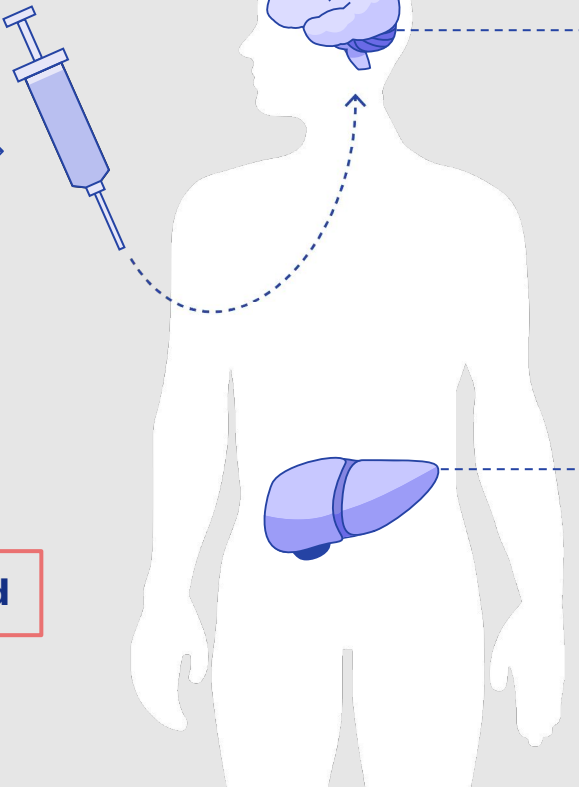
AAV capsid

+

genetic payload



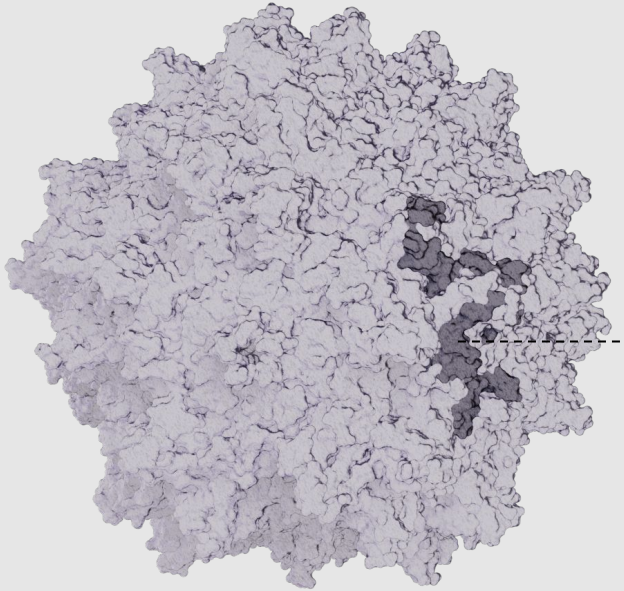
Easily **manufactured**



Targeting **brain**

De-targeting **liver**

The AAV capsid: a ~736 letter sequence design problem



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KKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTESVPDPQPI
GEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWL
GDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWG
YFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNN
GVKTIANNLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQ
YGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYEFENVPFH
SSYAHSQSLDRLMNPLIDQYLYYLSKTINGSGQNQQTLKFSVAGPSN
MAVQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSL
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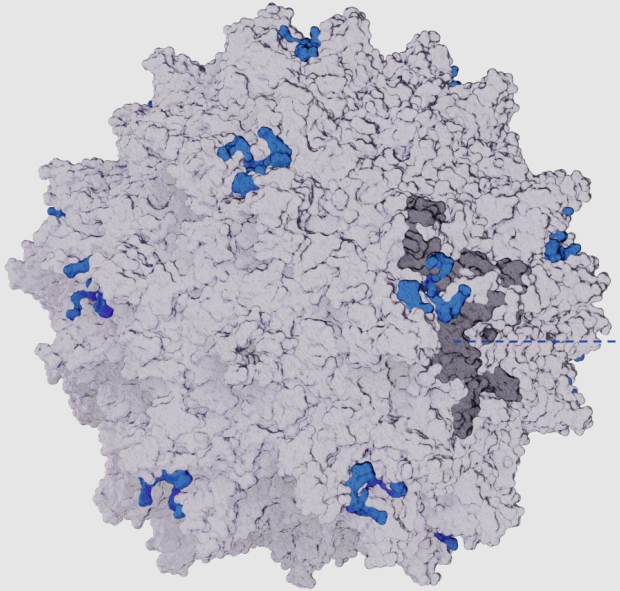
VYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADP
PTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY
YKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL*

A better capsid: Dyno bCap™ 1



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GEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWL
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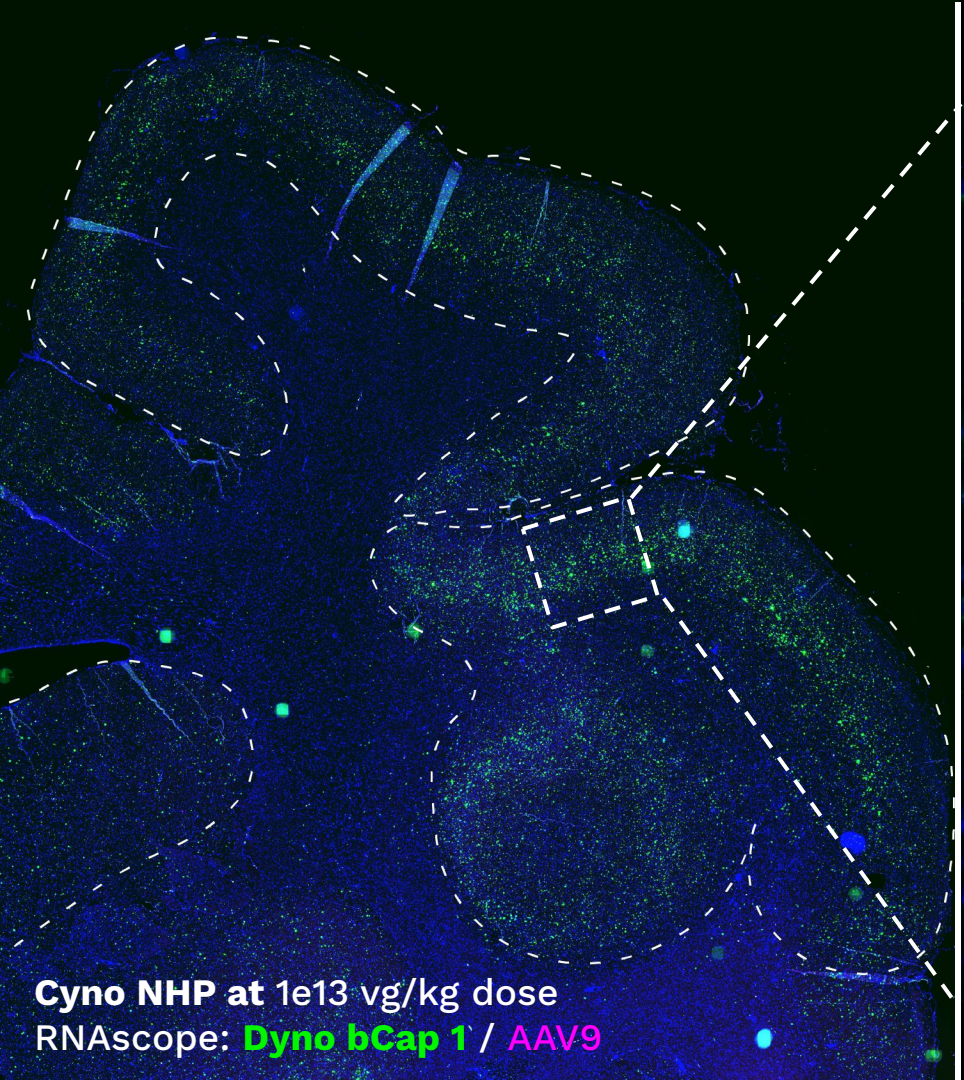
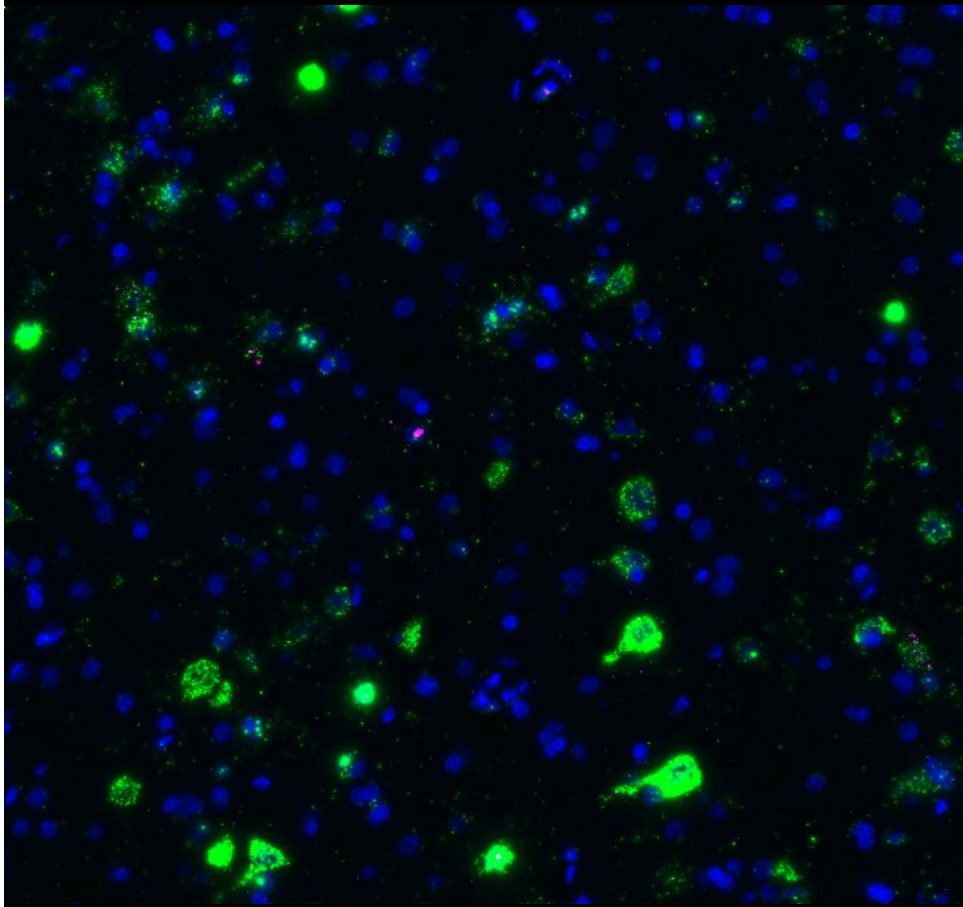
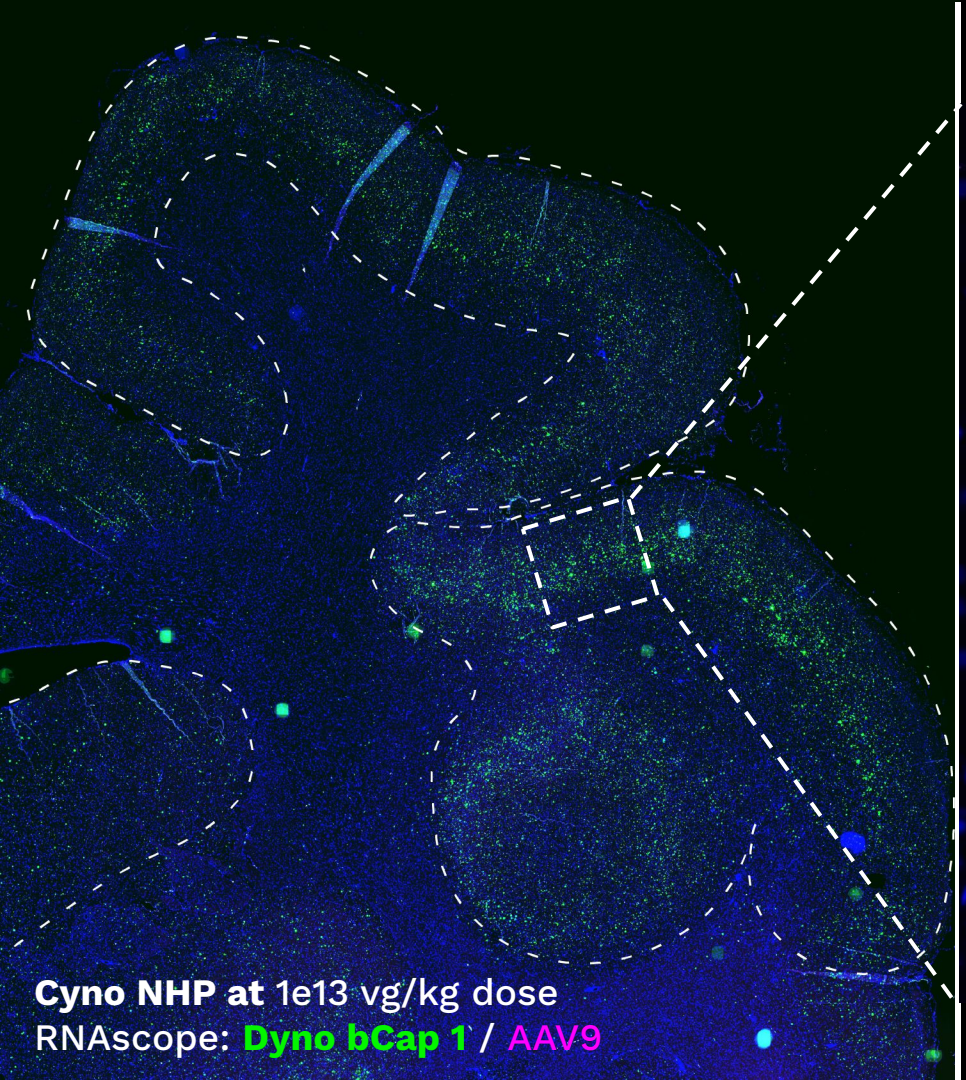
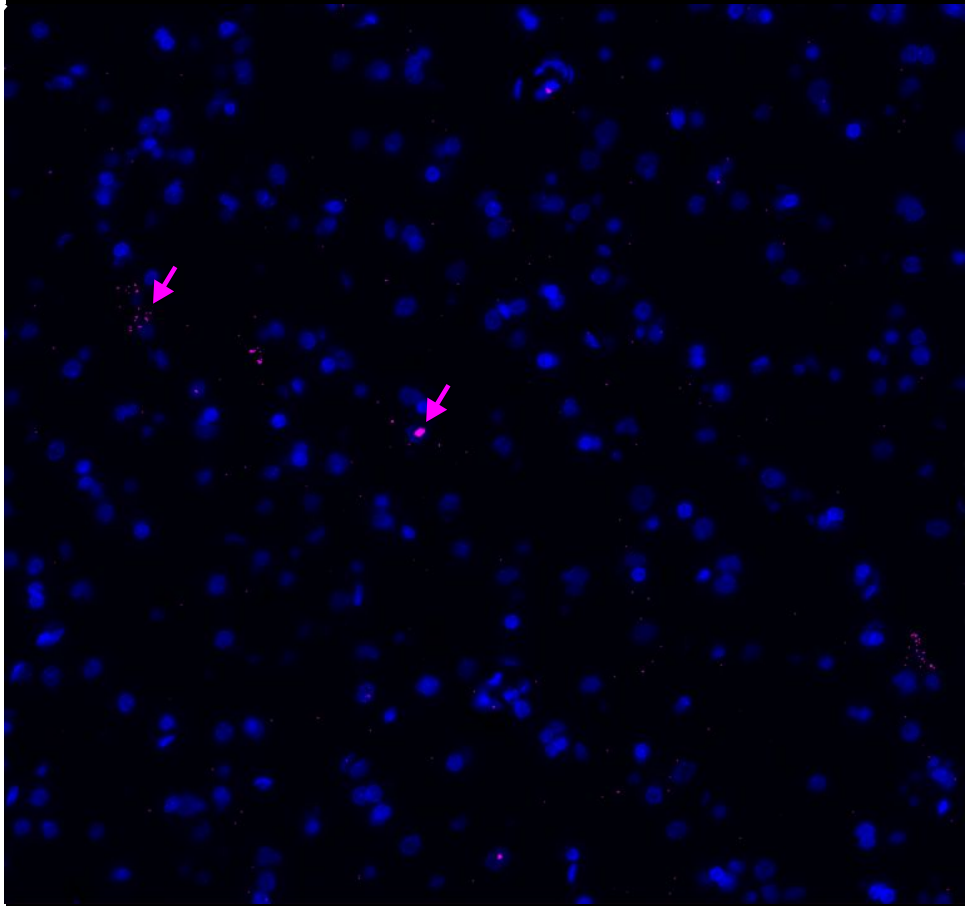


