

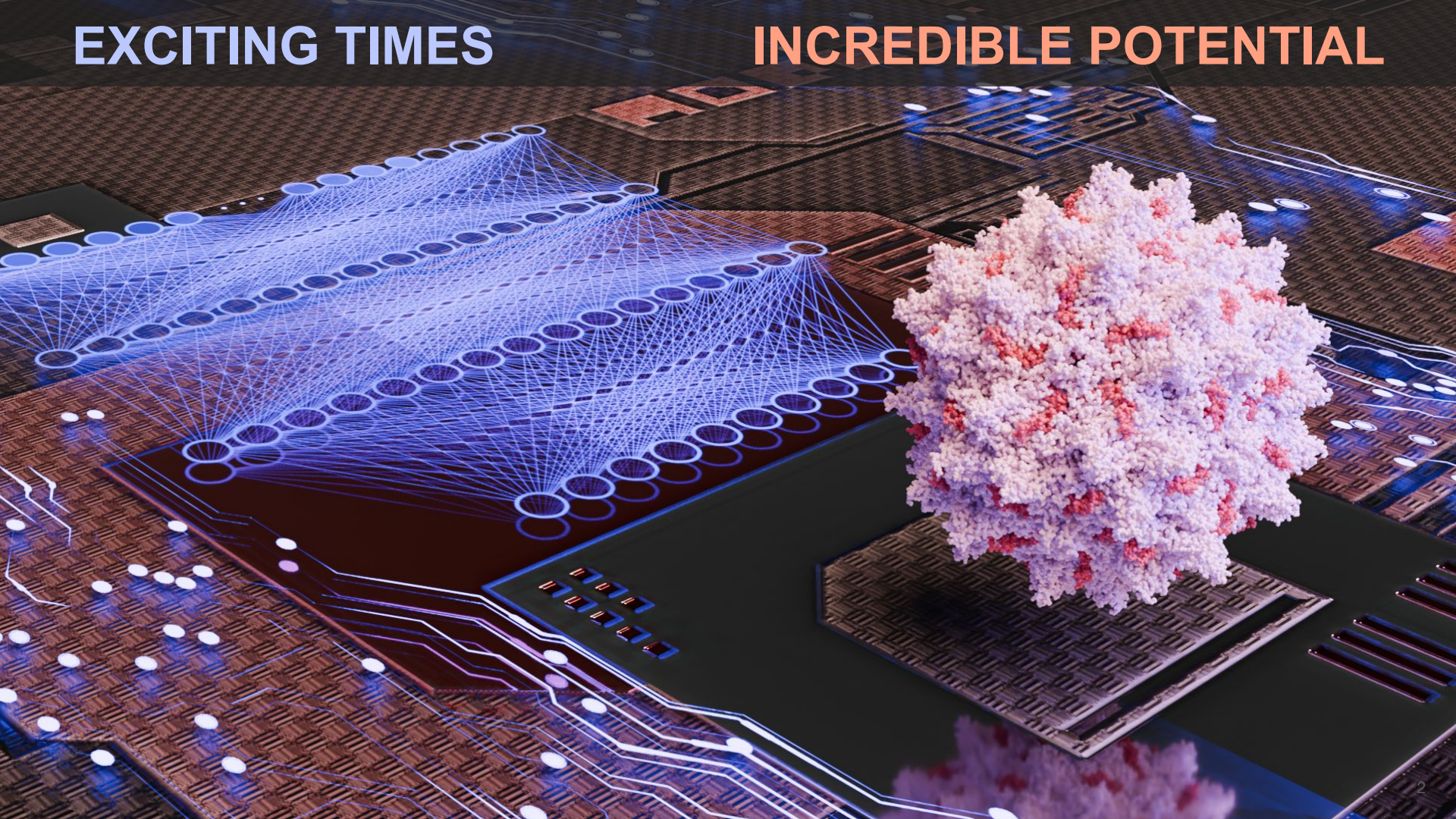
Dyno Therapeutics

AAV Capsid Design in the Era of AI

ASGCT 2024

EXCITING TIMES

INCREDIBLE POTENTIAL

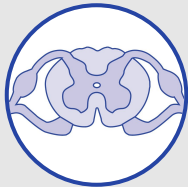


Progress worth celebrating

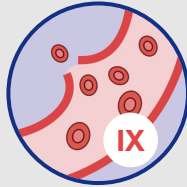
LUXTURNA
December 2017



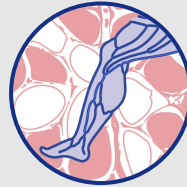
ZOLGENSMA
May 2019



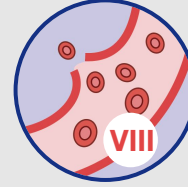
HEMGENIX
November 2022



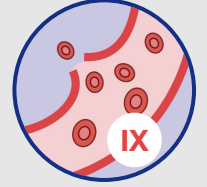
ELEVIDYS
June 2023



ROCTAVIAN
June 2023



BEQVEZ
April 2024

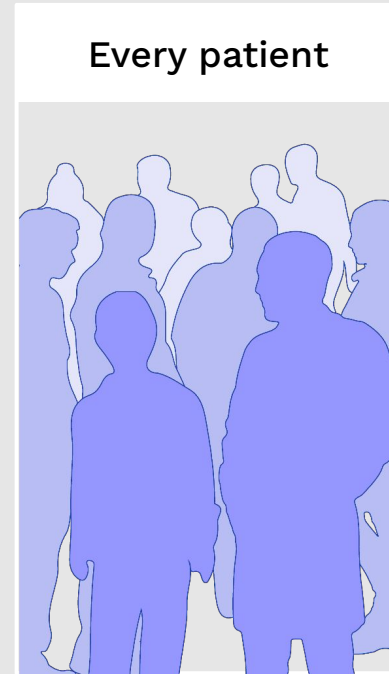
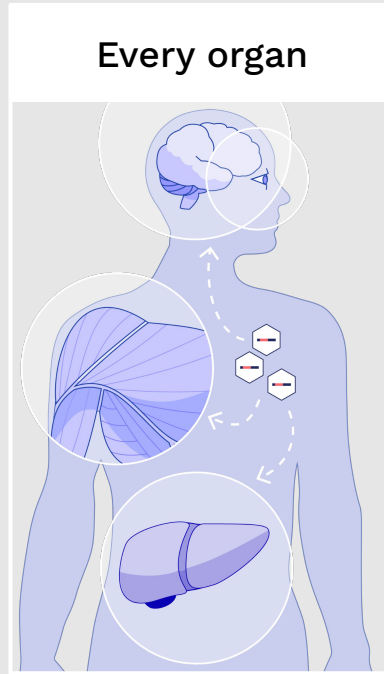
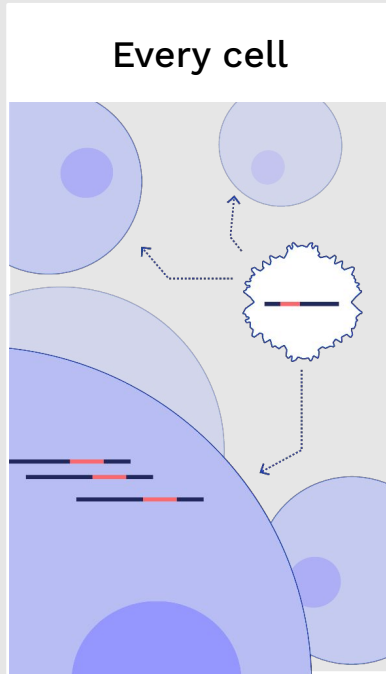


DELIVERY

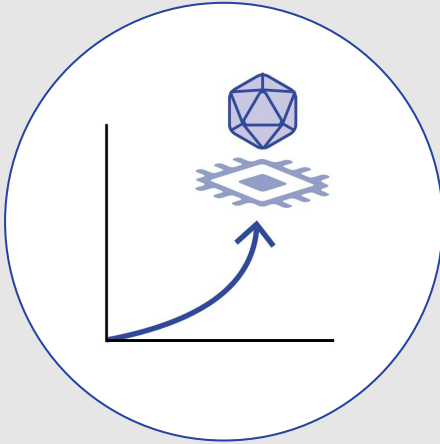
our shared challenge



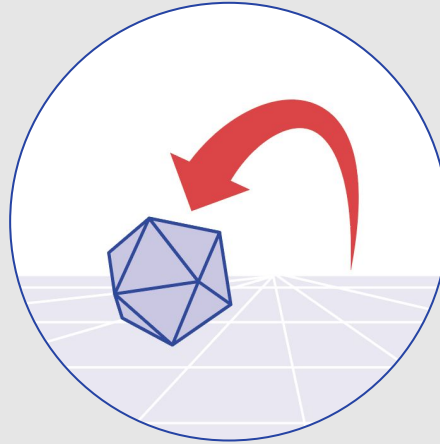
Dyno's goal is solving in vivo gene delivery