Motor cortex: 11% of cells transduced

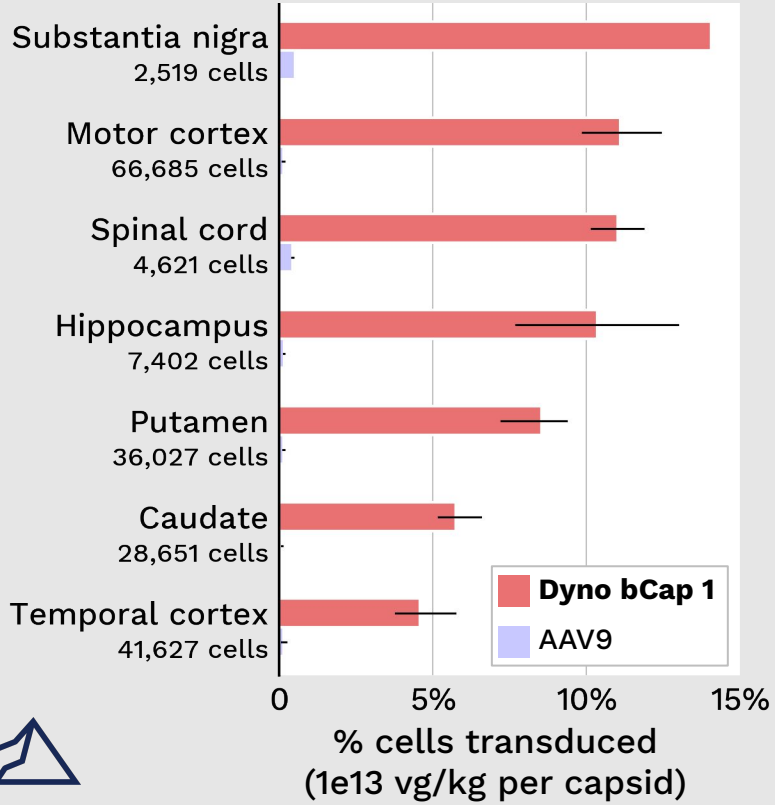


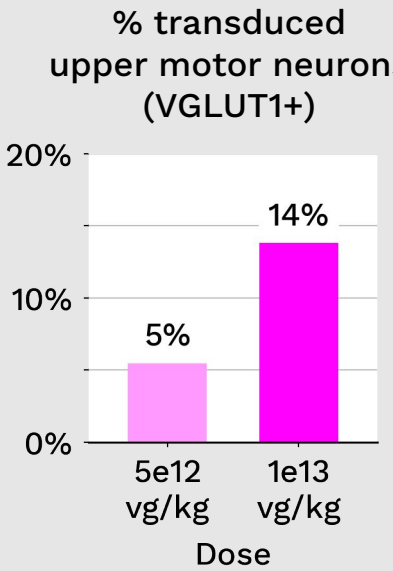


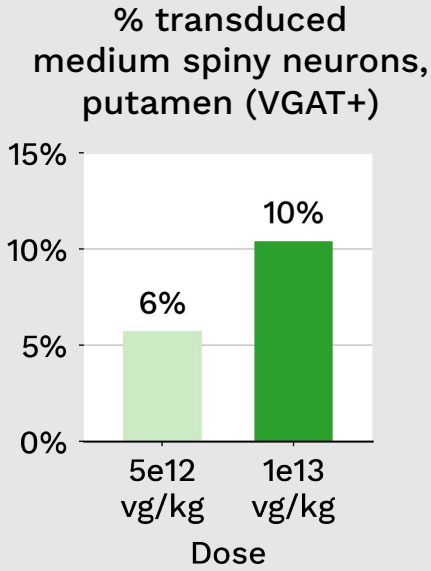
Motor cortex: minimal AAV9 transduction

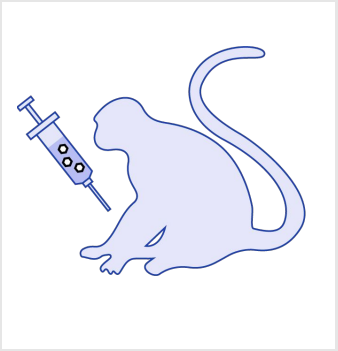


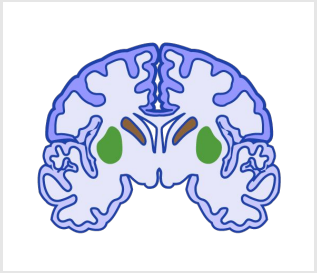
Dyno bCap 1 delivery is pan-brain and reaches clinically relevant neuronal populations

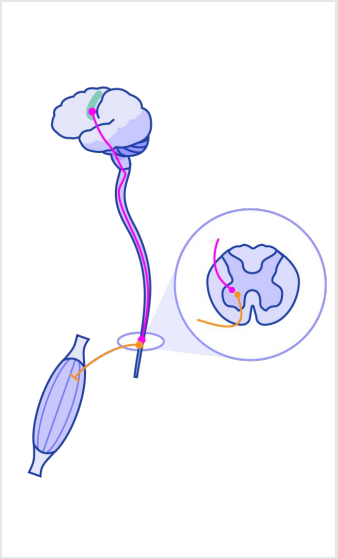


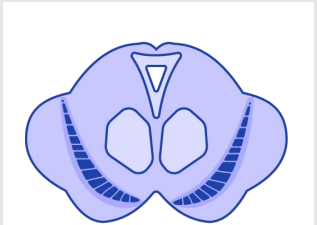












Dyno bCap 1 delivery

Delivers **pan-brain** and across the **CNS,** crossing the **blood-brain-barrier** after IV administration

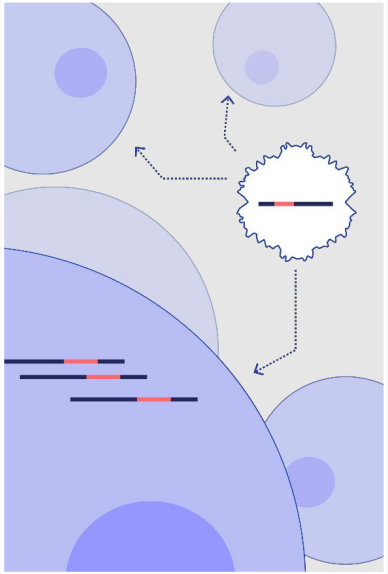
1x production vs AAV9
10x liver detargeting vs AAV9
100x brain transduction vs AAV9

Transduces neurons and other therapeutically relevant cell-types

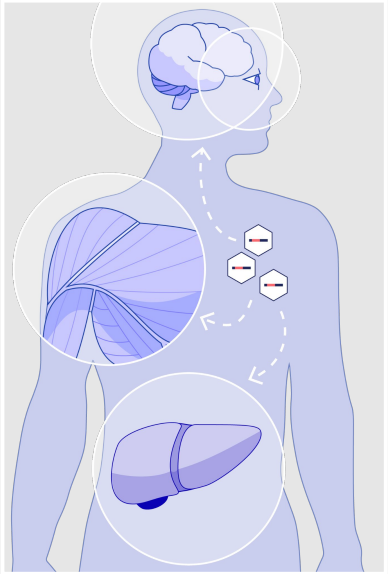
Transduction patterns relevant for **ALS**, **Huntington's** & **Parkinson's Disease**, ...

Expanding the reach of gene therapy

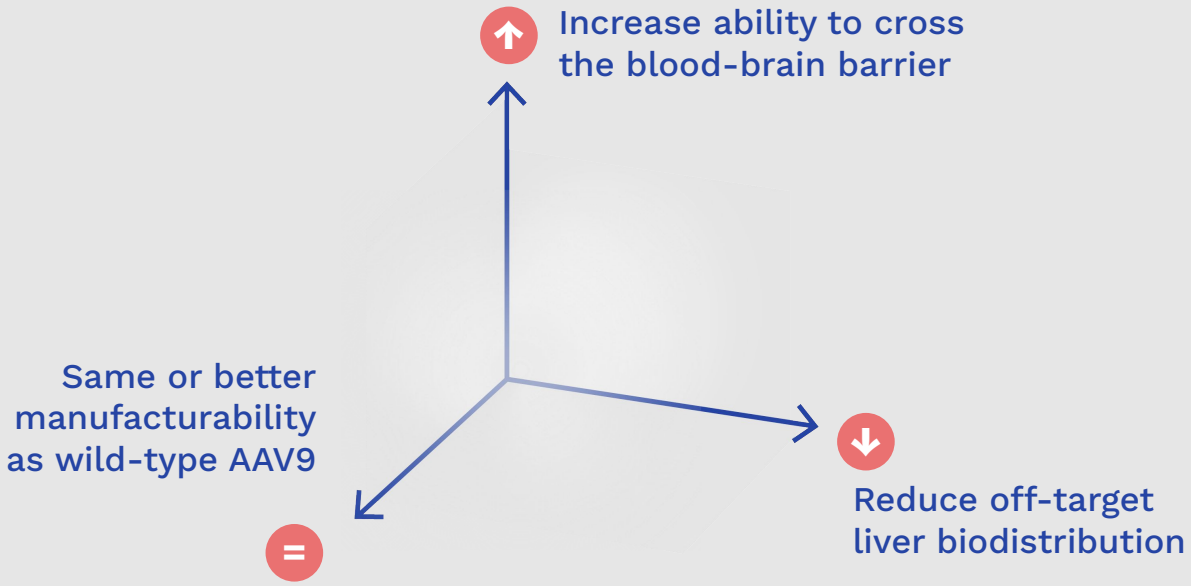
Every cell



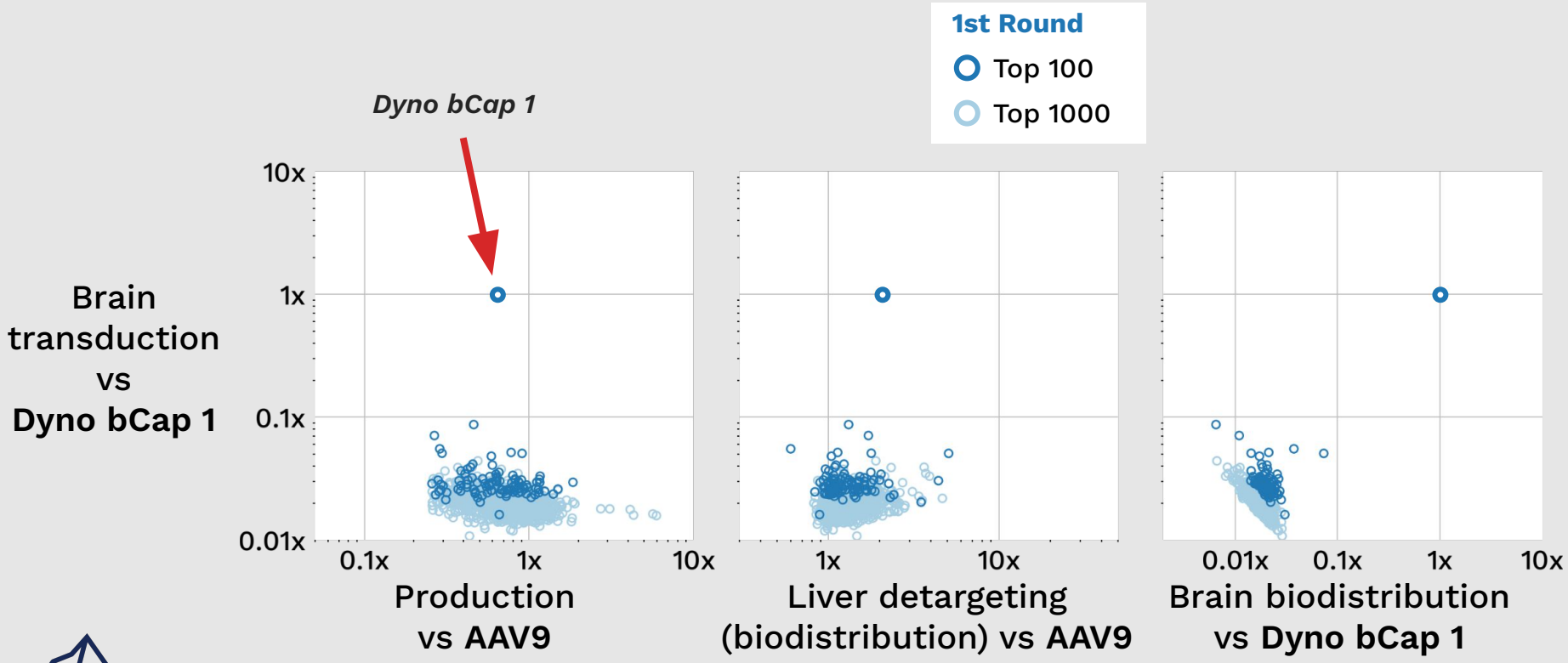
Every organ



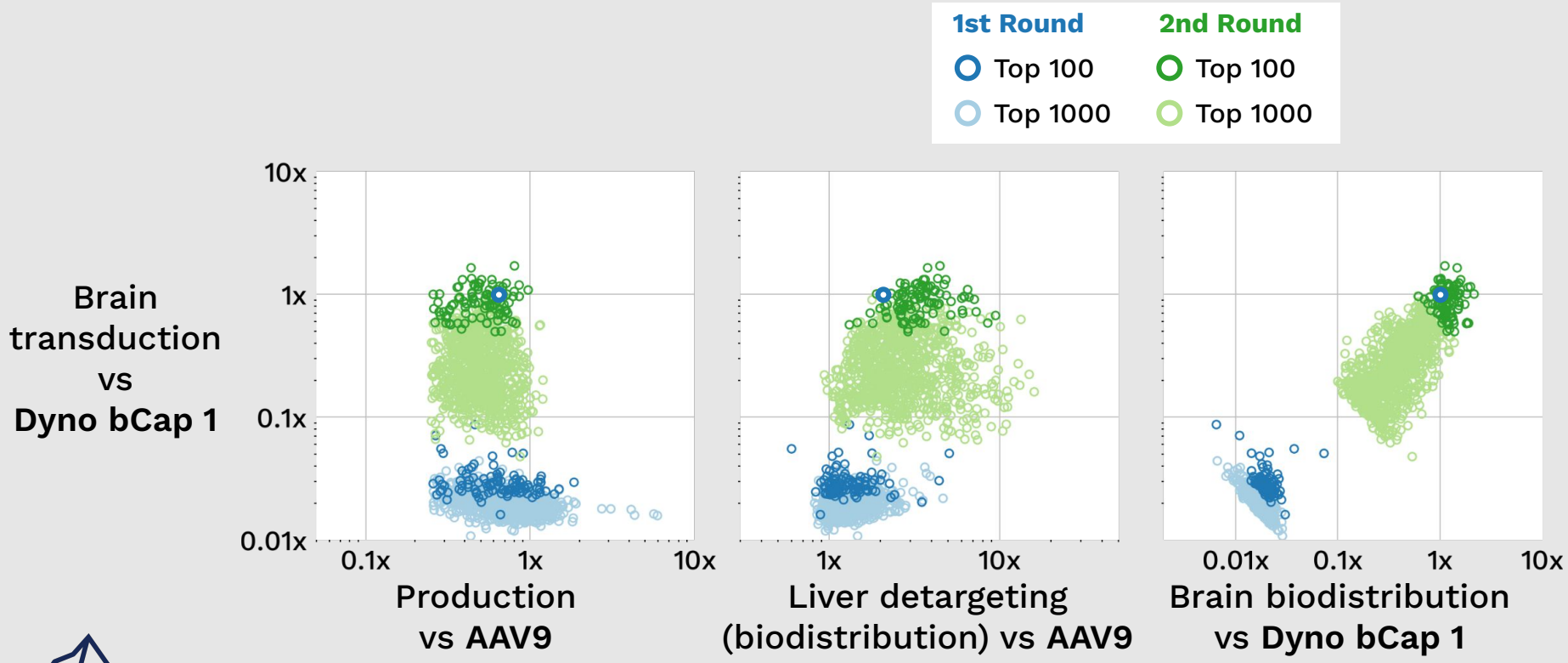
We optimize capsids across multiple properties



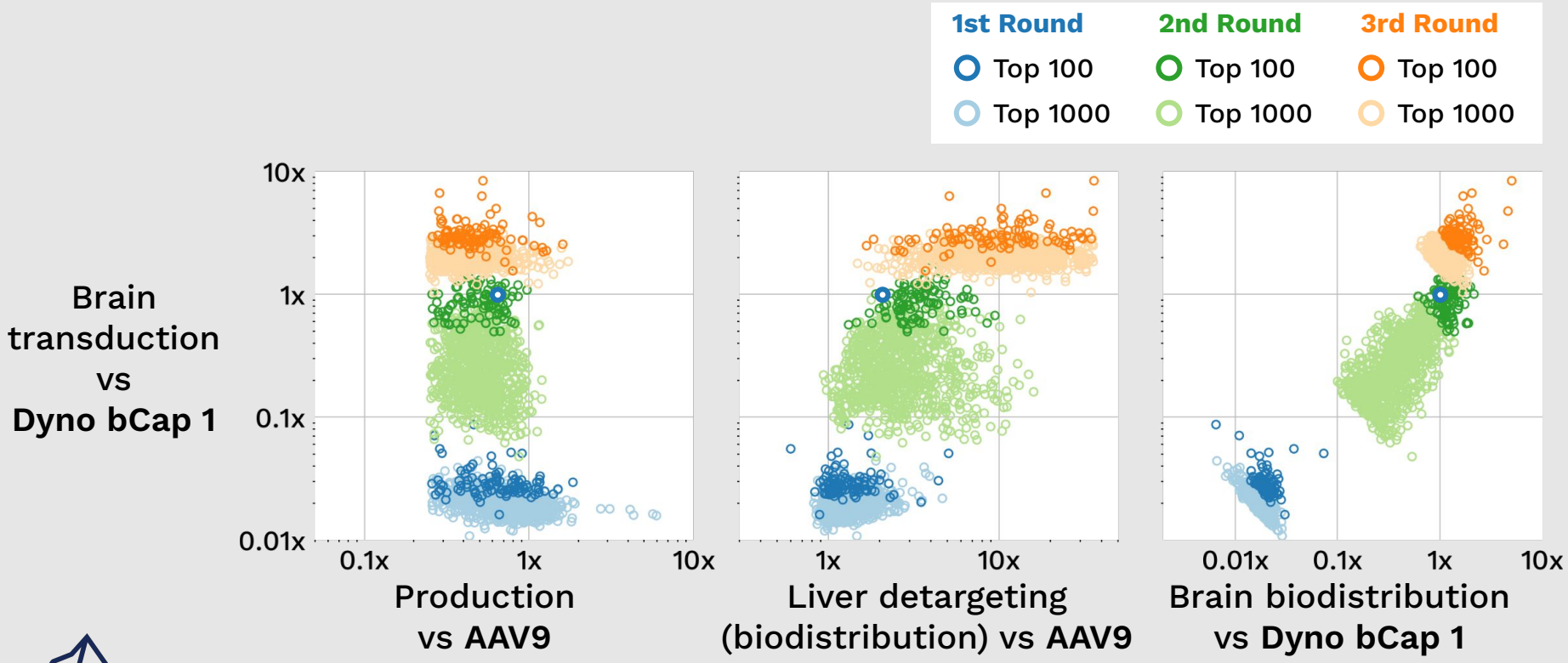
Each high-throughput round improves multiple capsid properties