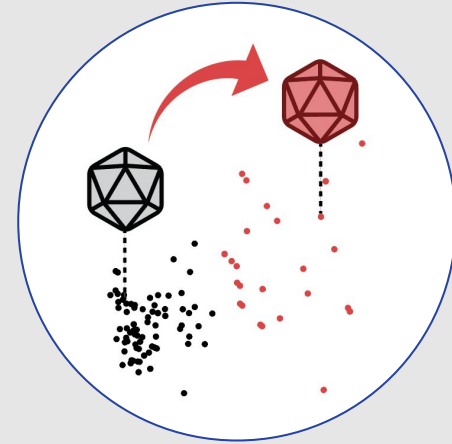
How AI can help



Exponential
change



LEAPSM
Technology



Synthetic
Serotypes



AI

that exponential feeling



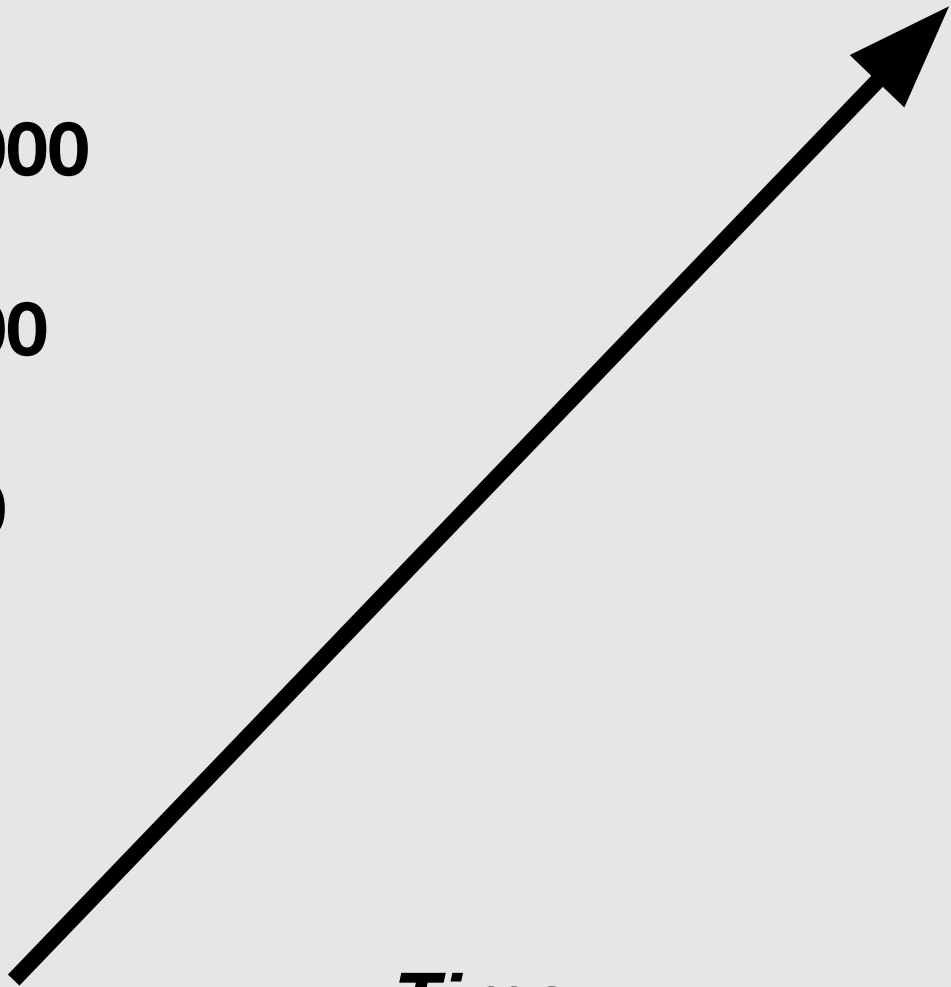


1000

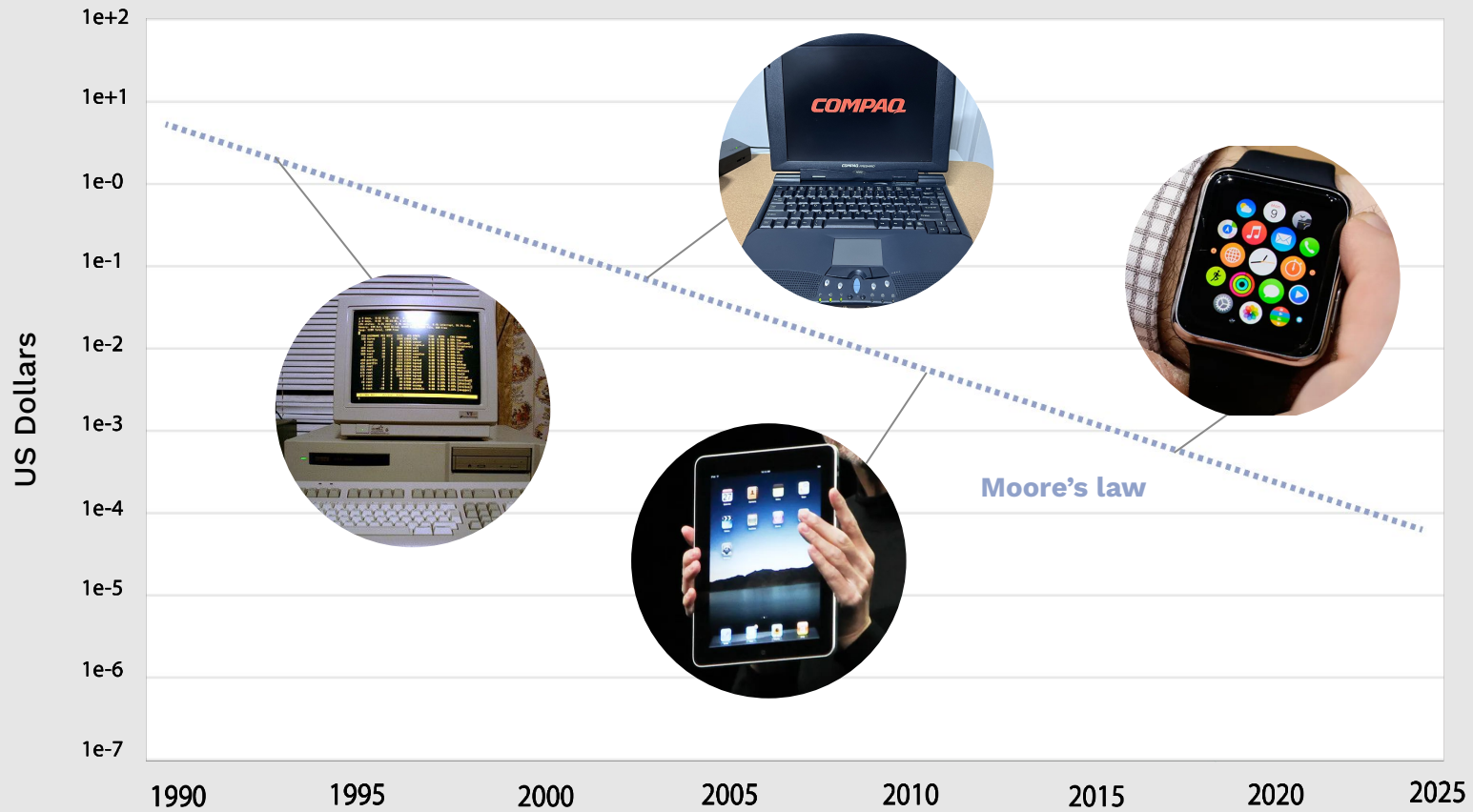
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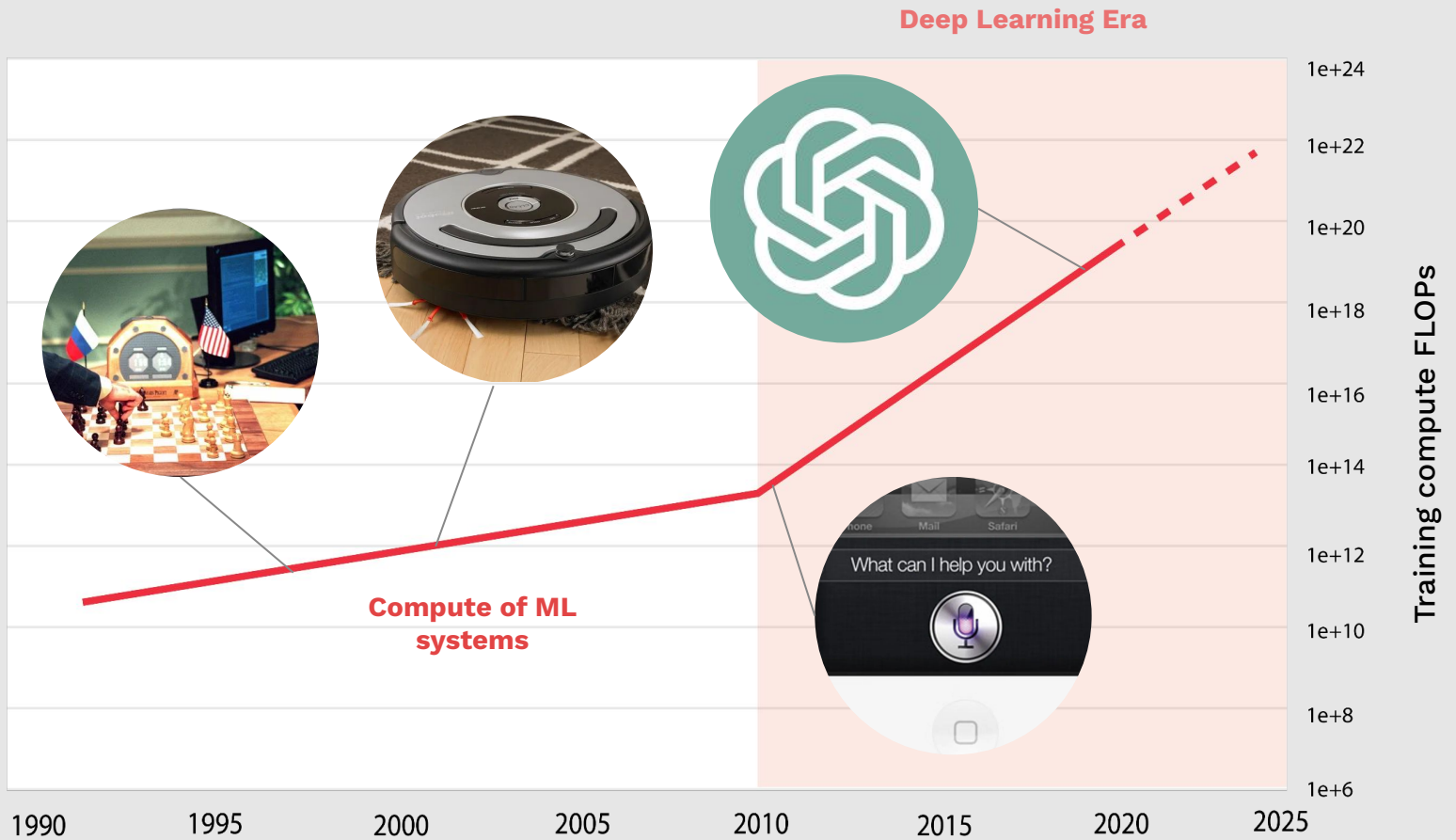
10

1

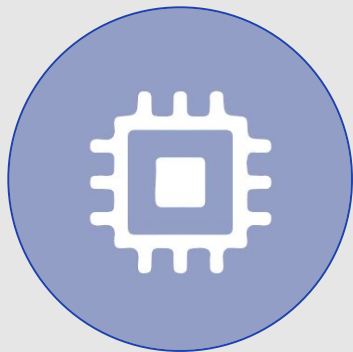


Time →





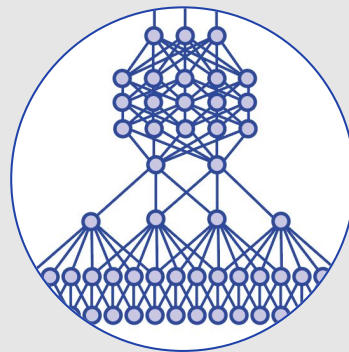
What sparked the AI revolution?



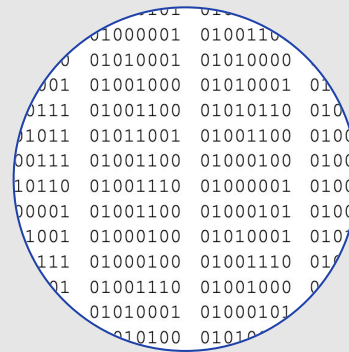
Compute



Infrastructure

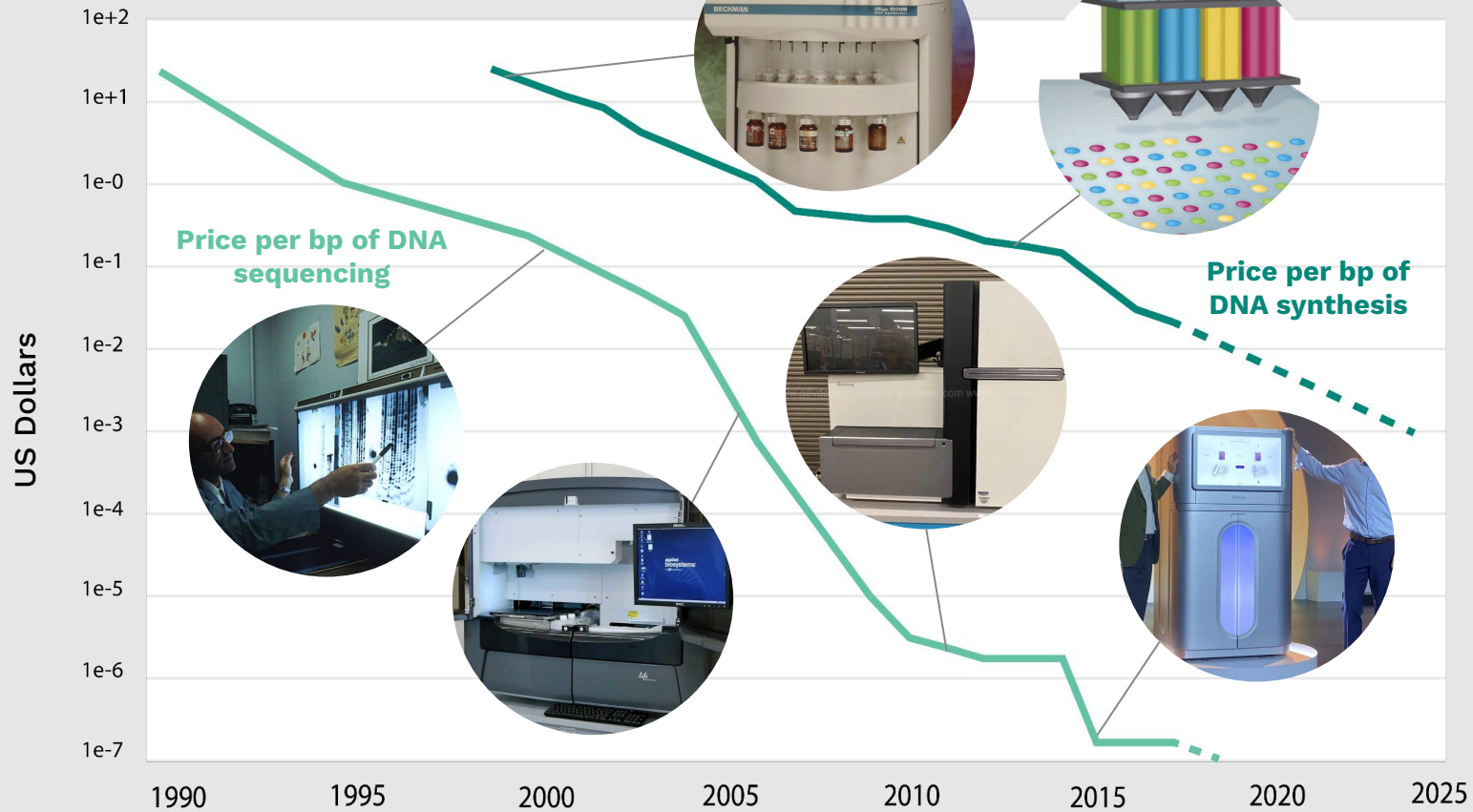


Algorithms



Data





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

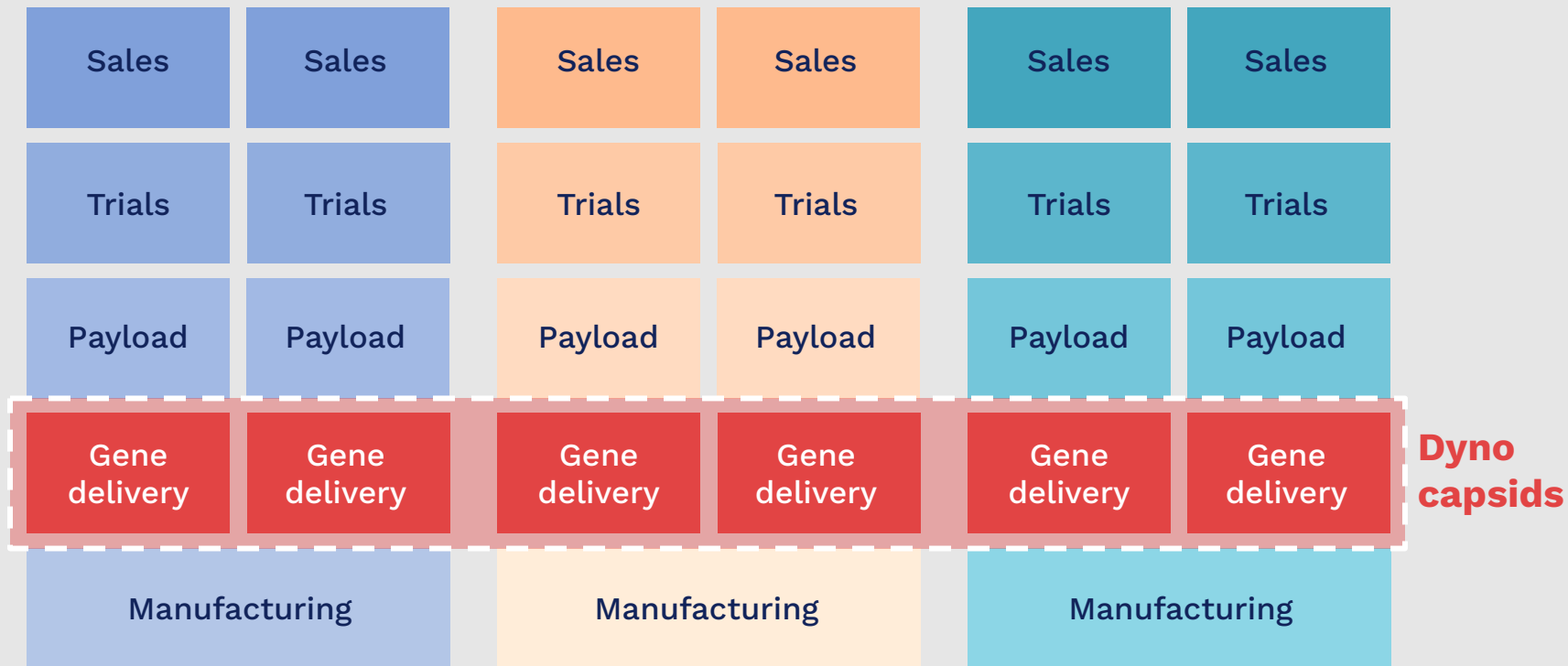


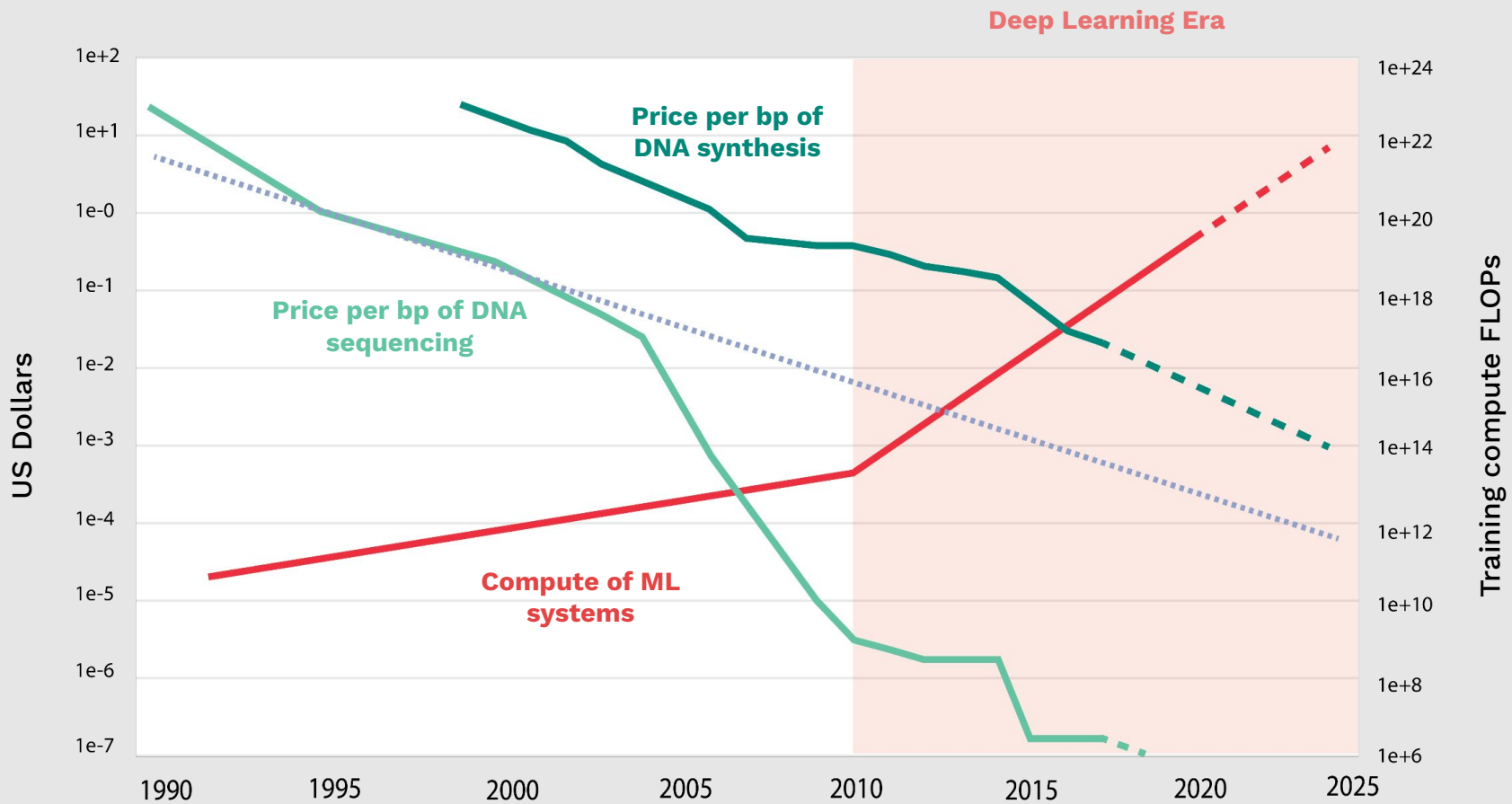
Partnership-centric business
model = 100% alignment

Dyno's partnerships to date...