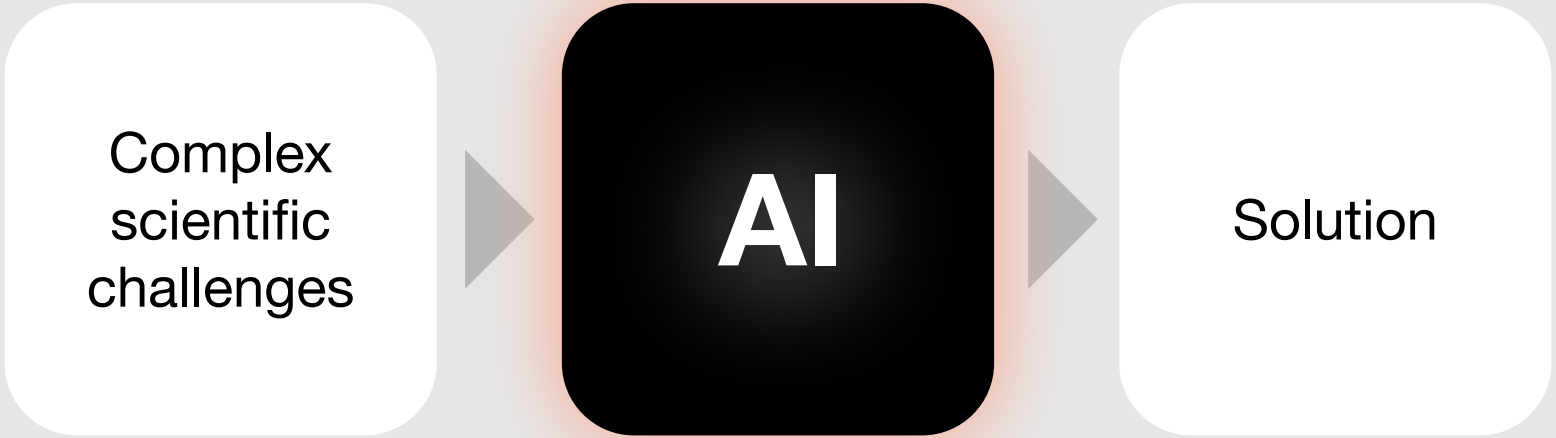
Each high-throughput round improves multiple capsid properties