Our ambition is solving delivery generally and broadly





Dyno's platform

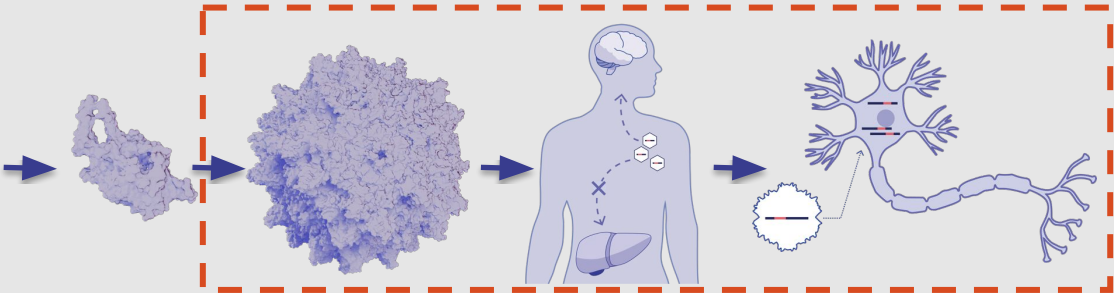


Data excellence

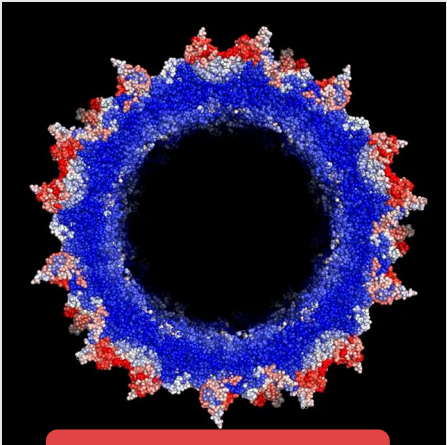


Dyno: An AI-powered in vivo capsid engineering platform

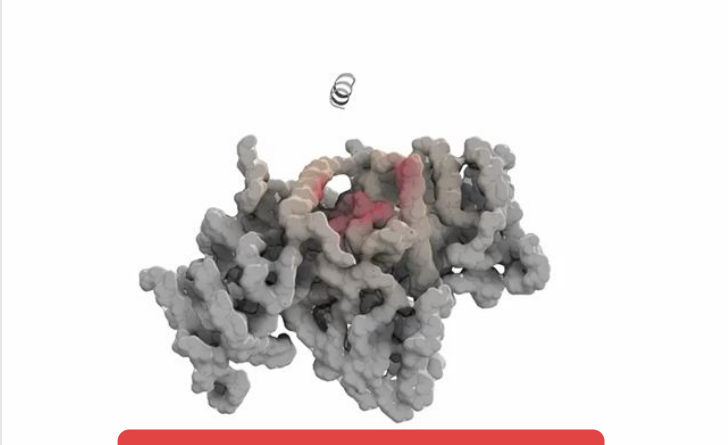
MAADGYLPDWLED
NLSEGIREWALK
PGAPQPKANQQHQ
DNARGLVLPGYKY
LGPGNGLDKGEP...



Experimental data
required to enable
AI-powered design



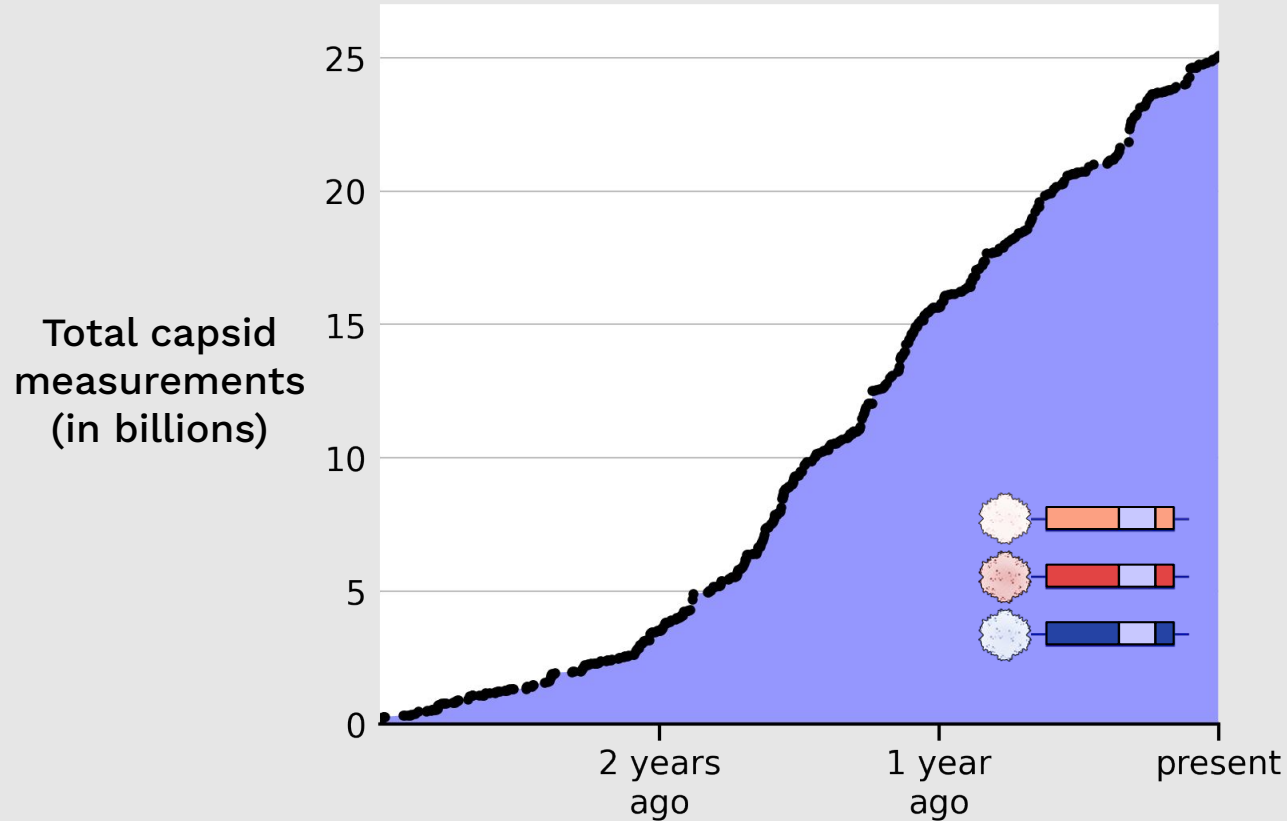
Production



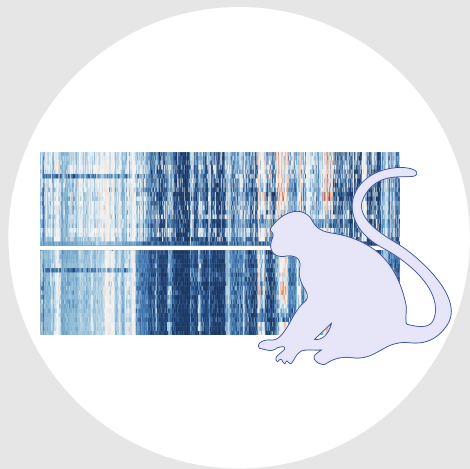
Receptor docking



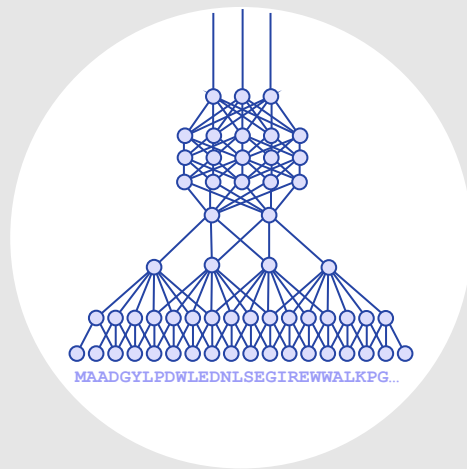
We make billions of measurements every month