Each high-throughput round improves multiple capsid properties

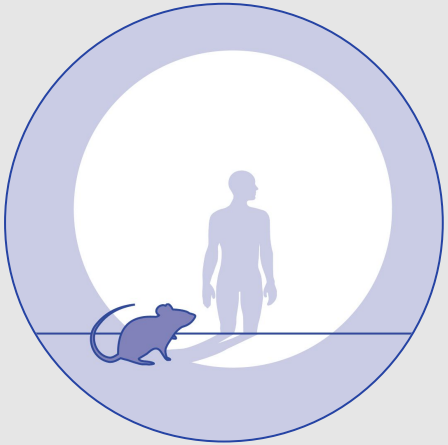


The challenge of designing for high-performance



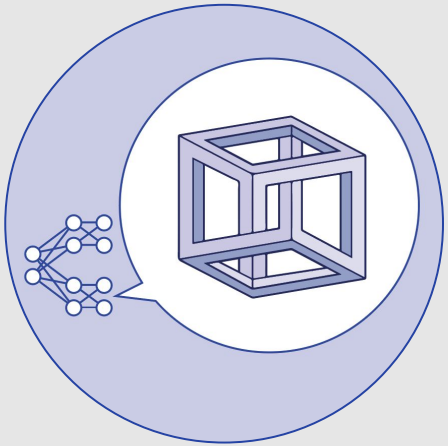
One does not simply … apply AI

When hype faces reality



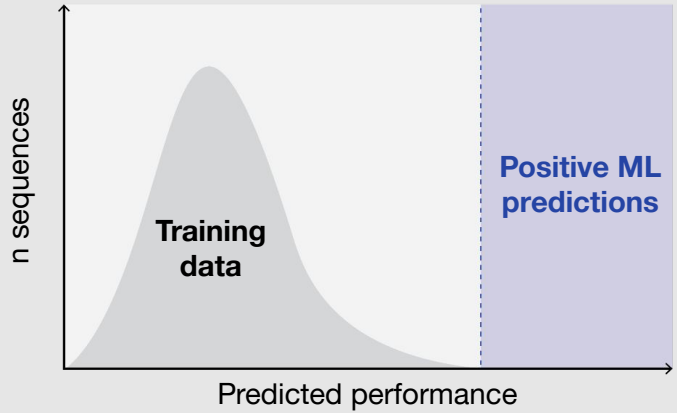
Mice
lie

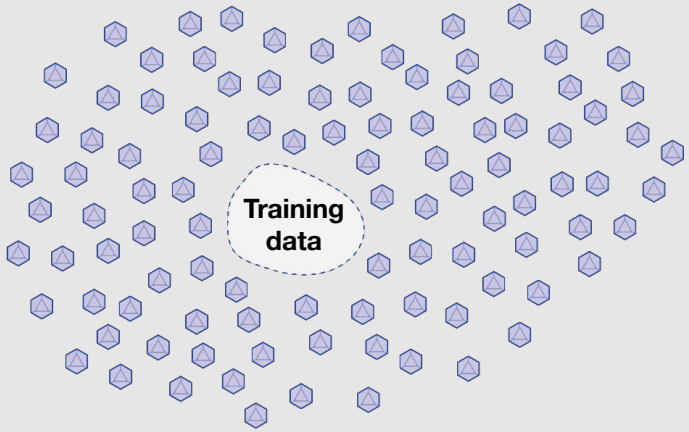
Monkeys
exaggerate



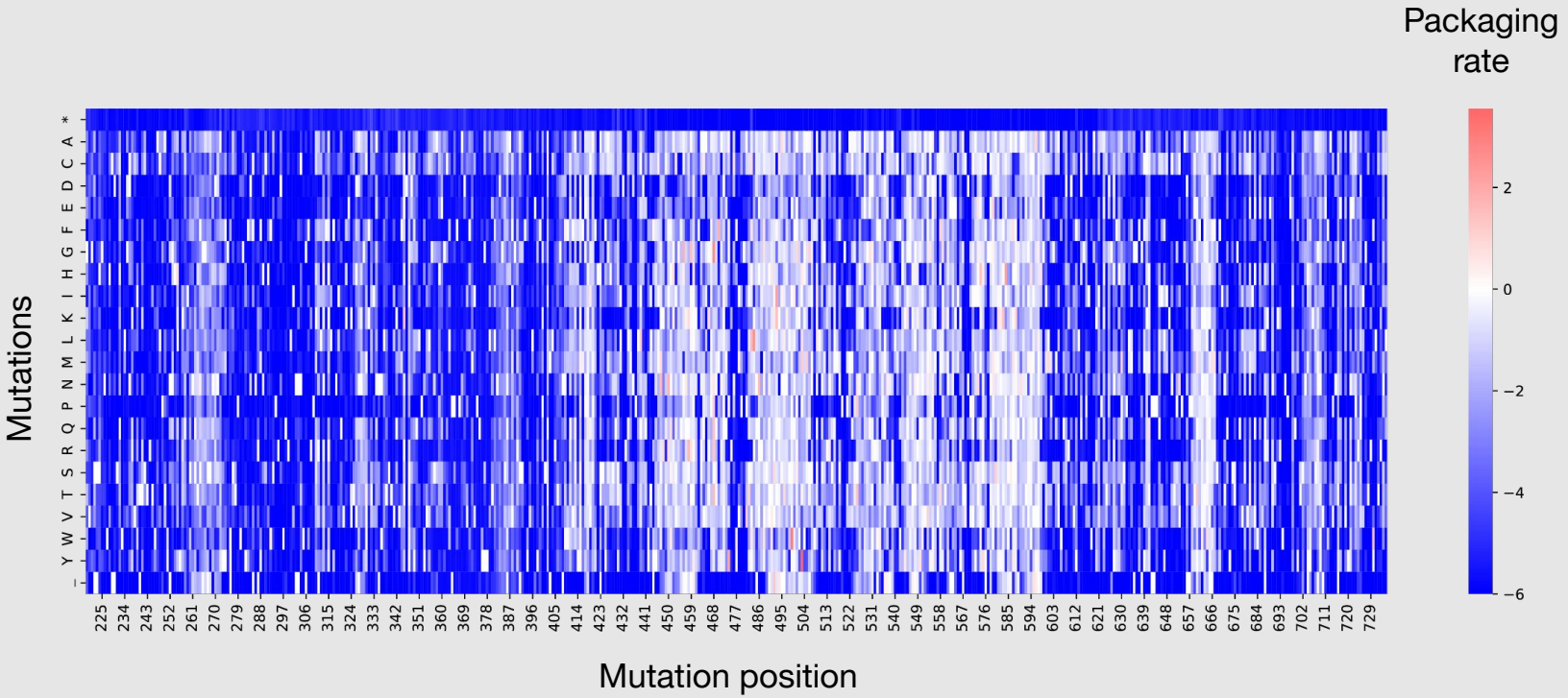
AIs
hallucinate

Aiming to predict performance beyond the training set

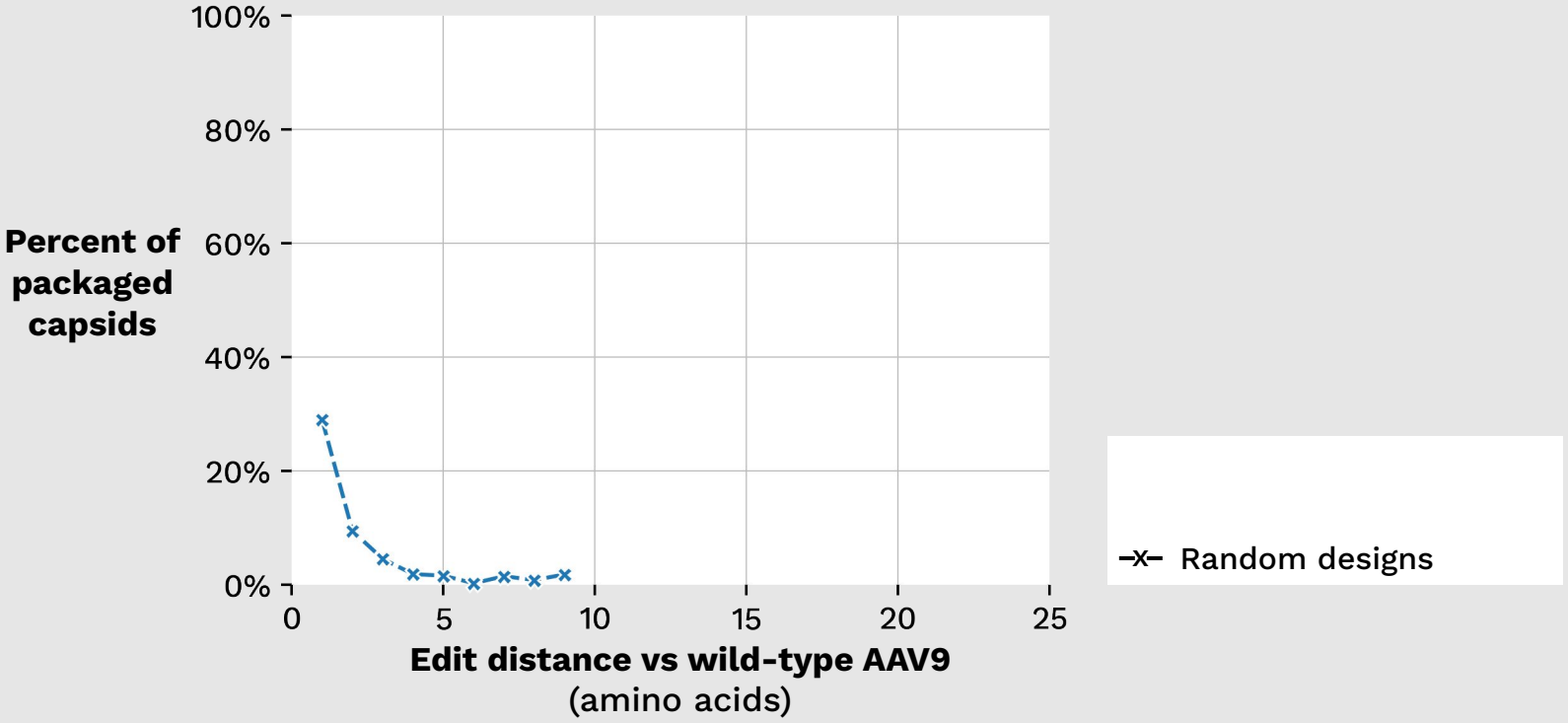




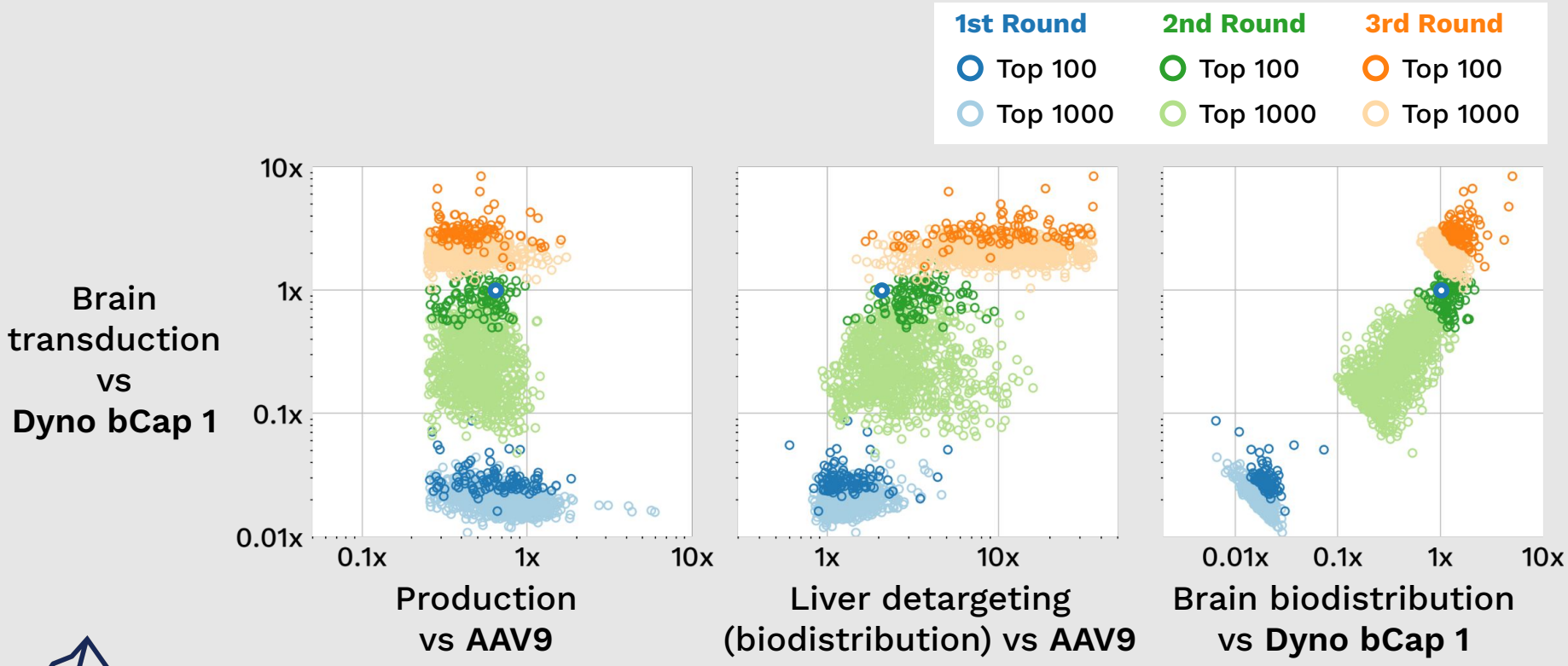
Most capsid mutations are deleterious



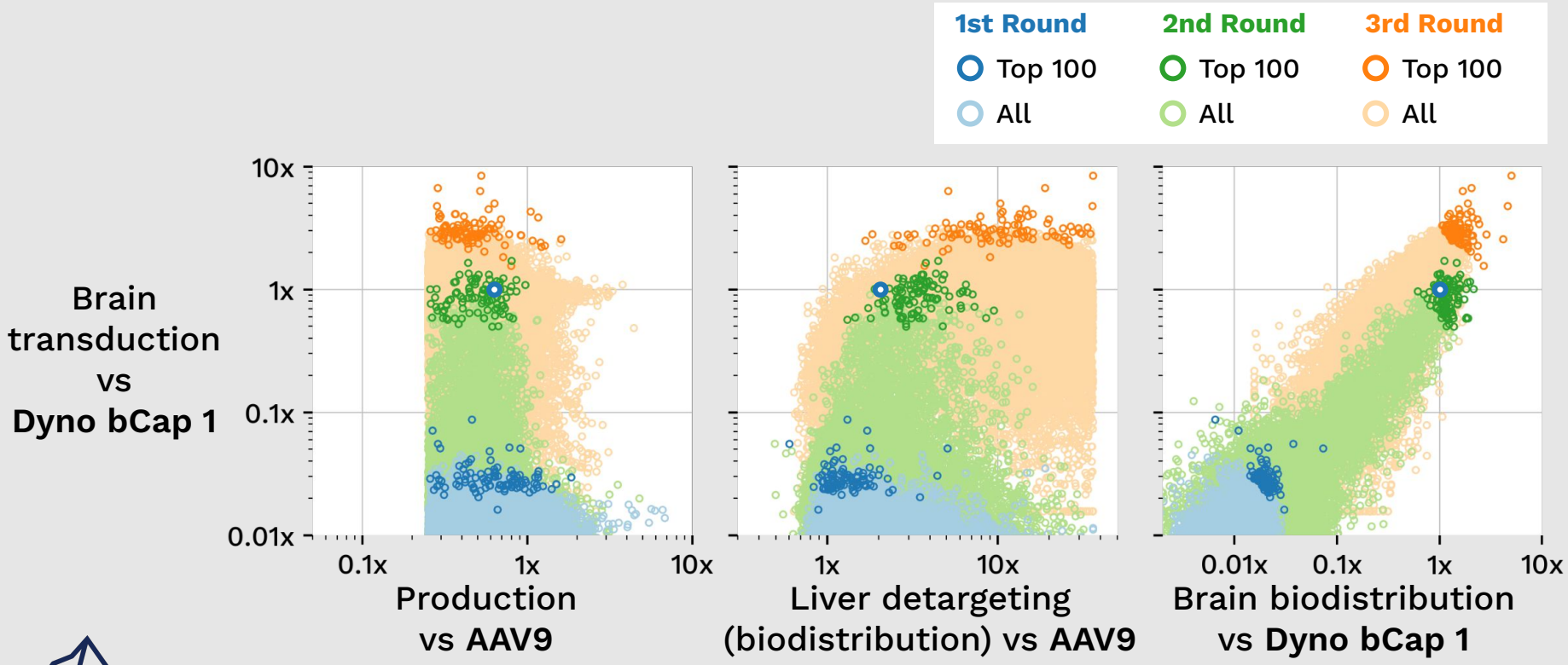
Most capsid mutations are deleterious



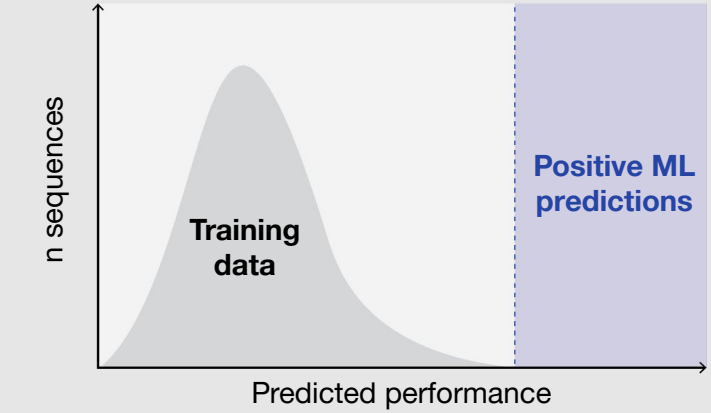
Prediction beyond the training set is challenging

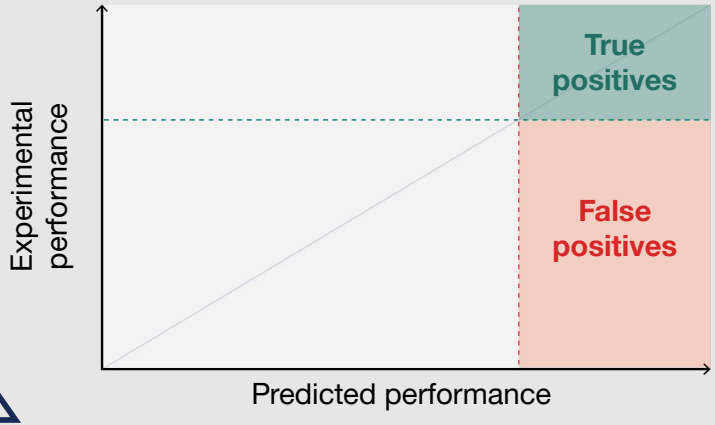


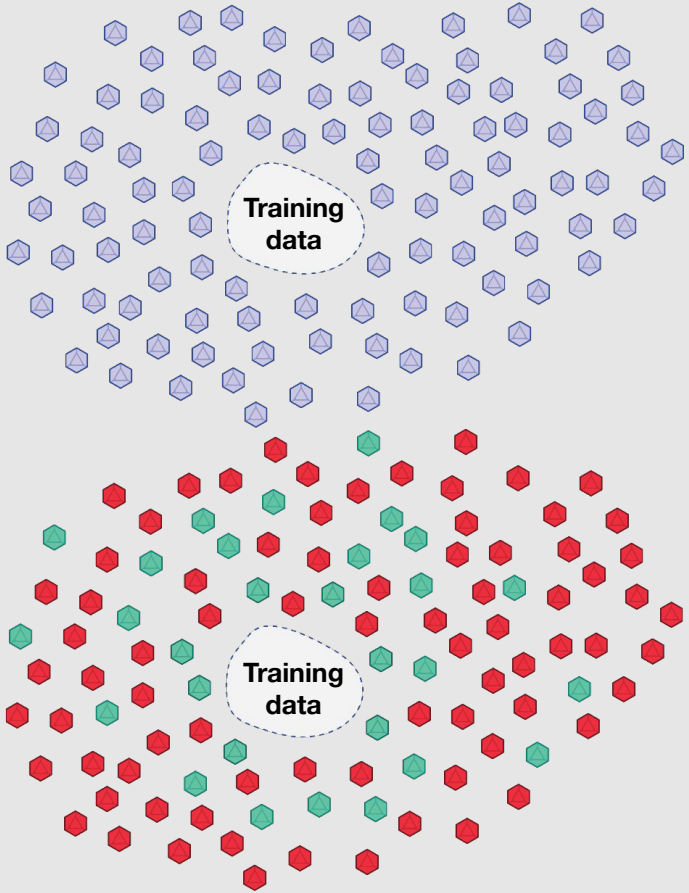
Prediction beyond the training set is challenging



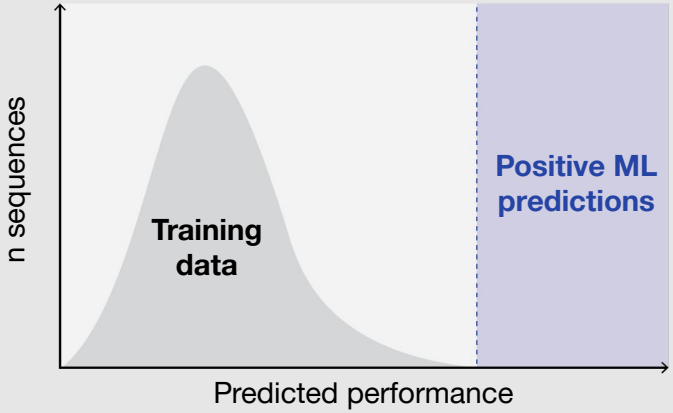
Improving the efficiency of high-performance prediction

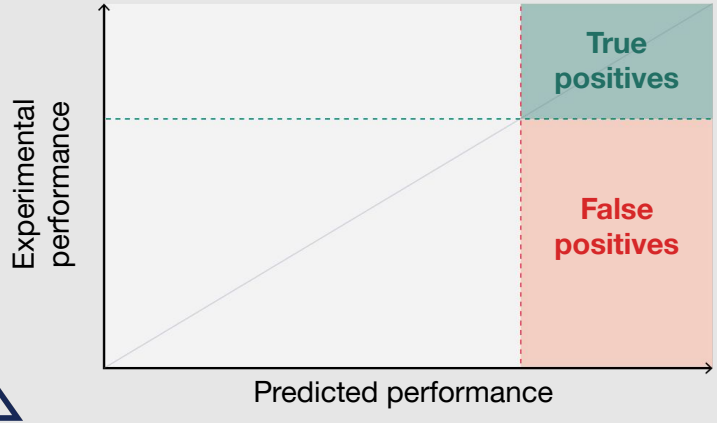


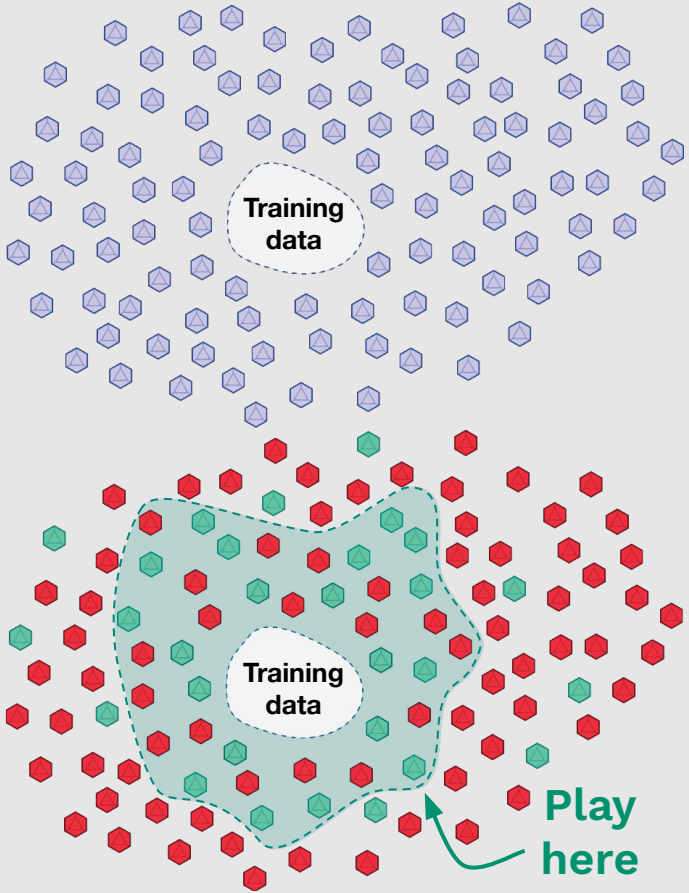




Improving the efficiency of high-performance prediction



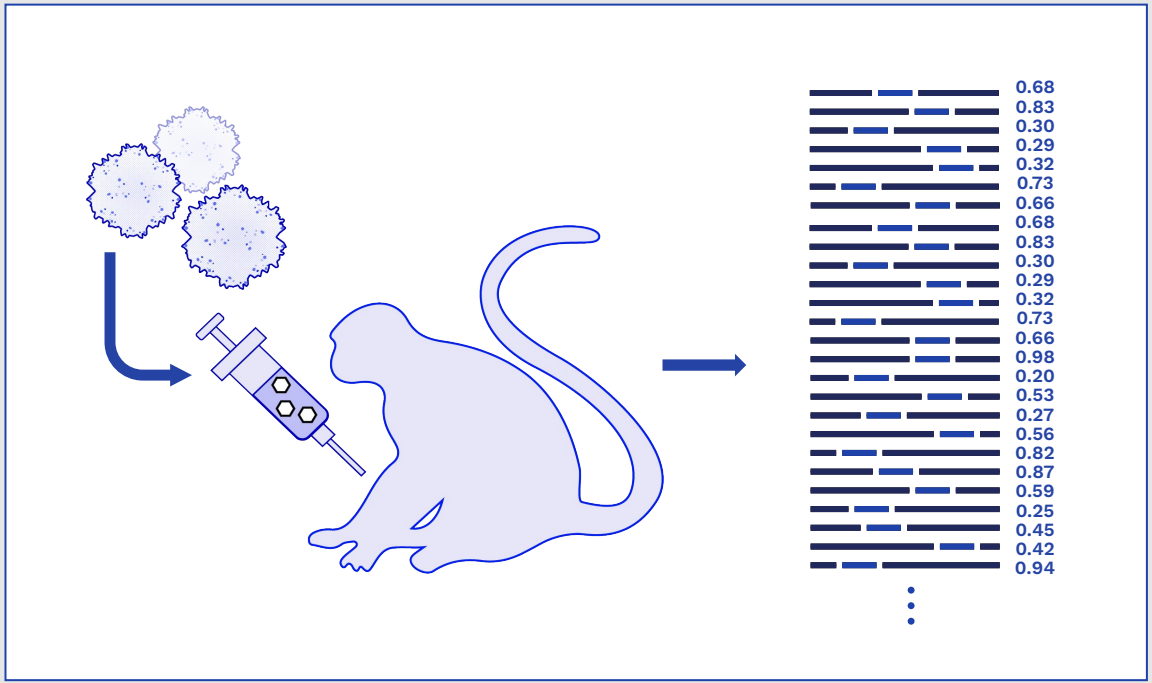




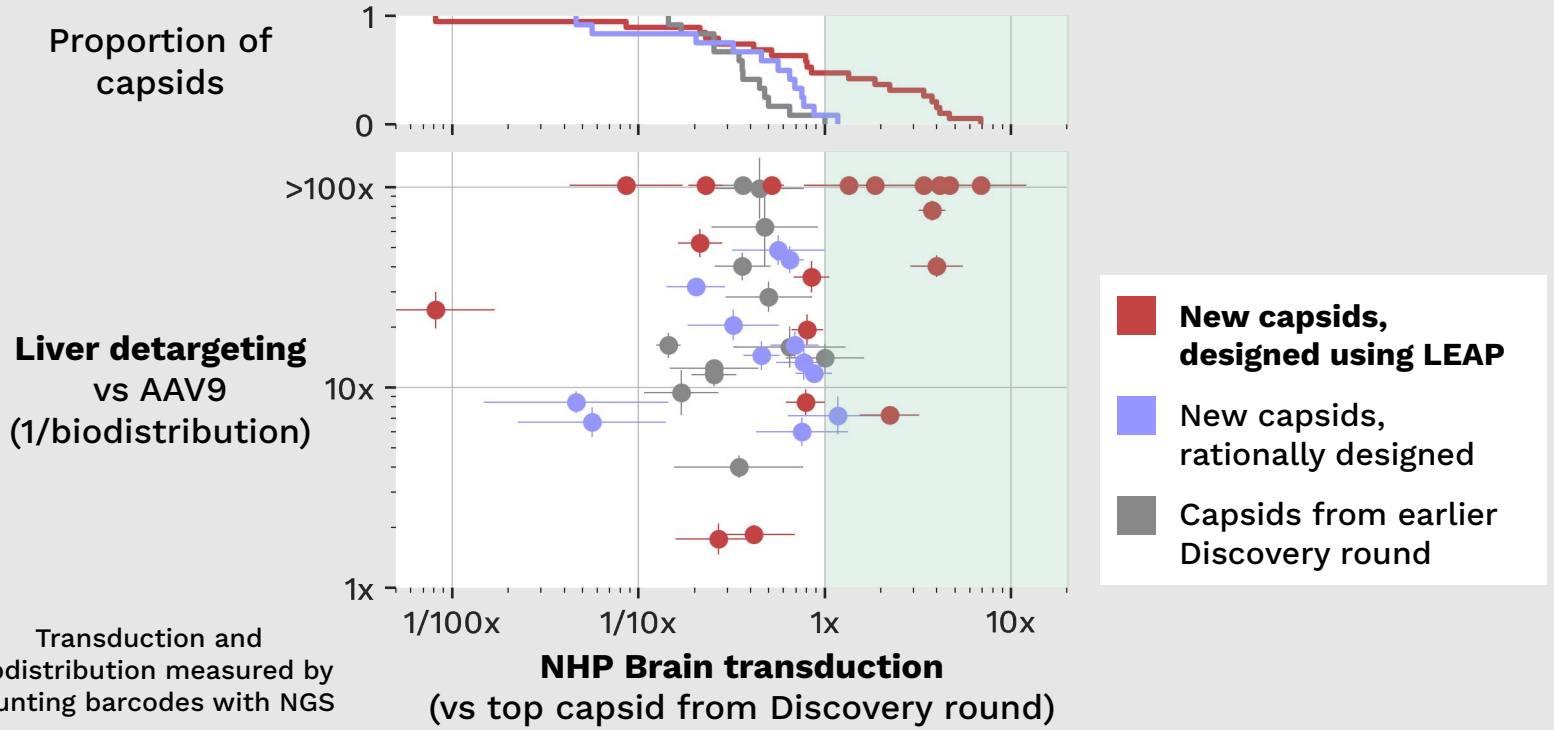
Improving the efficiency of high-performance prediction