Dyno's platform



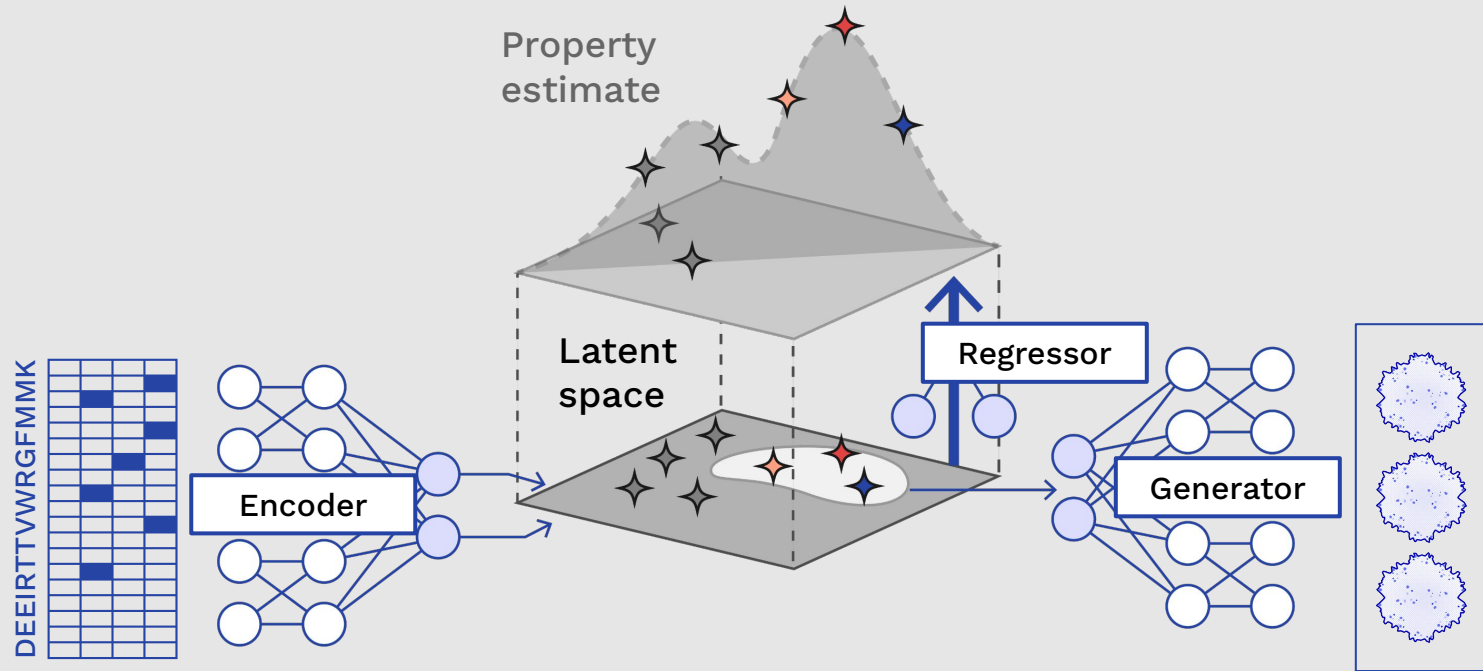
Data excellence



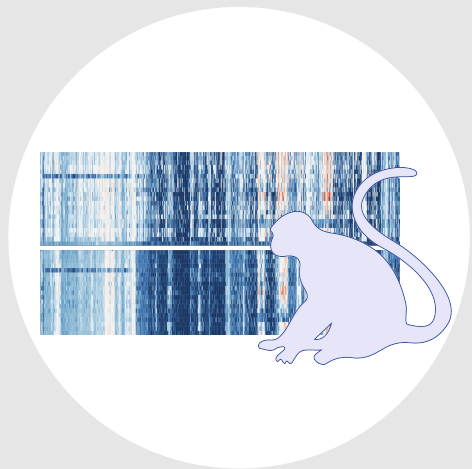
AI excellence



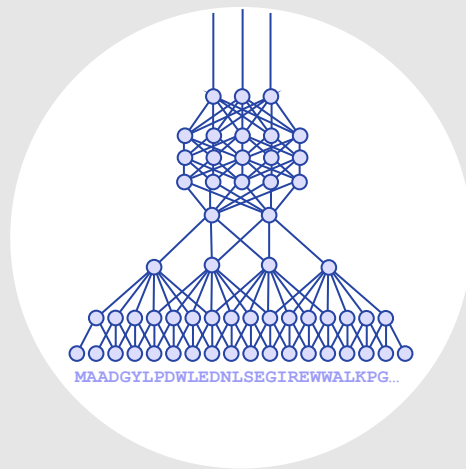
We program AI to generate optimized capsid sequences



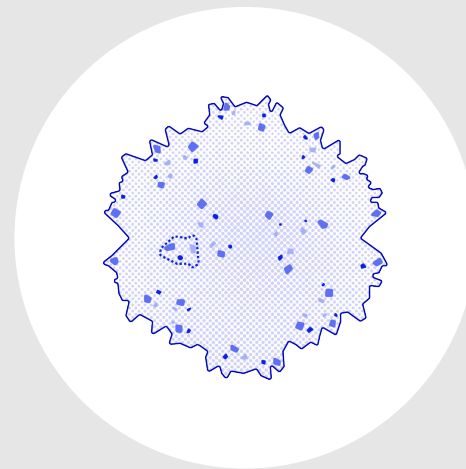
Dyno's platform



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

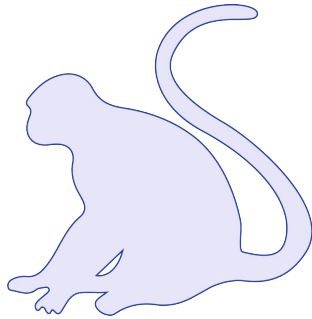
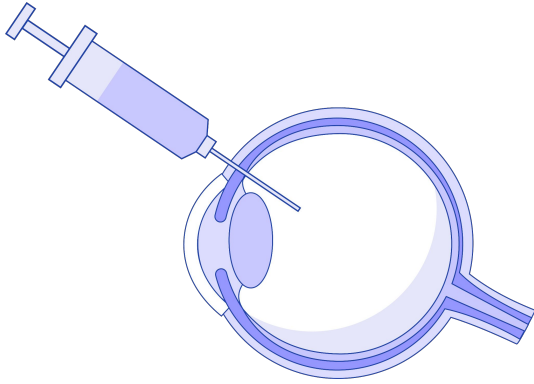


Dyno eCap™ 1 delivery

Designed for **IVT eye delivery**

1x production vs AAV2

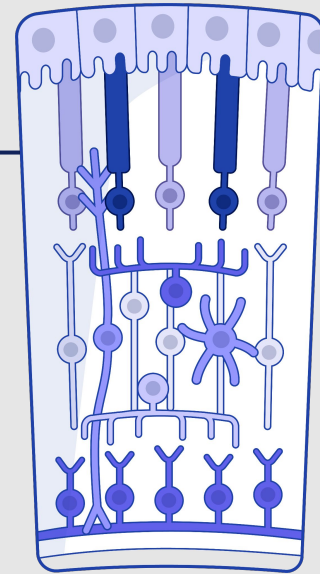
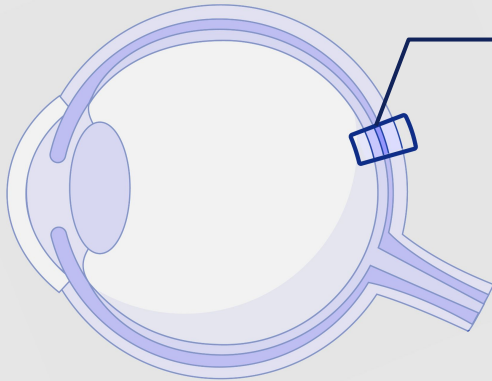
80x retina transduction vs AAV2
in Cyno monkeys



NHP Validation studies

Where along the retina?

Which retinal layers?



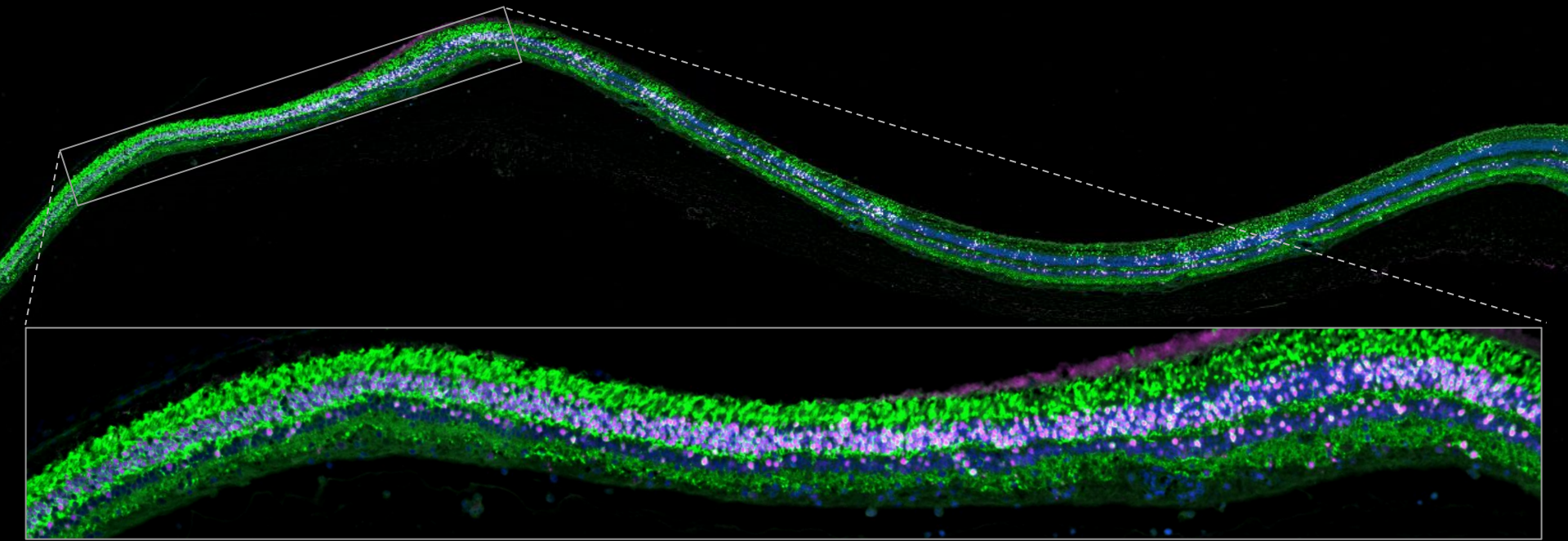
outer nuclear layer (ONL)

inner nuclear layer (INL)

ganglion cell layer (GCL)



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



USE CASE
1

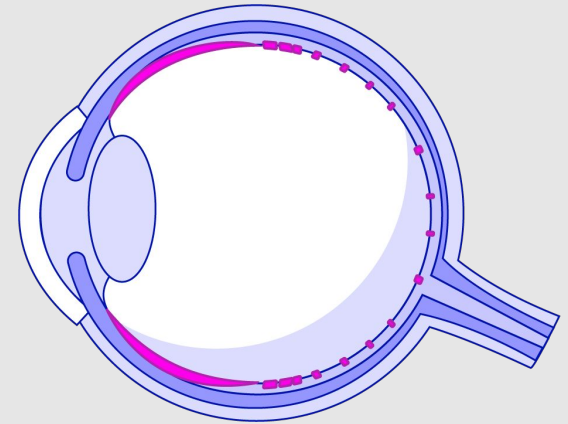
Secreted therapeutic biofactory

Delivery challenge:

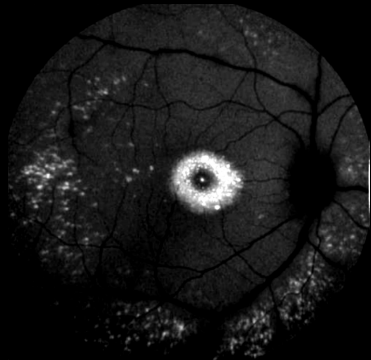
Safe and easy-to-administer delivery across retina, **reaching enough cells** for secreted proteins to achieve a therapeutic dose

Patient unmet need:

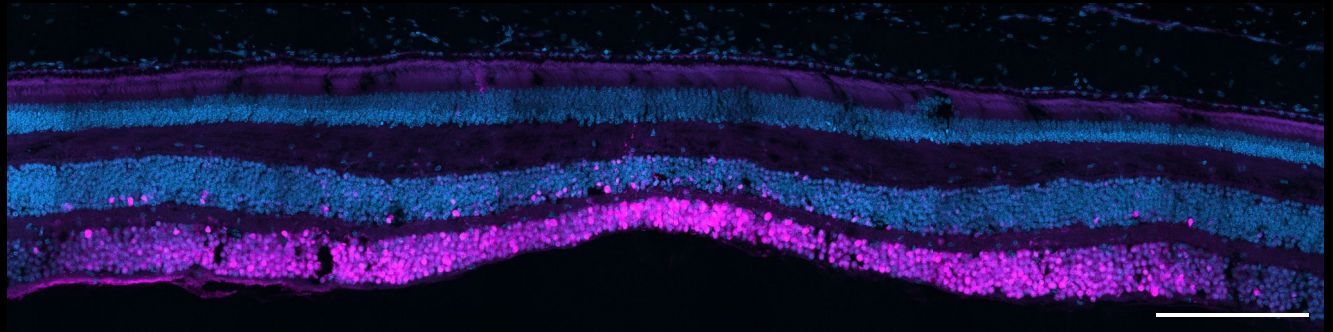
Age-related Macular Degeneration (AMD)
Dry AMD with Geographic atrophy (GA)
Diabetic Macular Edema (DME)



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 μ m

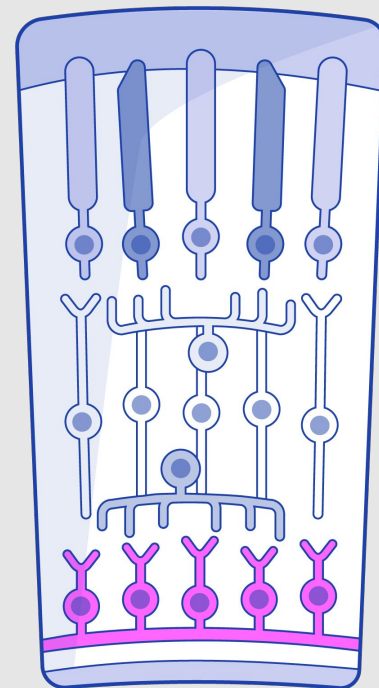
Glaucoma

Delivery challenge:

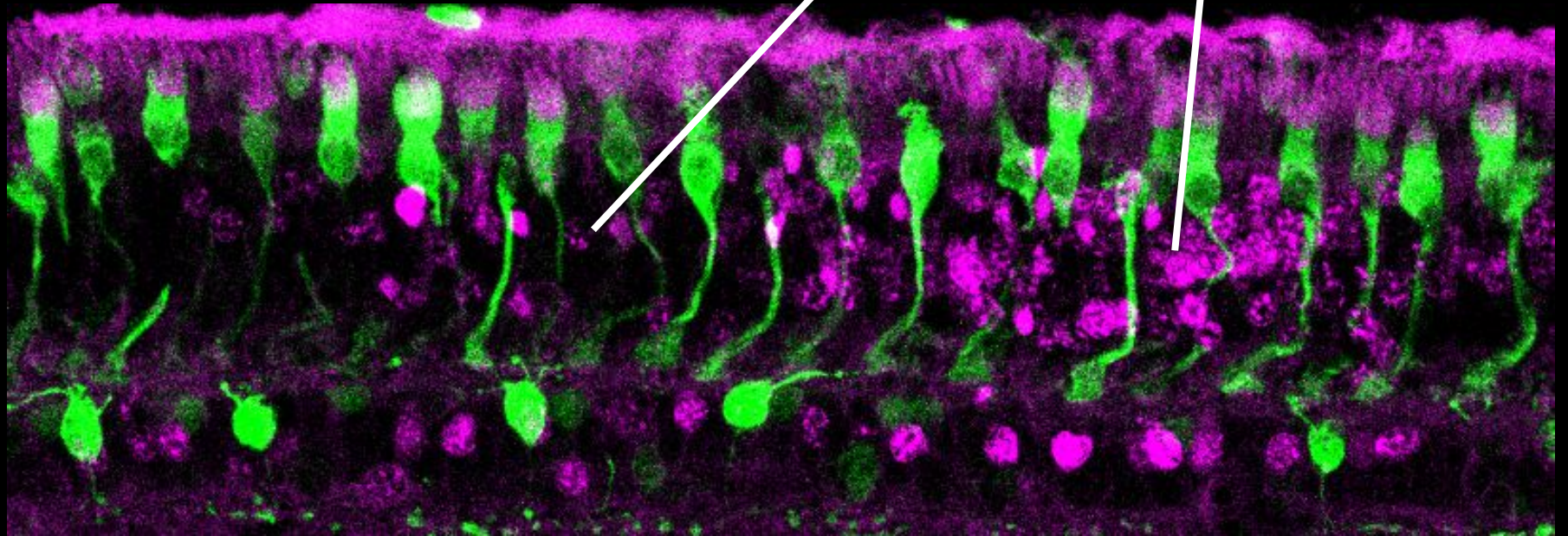
Safe and easy-to-administer delivery to **RGCs** responsible for central vision in the **macula**

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

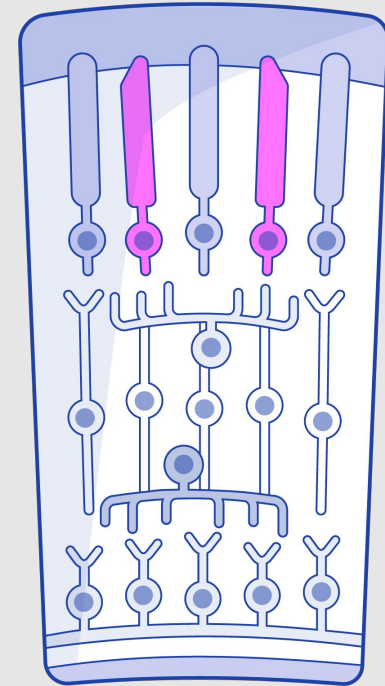
Inherited retinal diseases

Delivery challenge:

Reach enough photoreceptors to prevent their degeneration and modify disease progression

Patient unmet need:

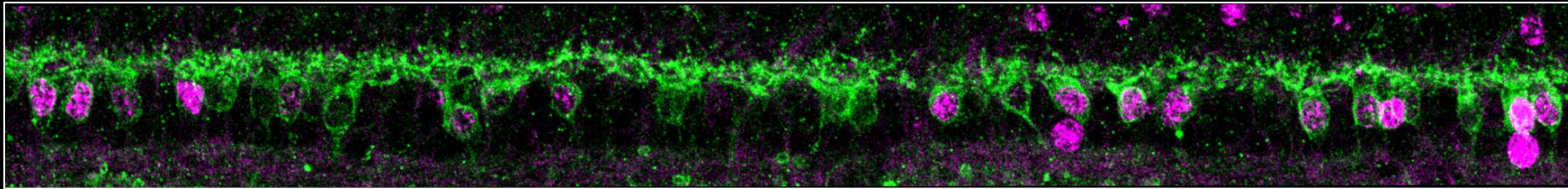
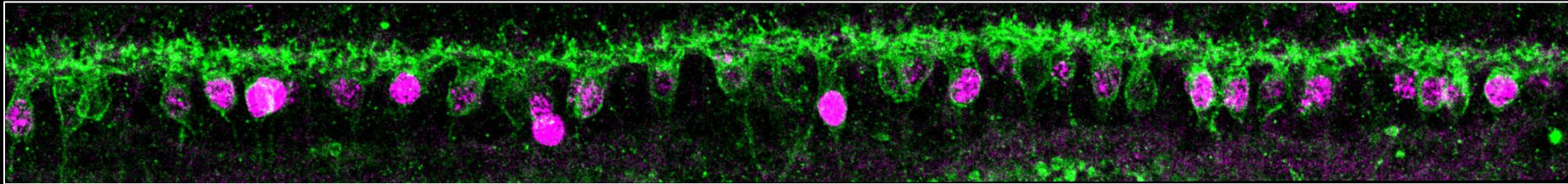
Retinitis pigmentosa is the leading cause of progressive vision loss early in life



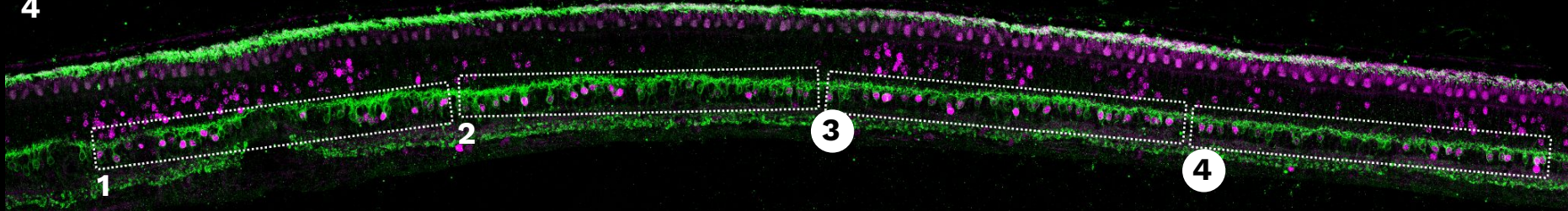
Highly efficient transduction of bipolar cells with Dyno eCap 1

3

PKCa (bipolar cells) / Dyno eCap 1



4



USE CASE
4

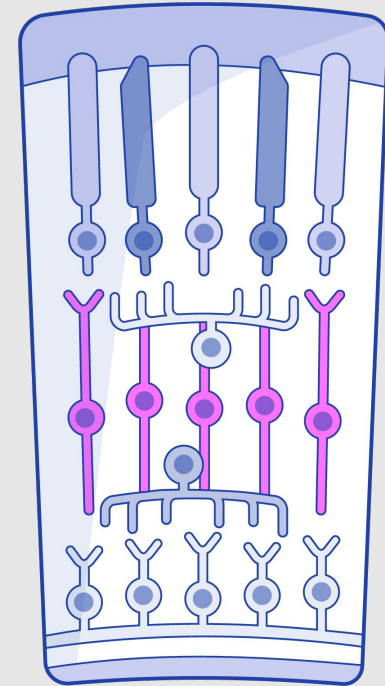
Optogenetic therapy

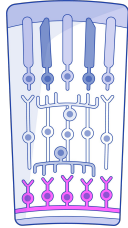
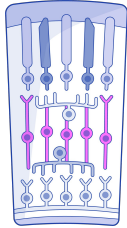
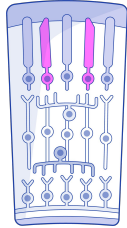
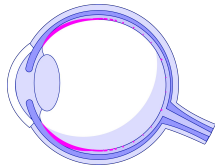
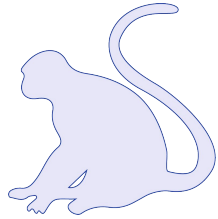
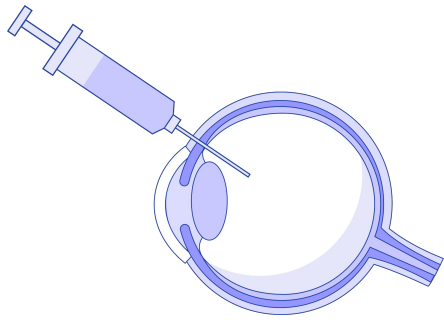
Delivery challenge:

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

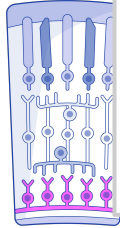
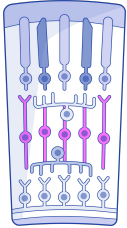
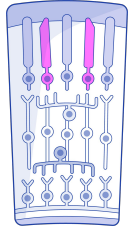
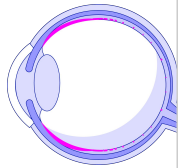
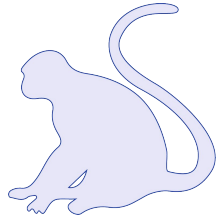
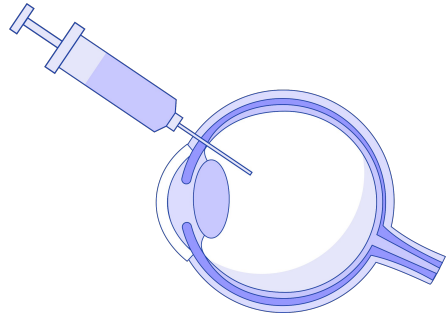
1x production vs AAV2

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



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

e delivery

AAV2

on vs AAV2

ina cell types

glion cells,

ptoreceptors

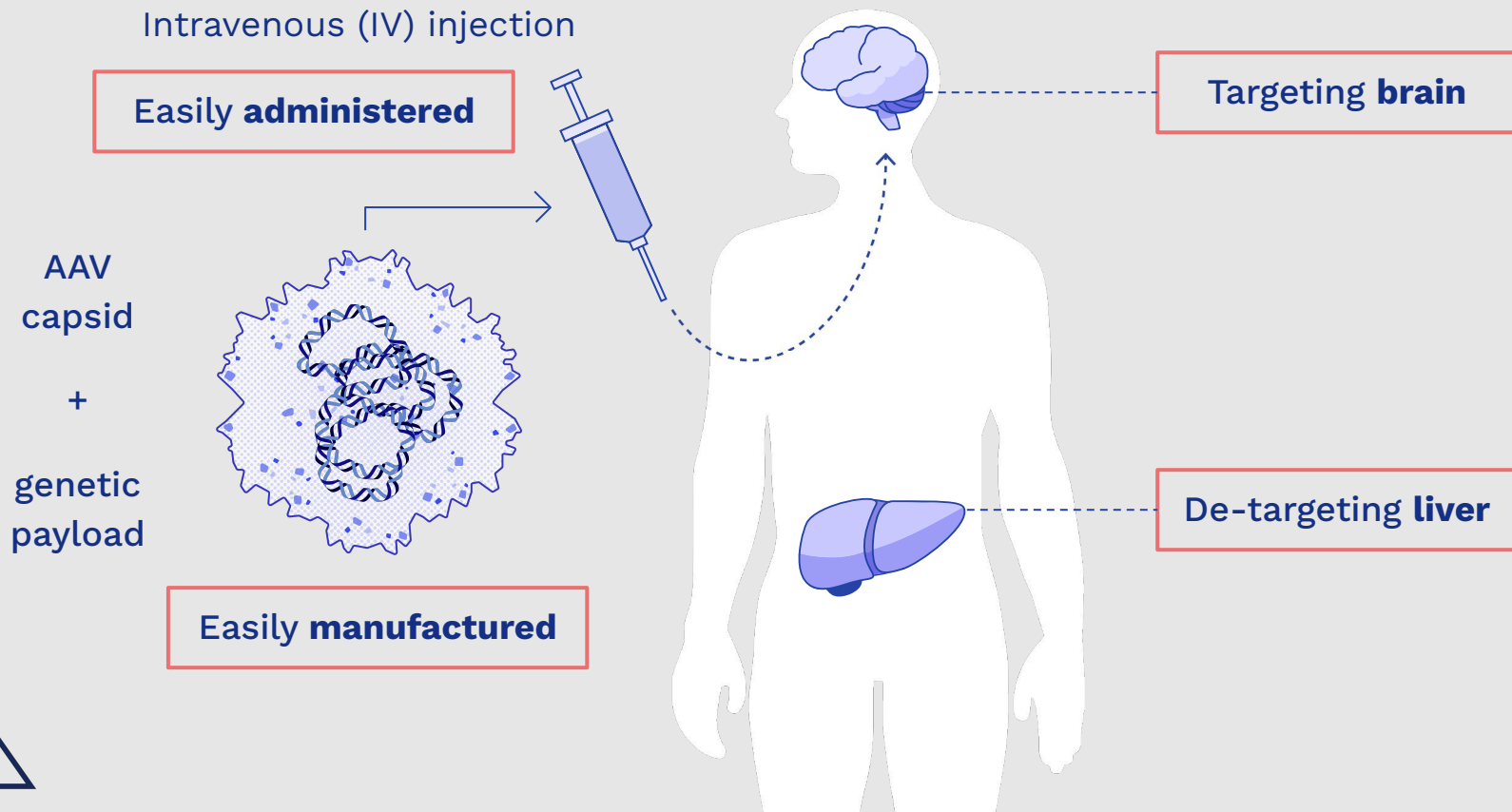
neuroprotection,

optogenetic & photoreceptor targeted

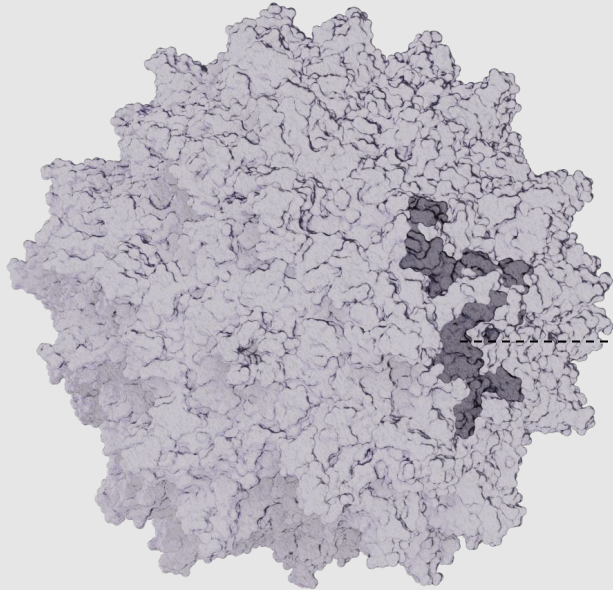
ocular gene therapies



Challenge: safe and effective gene delivery



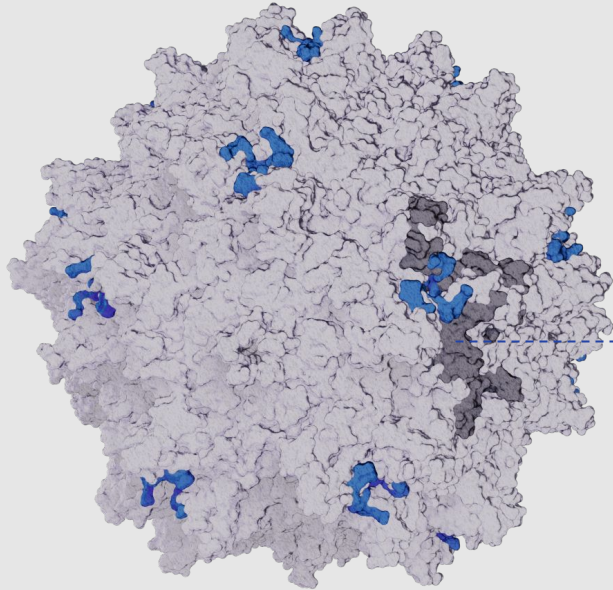
The AAV capsid: a ~736 letter sequence design problem



```
MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVL  
PGYKYLGPNGLDKGE PVNAADAAALEHDKAYDQQLKAGDNPYLKYN  
HADAEFQERLKEDTSFGGNLGRAVFQAKKRLLEPLGLVEEAAKTAPG  
KKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTEVDPDQPI  
GEPAAAPSGVGSALTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWL  
GDRVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWG  
YFDENRFHCHFSPRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNN  
GVKTIANNLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQ  
YGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYEFENVPFH  
SSYAHSQSLDRLMNPLIDQYLYLSKTINGSGQNQQTLKFSVAGPSN  
MAVQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSL  
MNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVDADKVMITNEE  
EIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNOGILPGMVWQDRD  
VYLQGPWIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADP  
PTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY  
YKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL*
```