>20M capsid sequences

>25B in vivo measurements

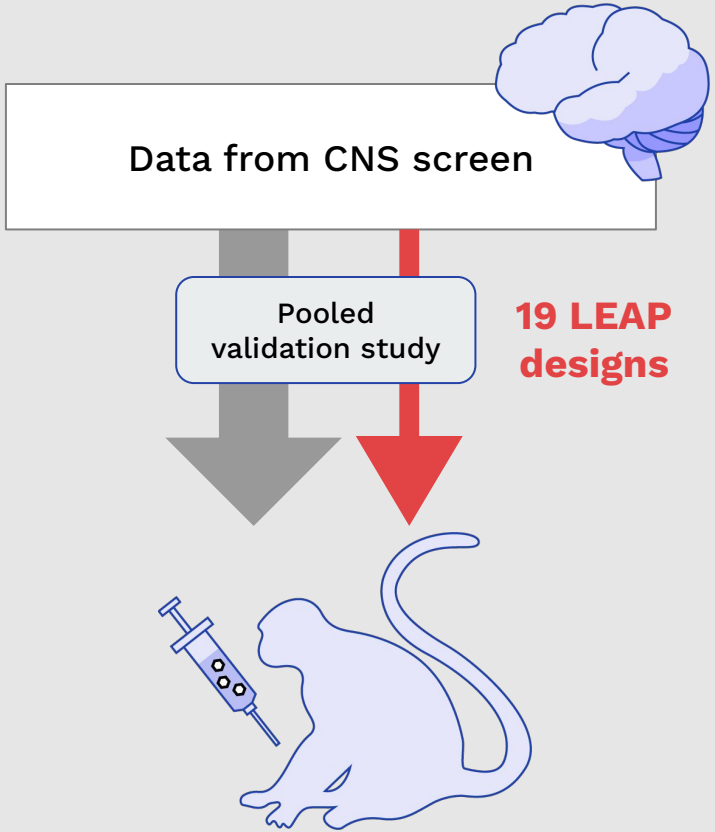


Low-shot Efficient Accelerated Performance (LEAP)



Transduction and biodistribution measured by counting barcodes with NGS

Low-shot Efficient Accelerated Performance



90%

17 **packaged** effectively

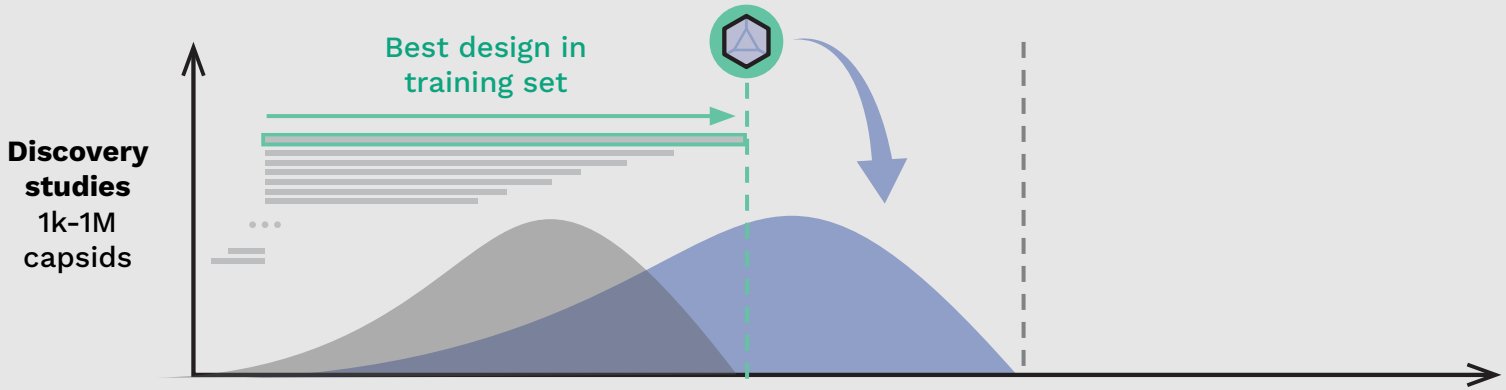
47%

9 performed **better than anything we had observed before**

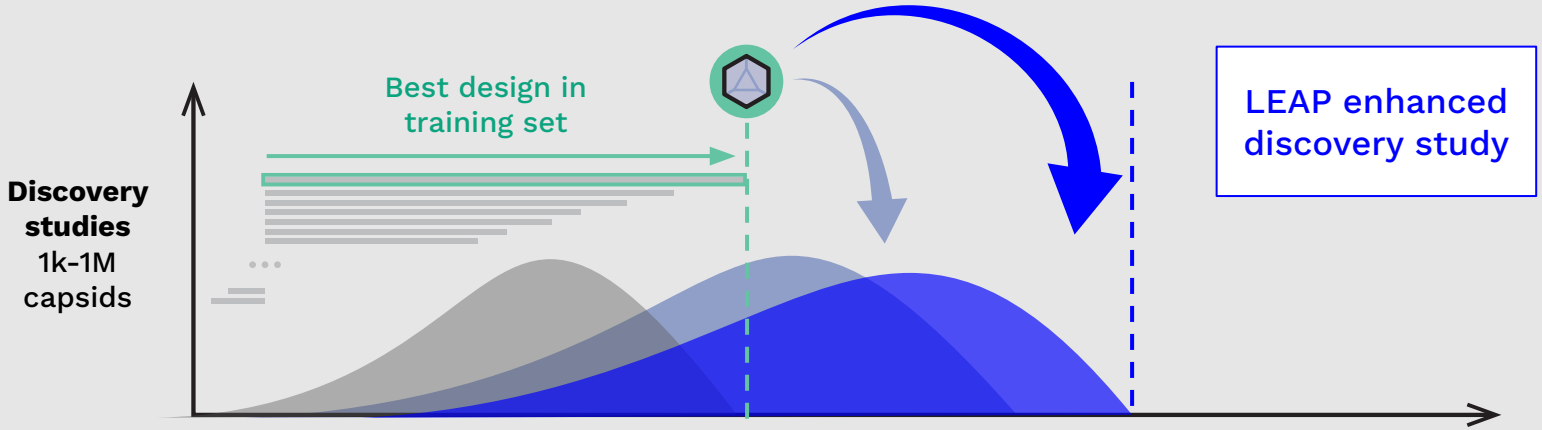
6x

Top capsid performed **6x better** than the best known prior capsid

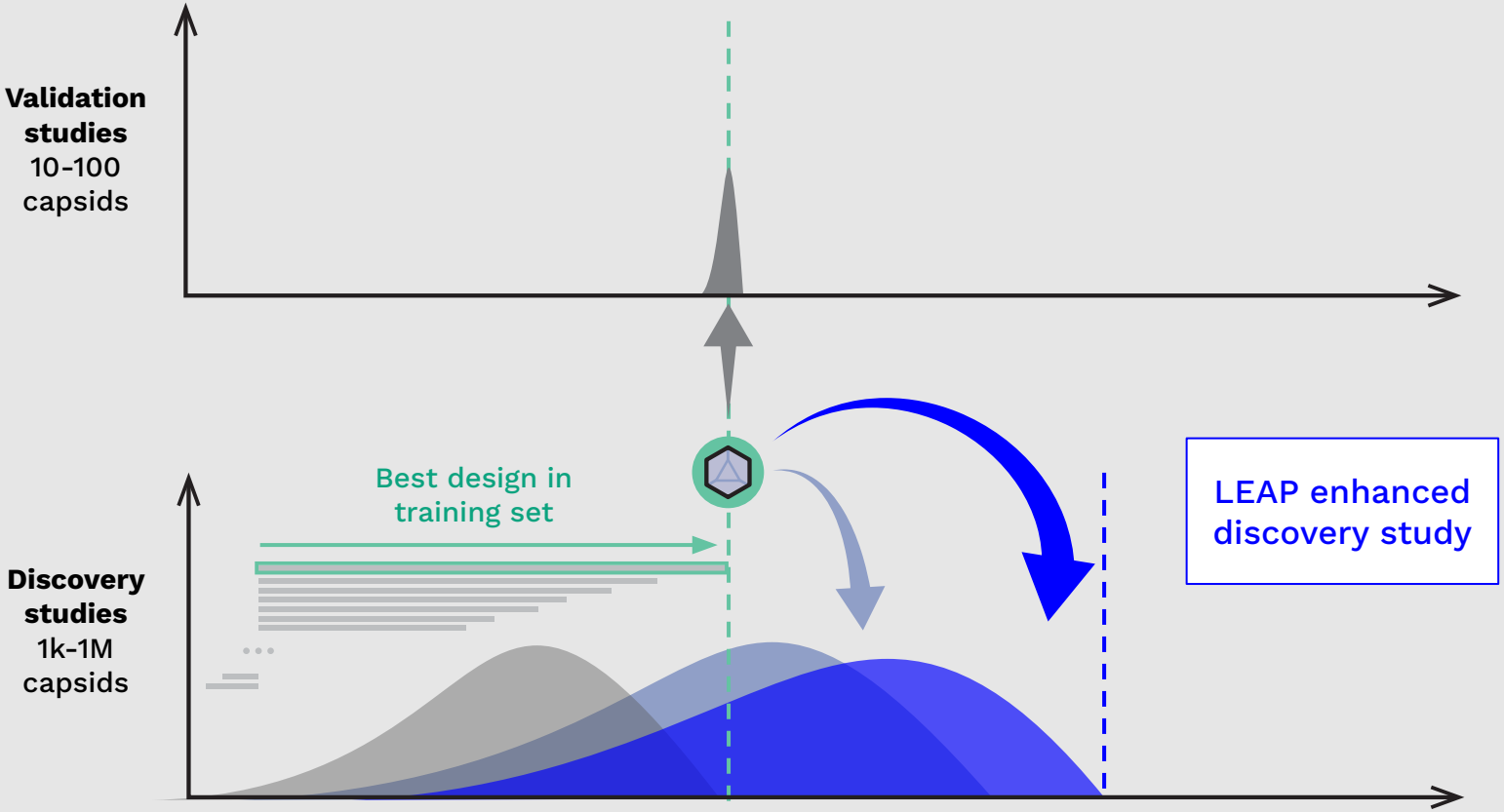
LEAP enhances capsid discovery



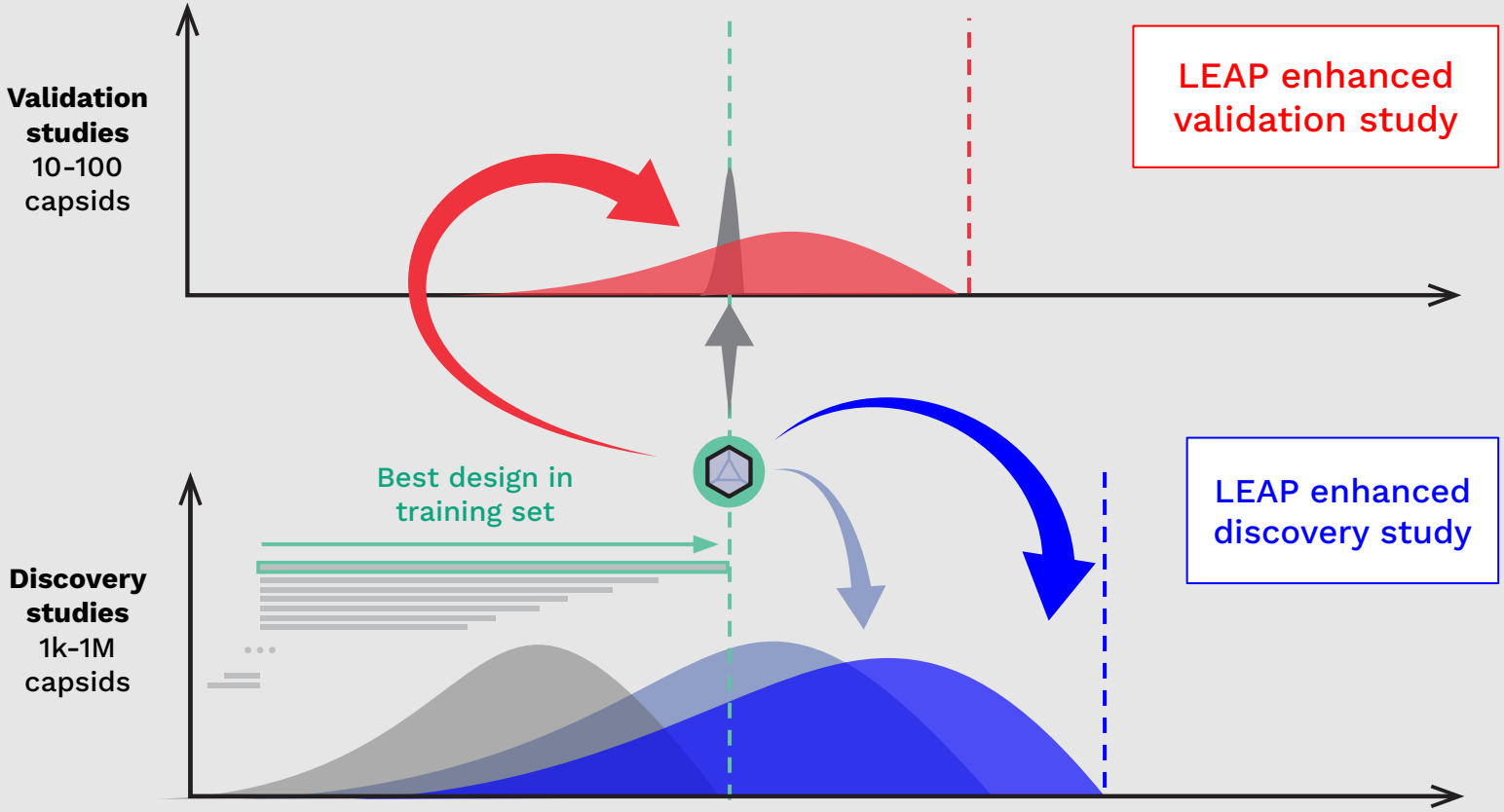
LEAP enhances capsid discovery



LEAP enhances capsid validation



LEAP enhances capsid validation



LE...on

Abstract #301

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

Mugdha Deshpande - Friday May 10
5:00pm - 5:15PM EDT, Ballroom 4

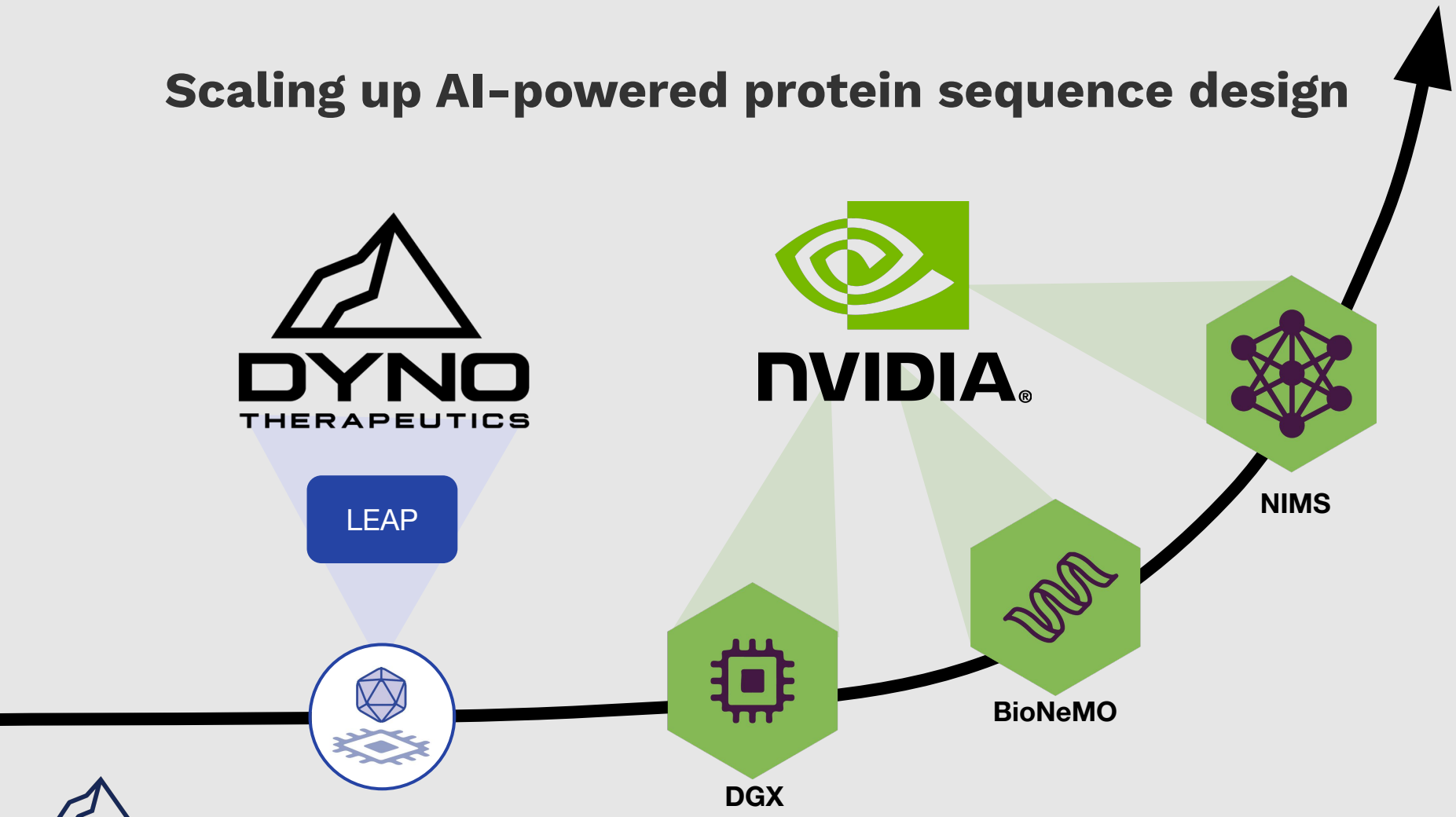
Validation studies
10-100 capsids

LEAP enhanced validation study

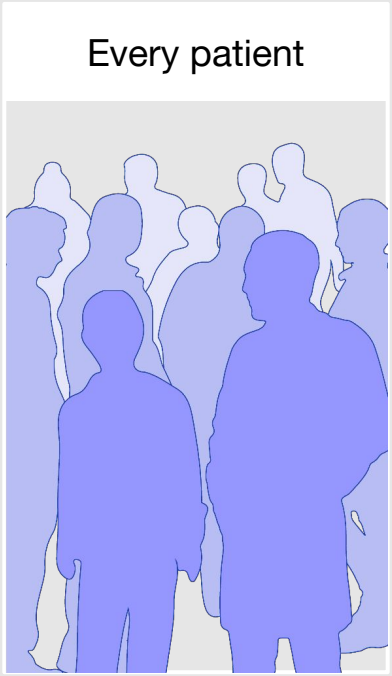
Discovery studies
1k-1M capsids

LEAP enhanced discovery study

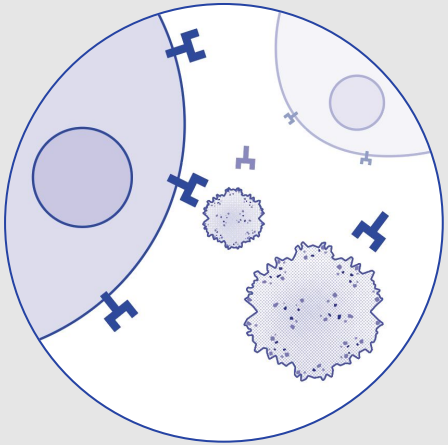
Scaling up AI-powered protein sequence design



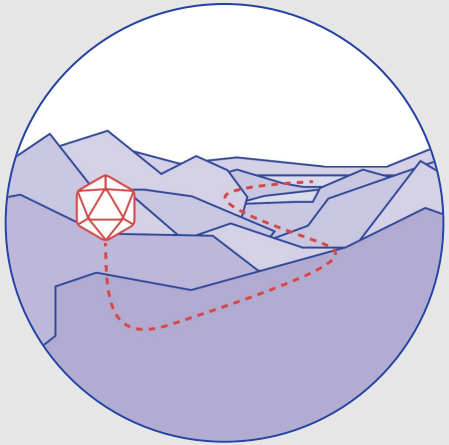
Expanding the reach of gene therapy



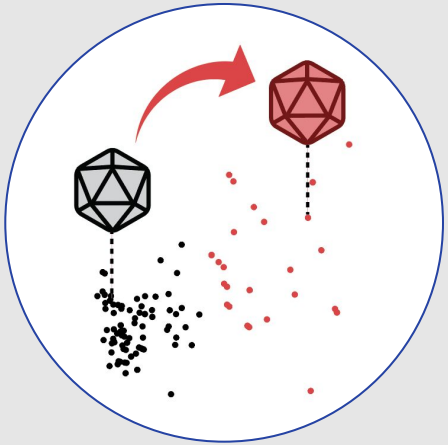
Expanding the reach of gene therapy



Problem

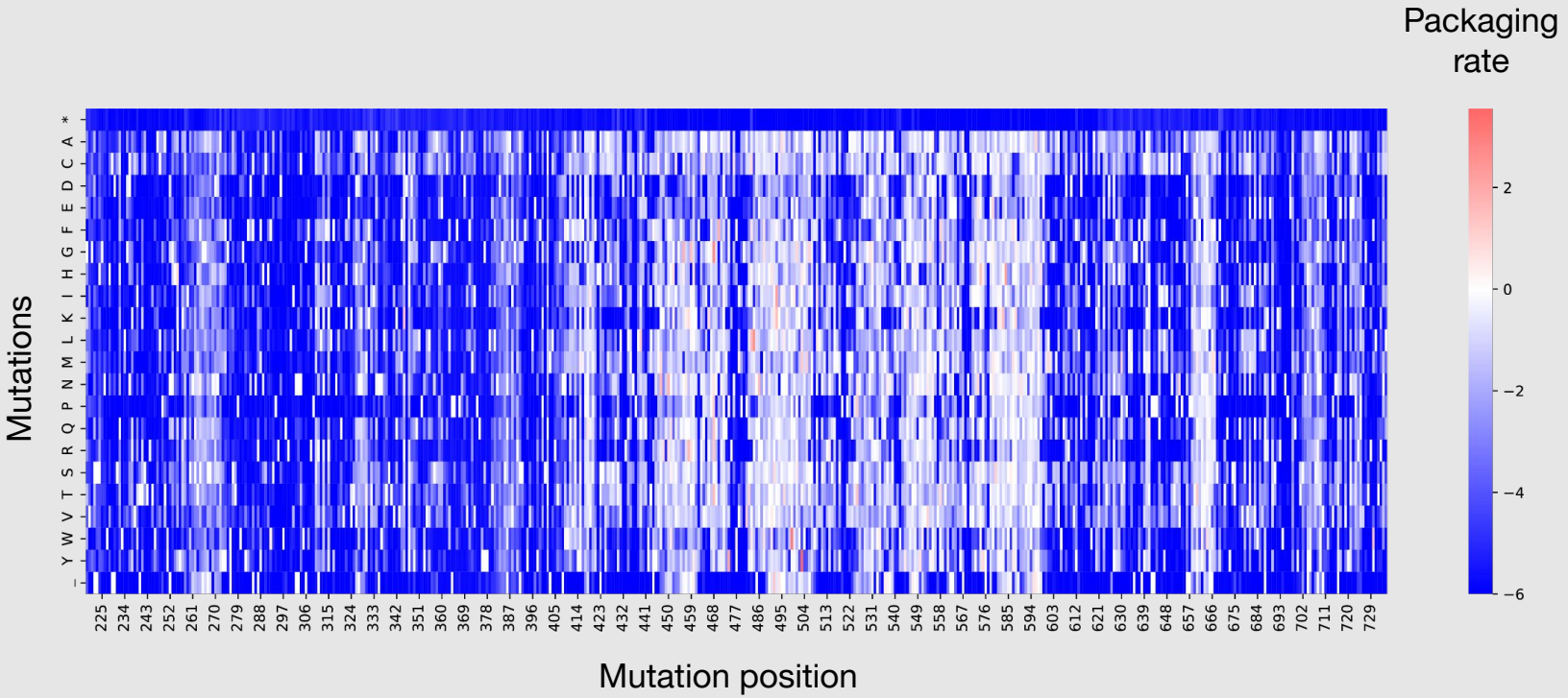


Challenge

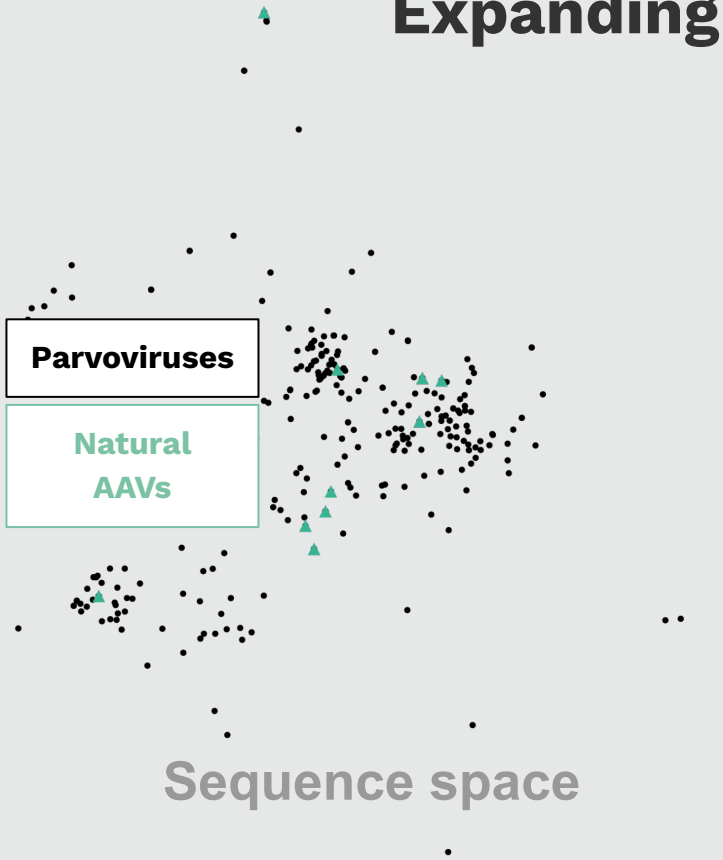


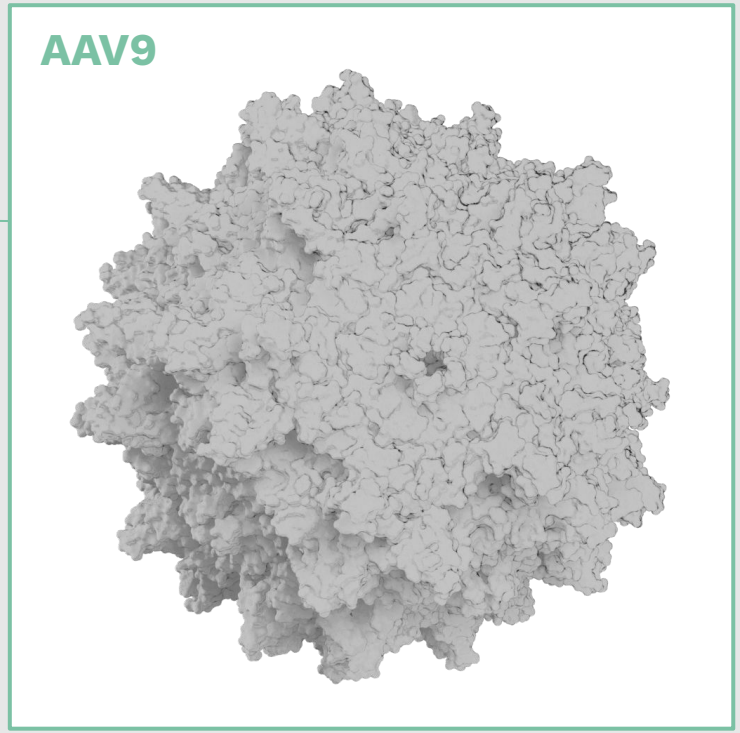
Solution

Most capsid mutations are deleterious

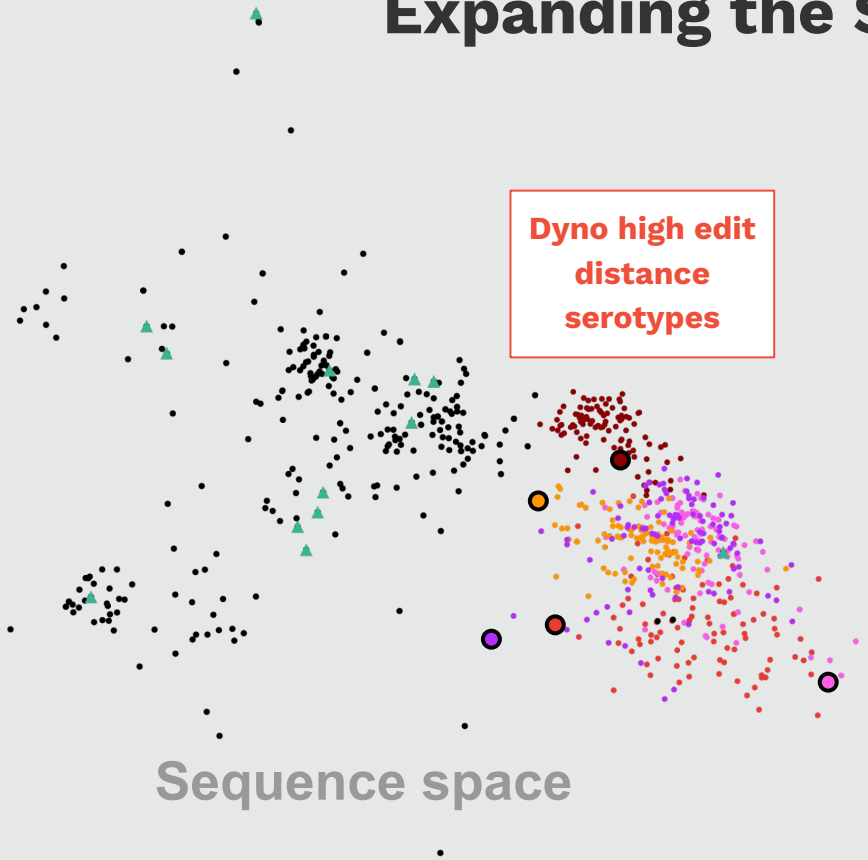


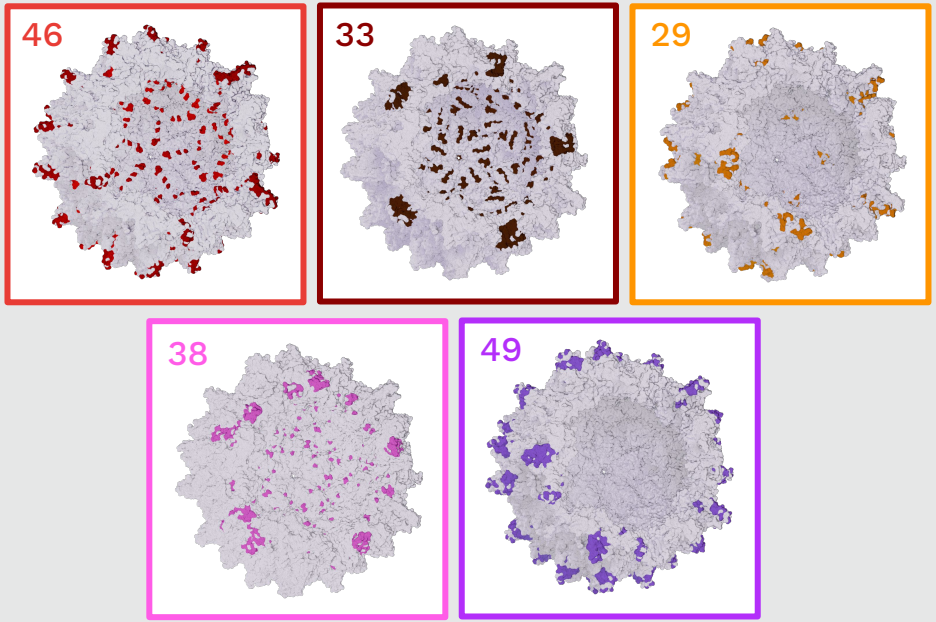
Expanding the Serotype Frontier



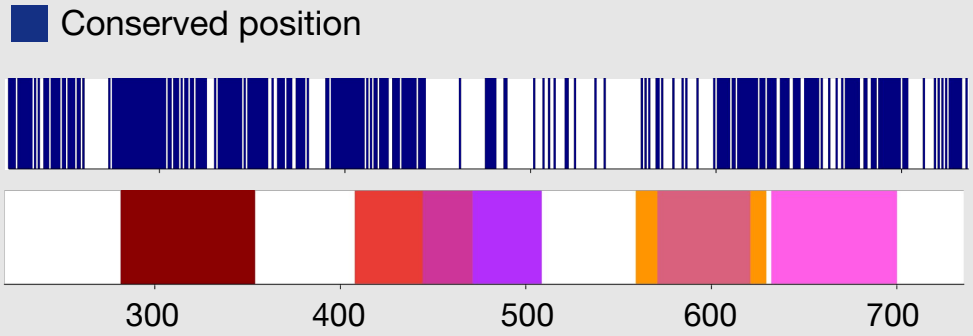


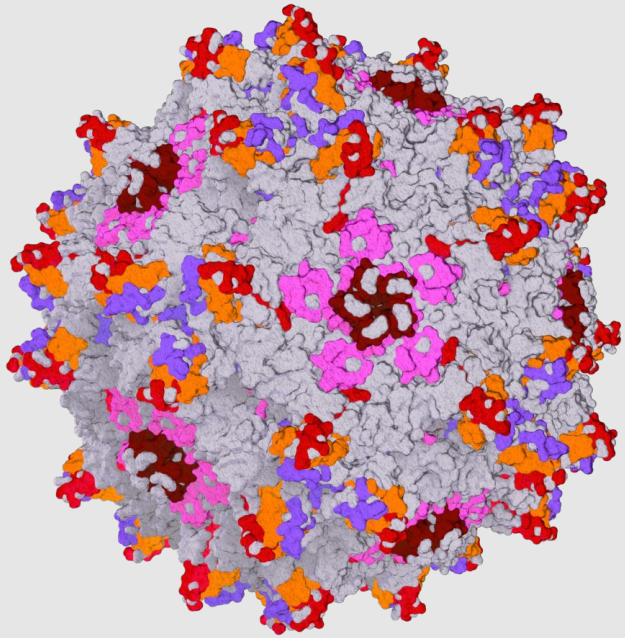
Expanding the Serotype Frontier



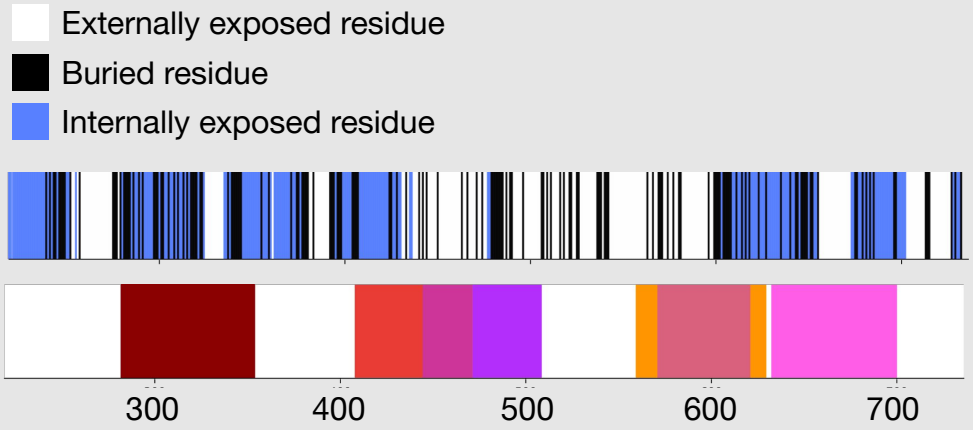


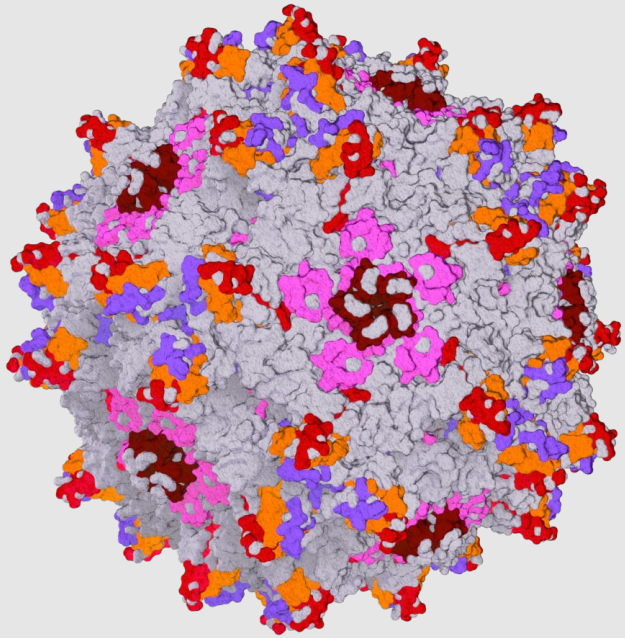
Modifying even conserved and buried regions



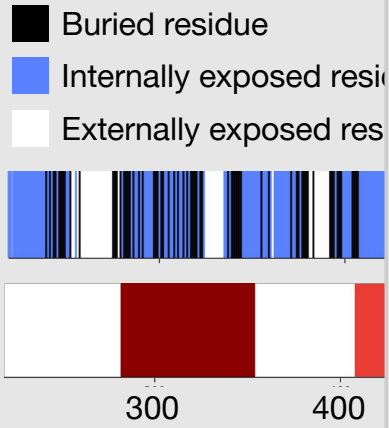


Modifying even conserved and buried regions



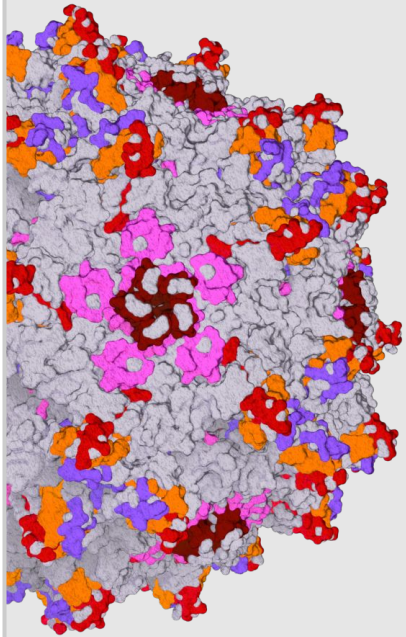


Modifyin d regions

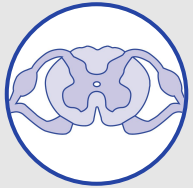
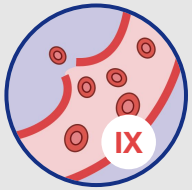
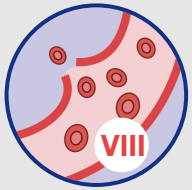
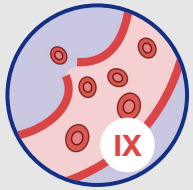


[Poster](#) #1465
Expanding the Serotype Frontier: Design of Synthetic AAV Capsids with Artificial Intelligence

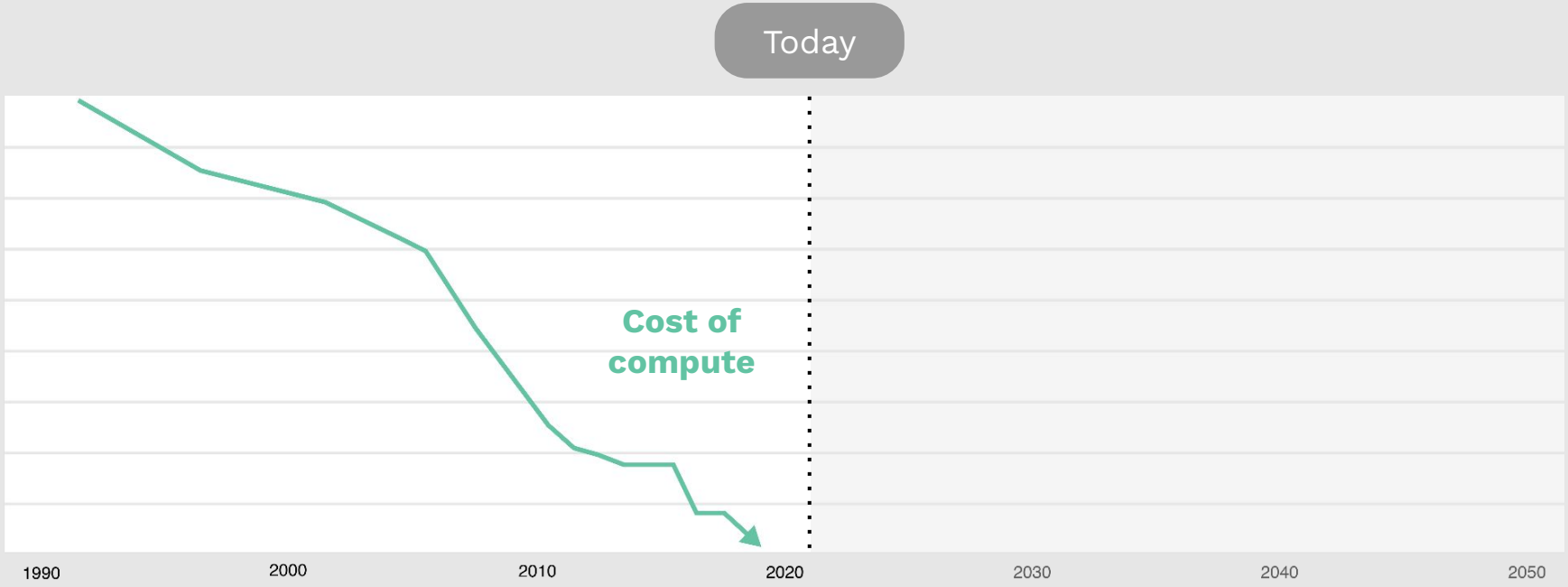
Saum Sinai
May 10, 2024 12:00 PM EDT,
Exhibit Hall



How can exponential change help more patients?

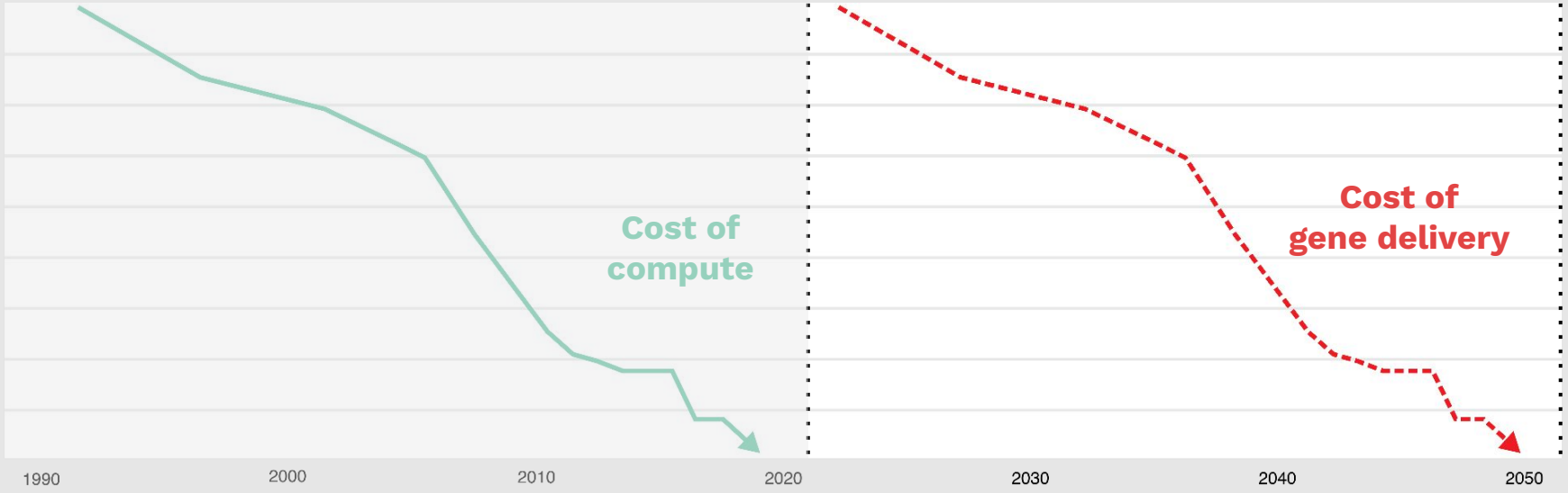
LUXTURNA	ZOLGENSMA	HEMGENIX	ELEVIDYS	ROCTAVIAN	BEQVEZ
December 2017	May 2019	November 2022	June 2023	June 2023	April 2024
					
$850,000	$2.1 million	$3.5 million	$2.9 million	$2.9 million	$3.5 million

Bringing the cost of delivery down to zero



Bringing the cost of delivery down to zero

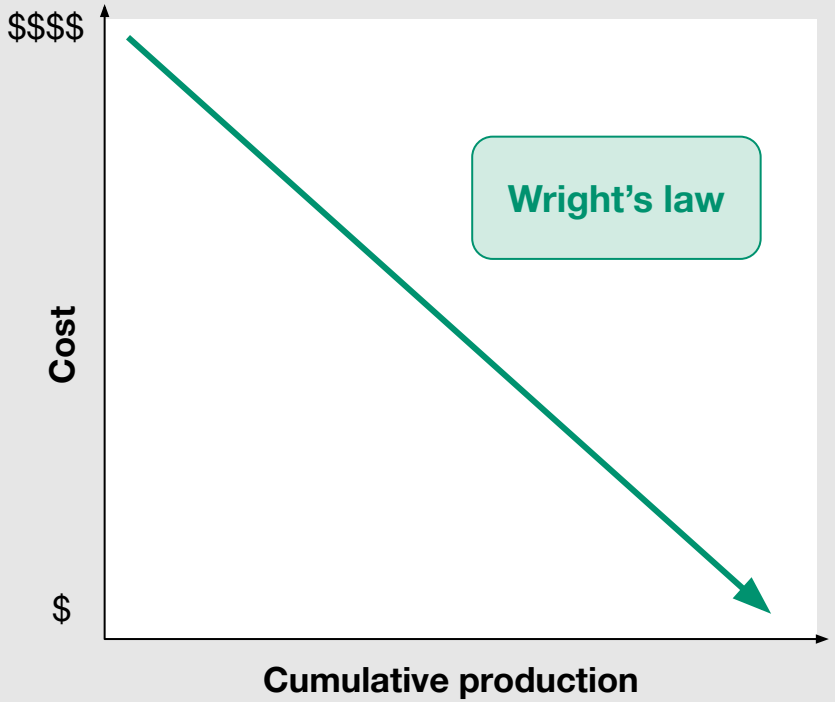
Desired future

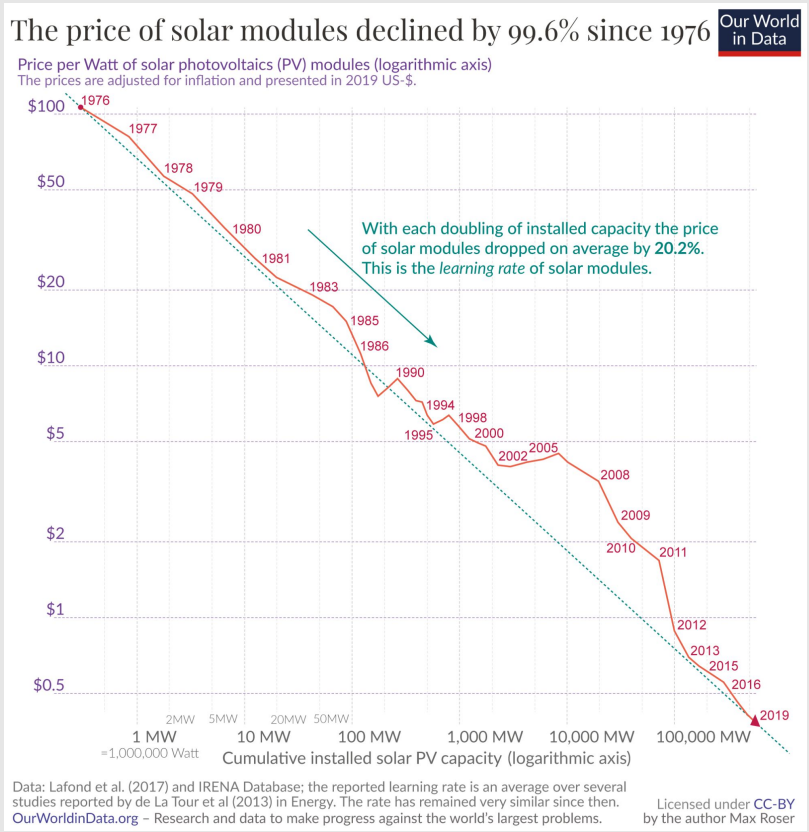



Entering
an AI Era

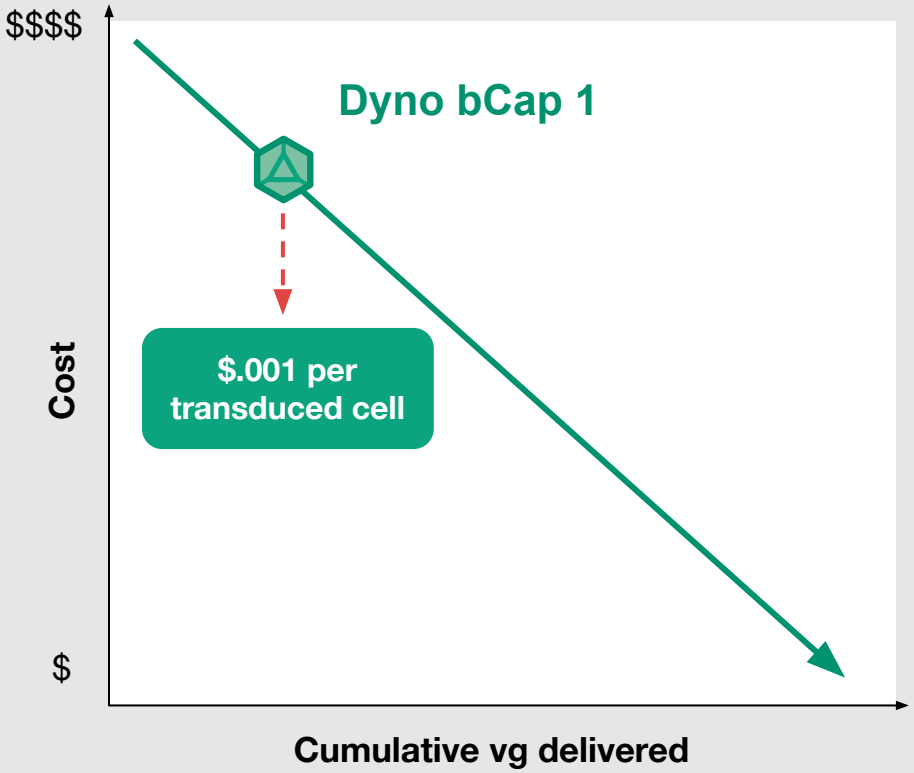
via the Century of Biology

Cost falls as production increases

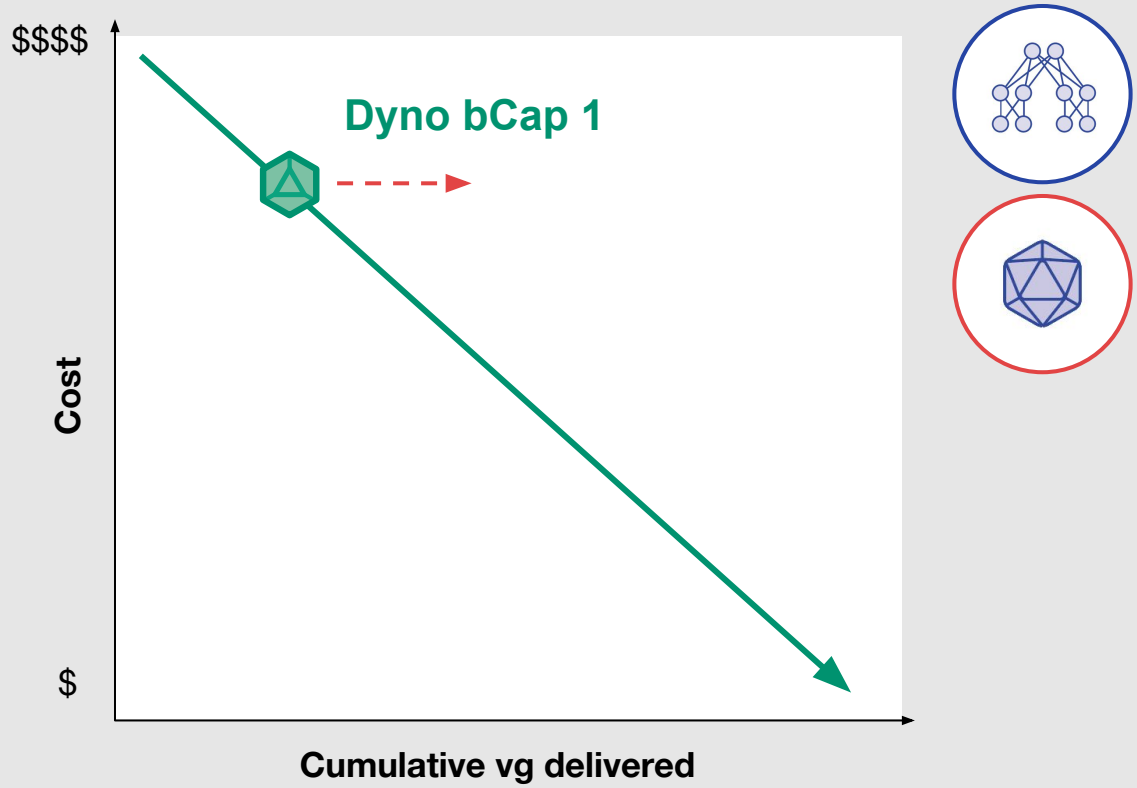




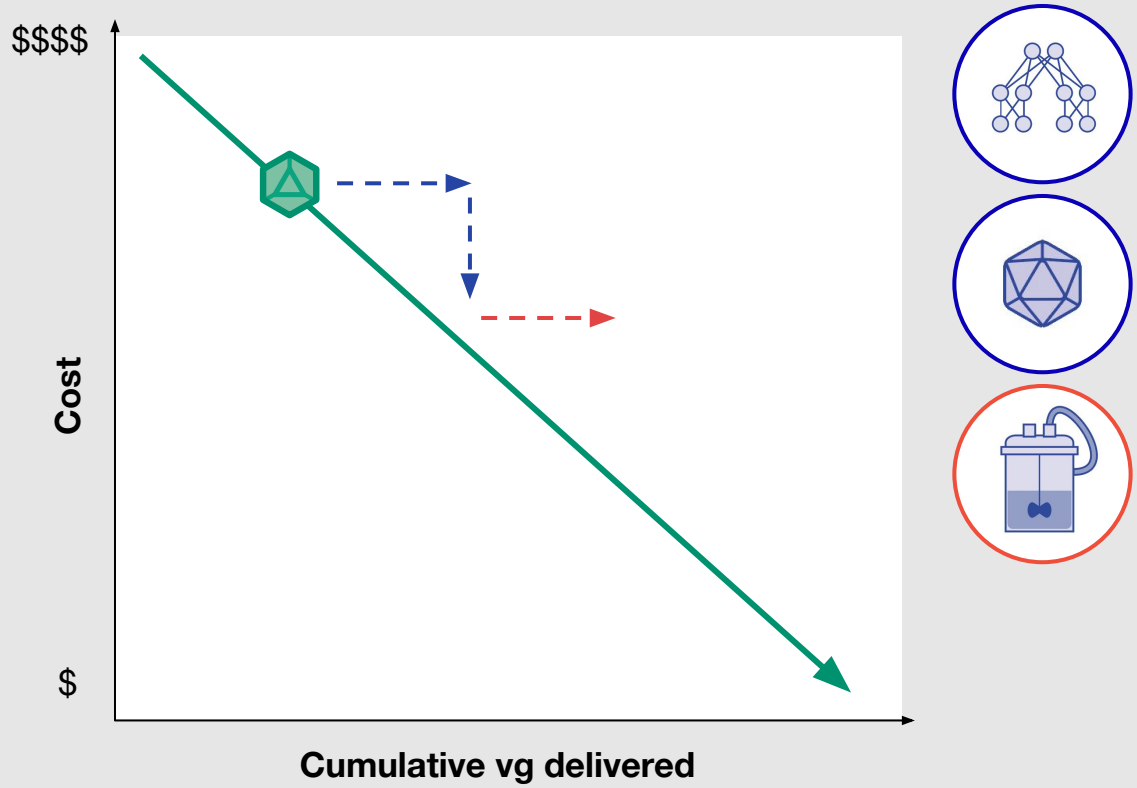
The century of biology



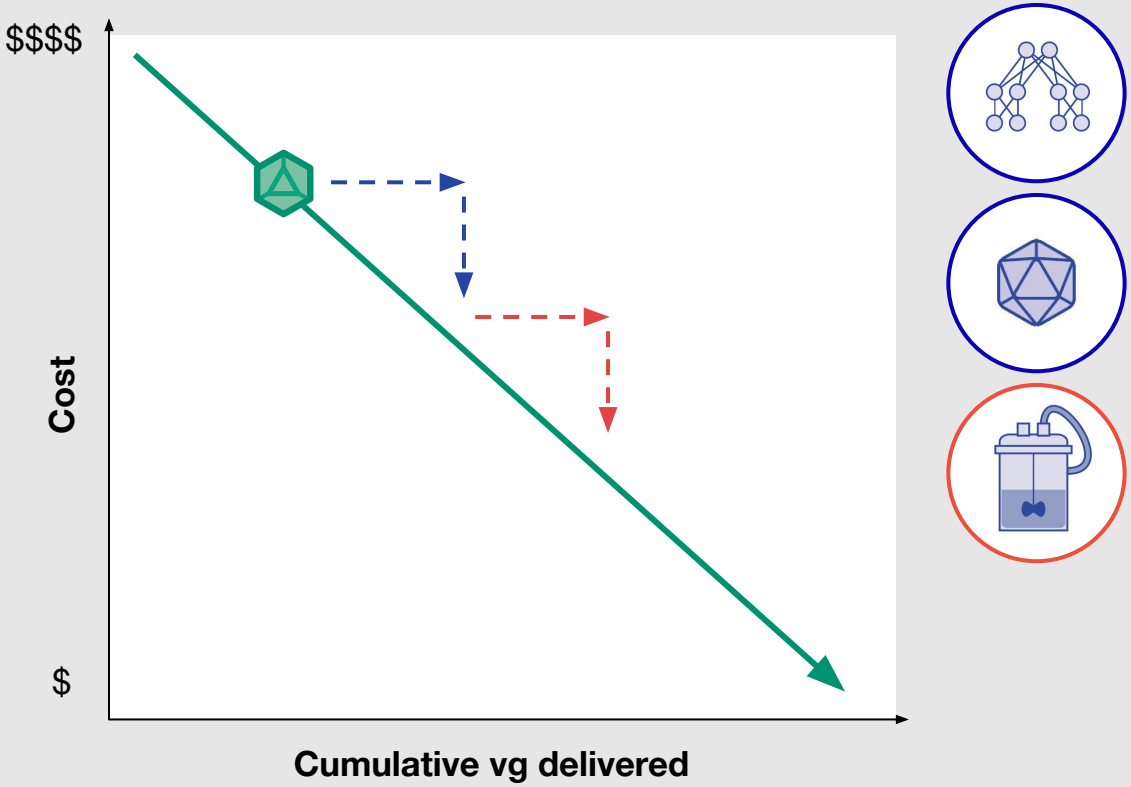
The century of biology



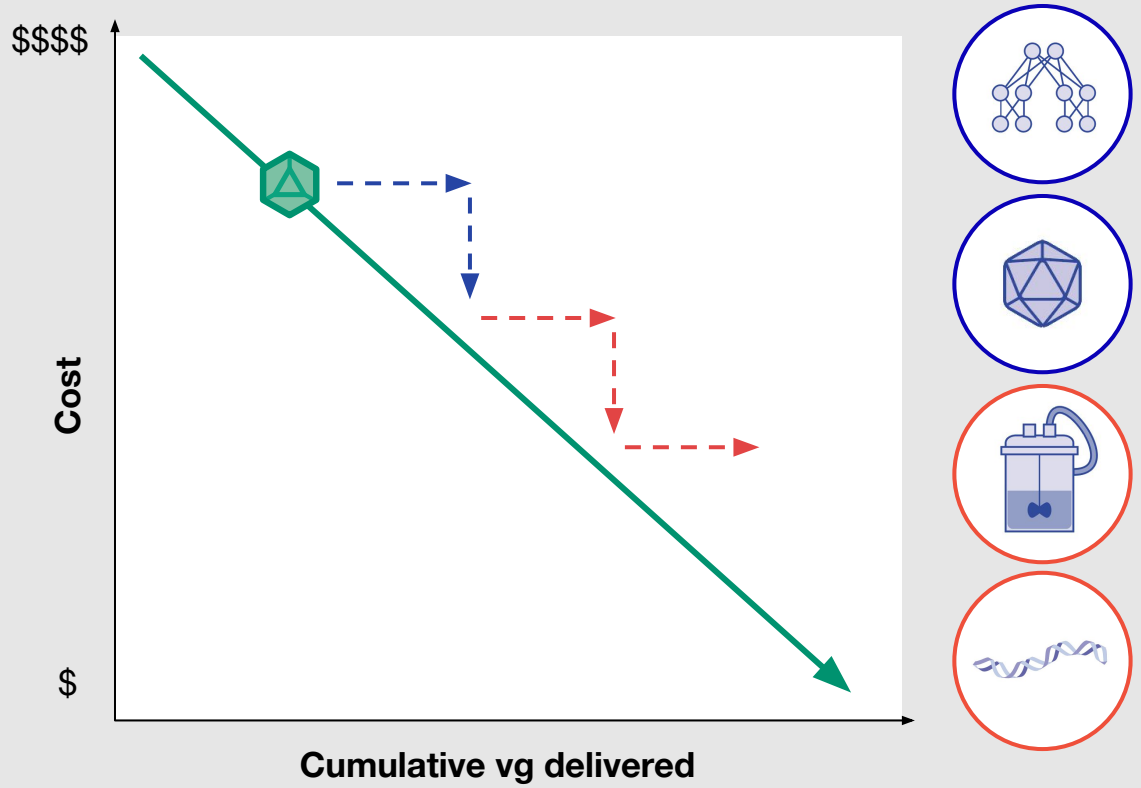
The century of biology



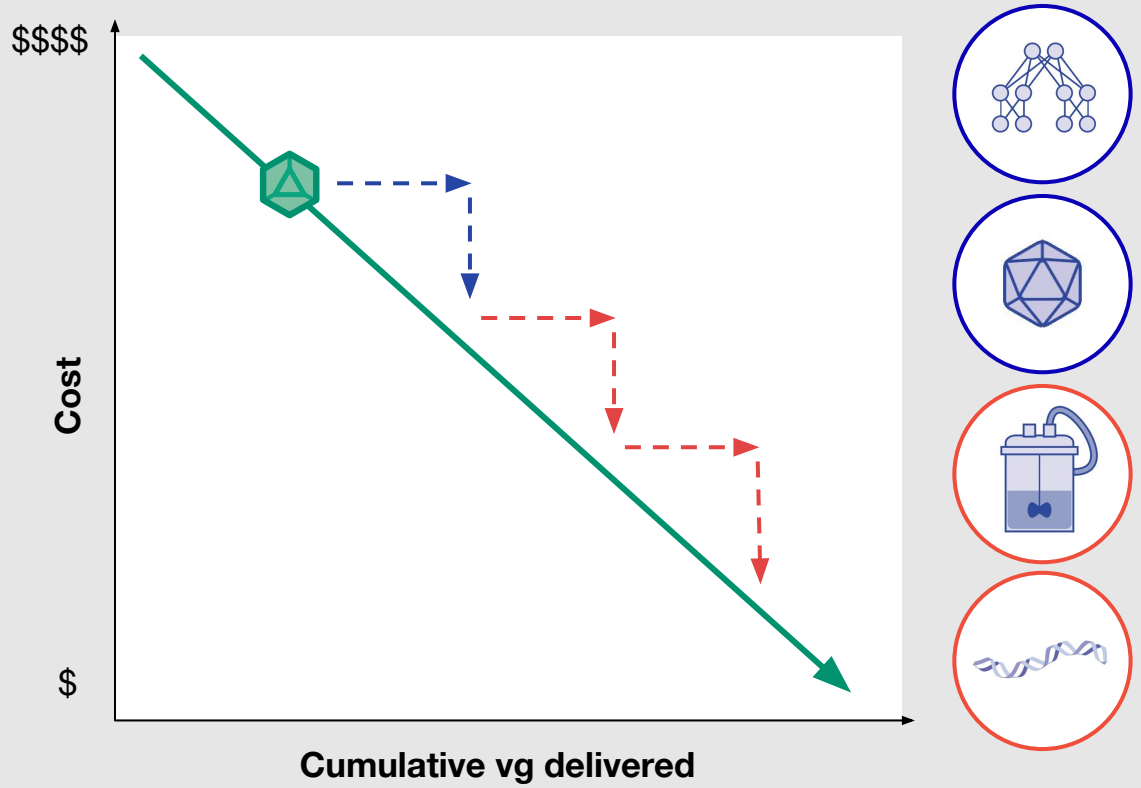
The century of biology



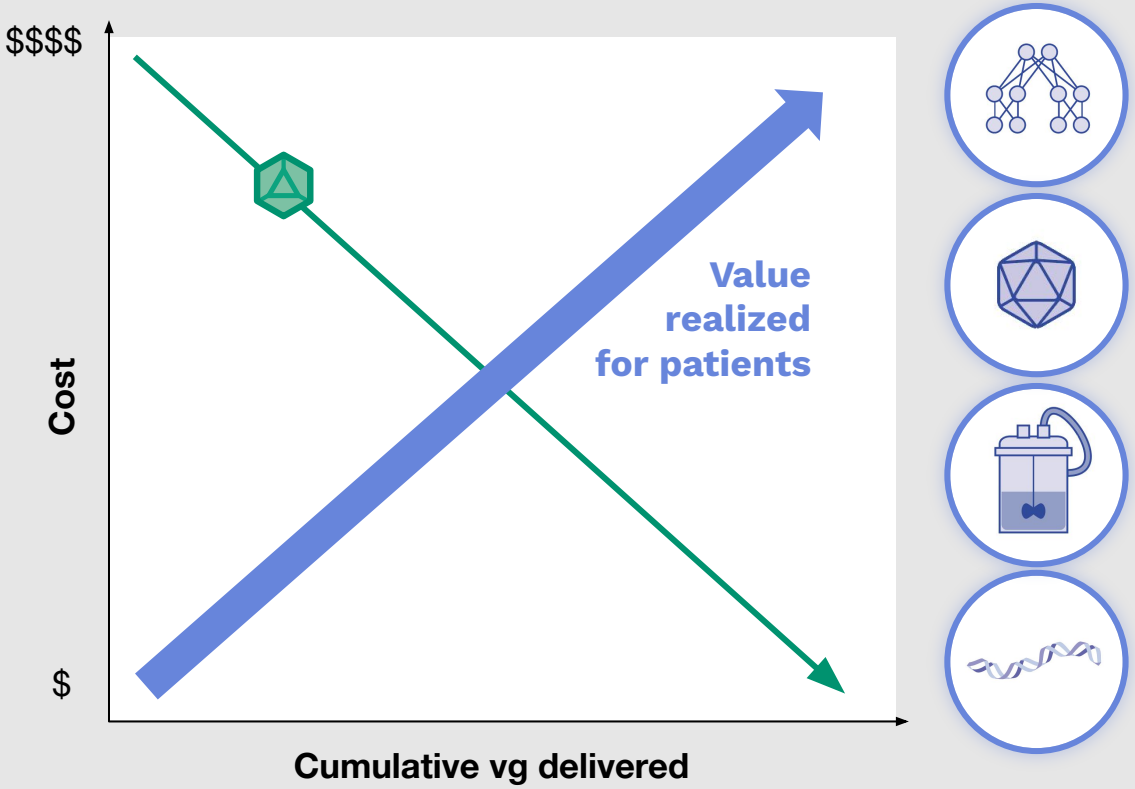
The century of biology



The century of biology



The century of biology




Everyone
can help