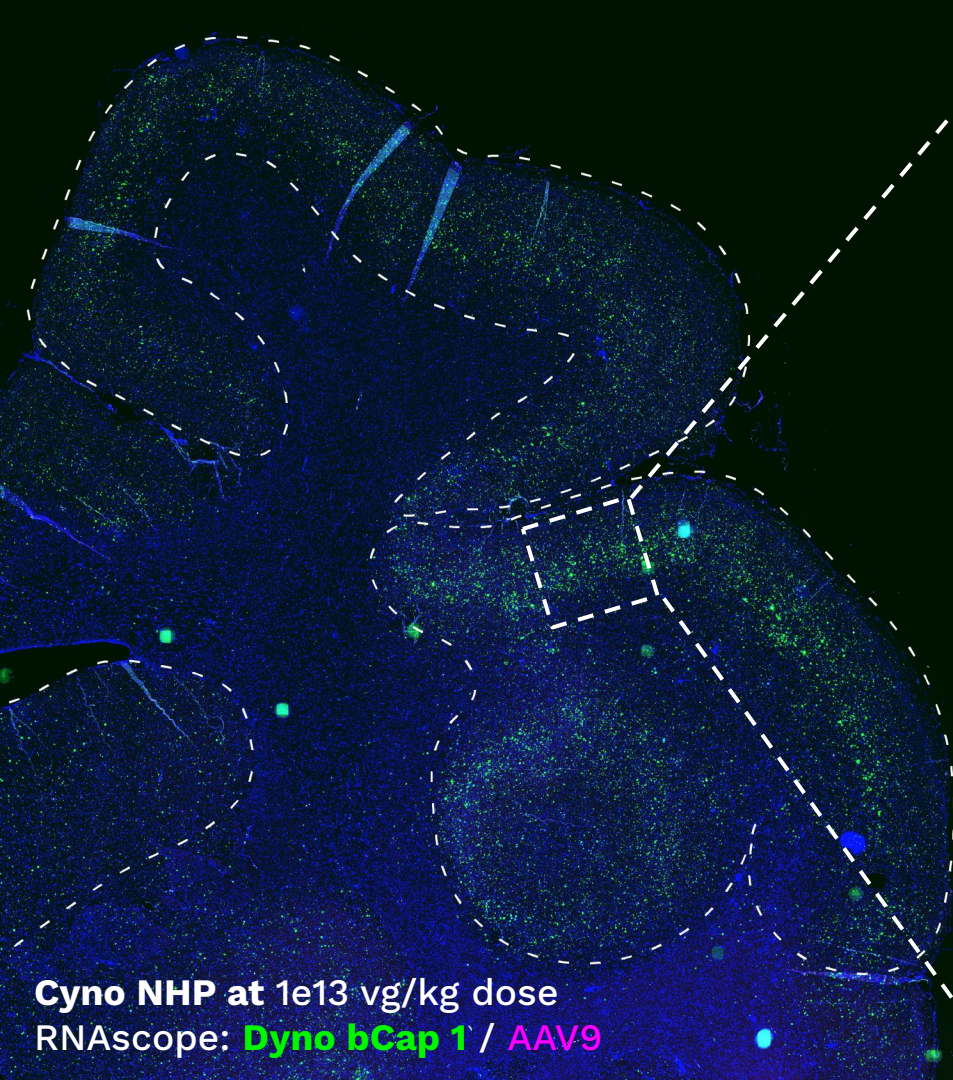


A better capsid: Dyno bCap™ 1



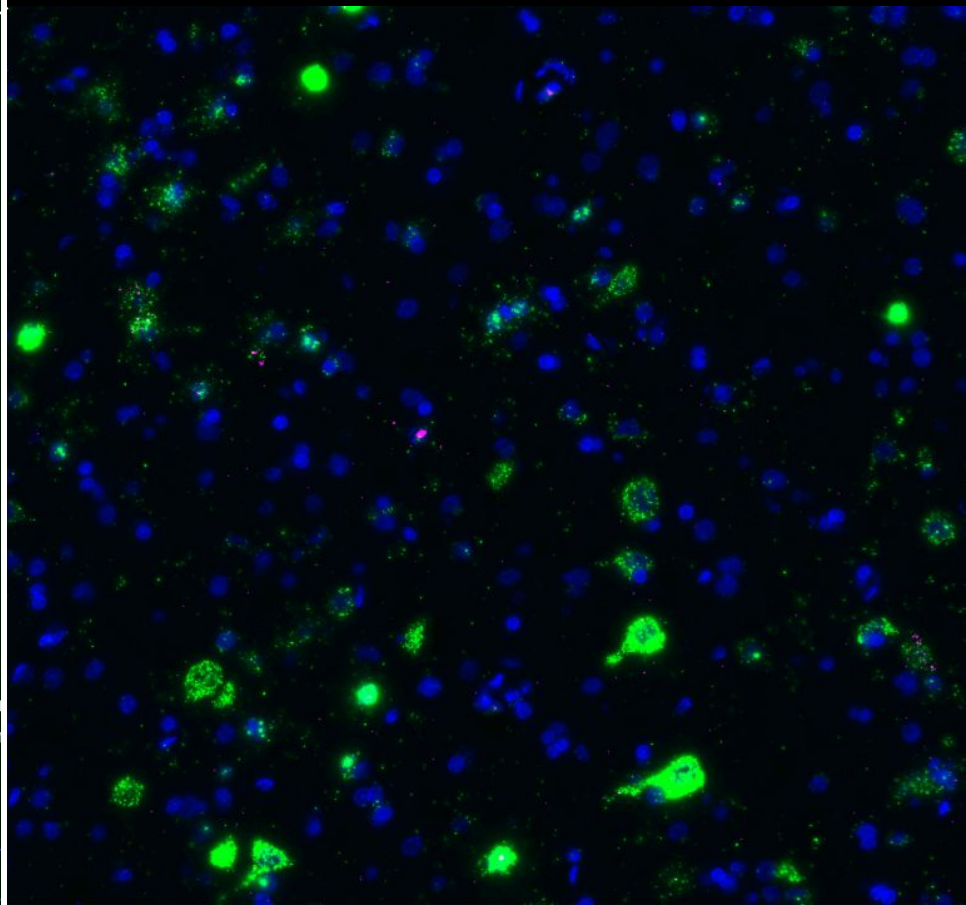
MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVL
PGYKYLPGNGLDKGE PVNAADAAALEHDKAYDQQLKAGDNPYLKYN
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KKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTEVDPDQPI
GEPAAAPSGVGSALTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWL
GDRVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWG
YFDENRFHCHFSPRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNN
GVKTIANNLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQ
YGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYEFENVPFH
SSYAHSQSLDRLMNPLIDQYLYLSKTINGSGQNQQTLKFSVAGPSN
MAVQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPASSWALNGRNSL
MNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVDADKVMITNEE
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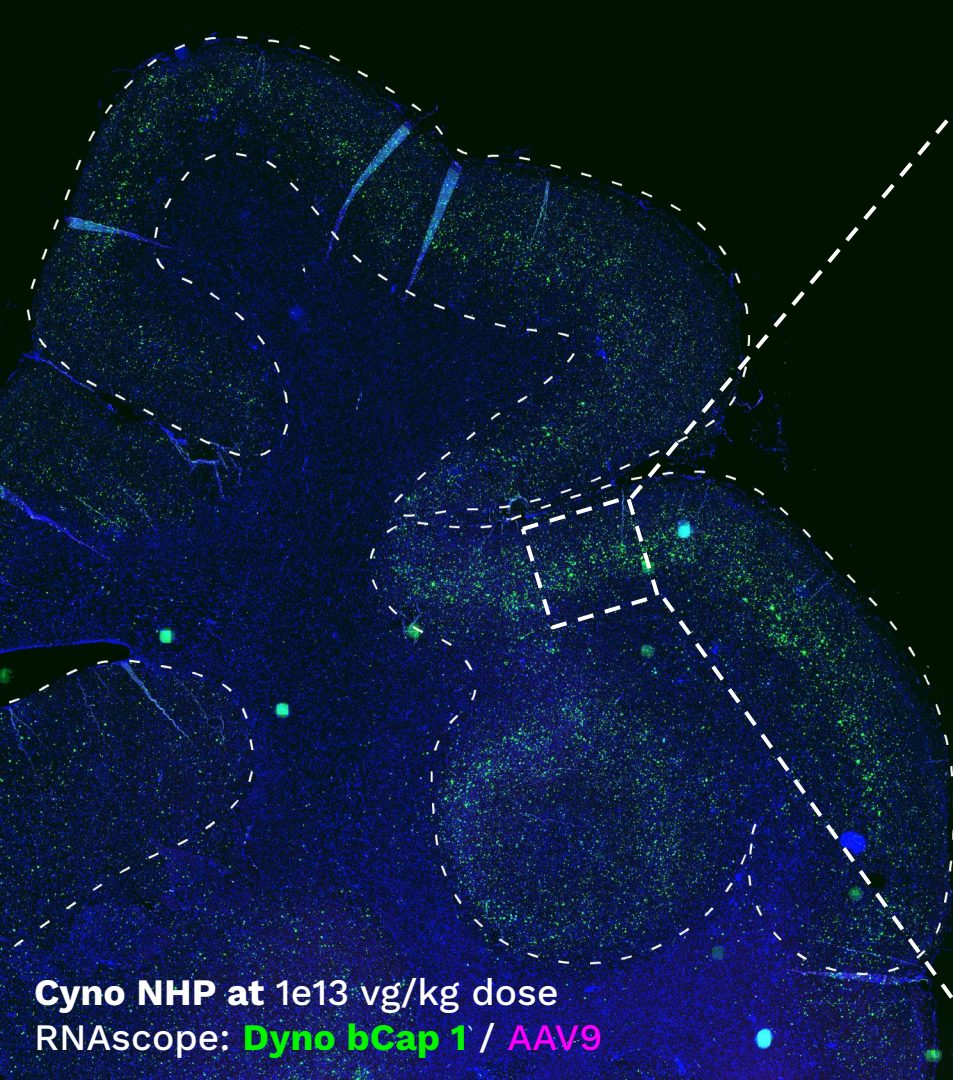




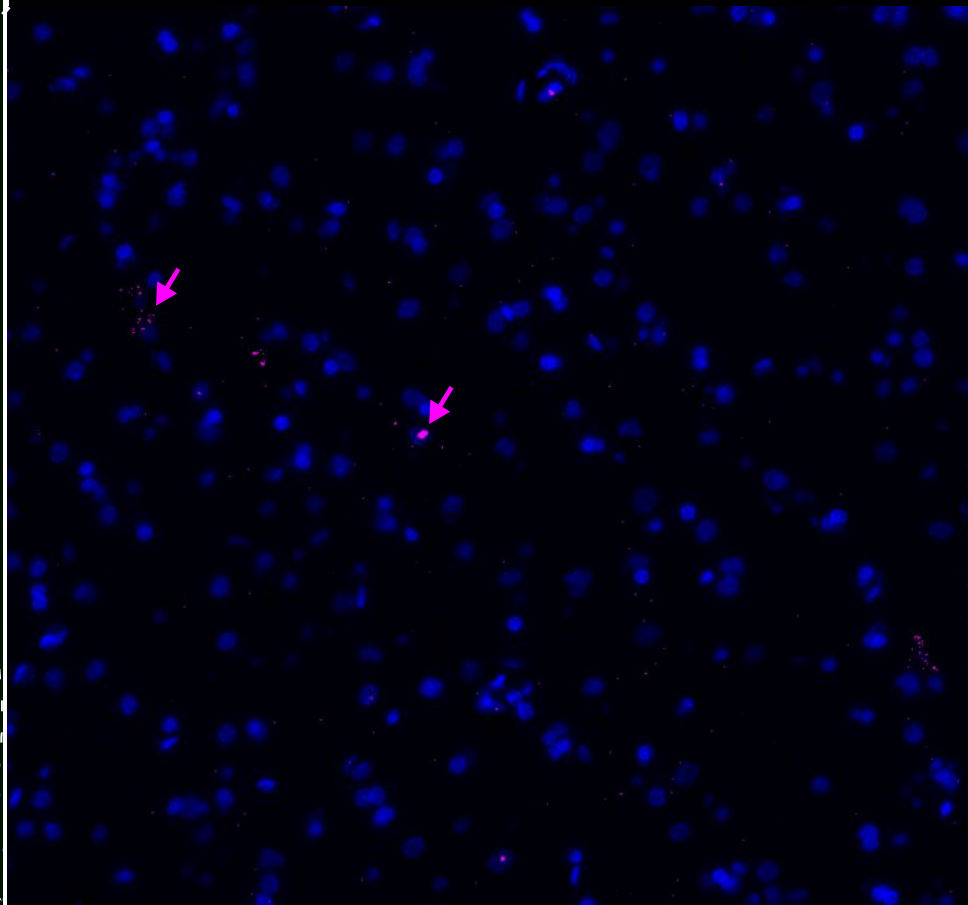
Cyno NHP at $1e13$ vg/kg dose
RNAscope: **Dyno bCap 1** / **AAV9**

Motor cortex: 11% of cells transduced

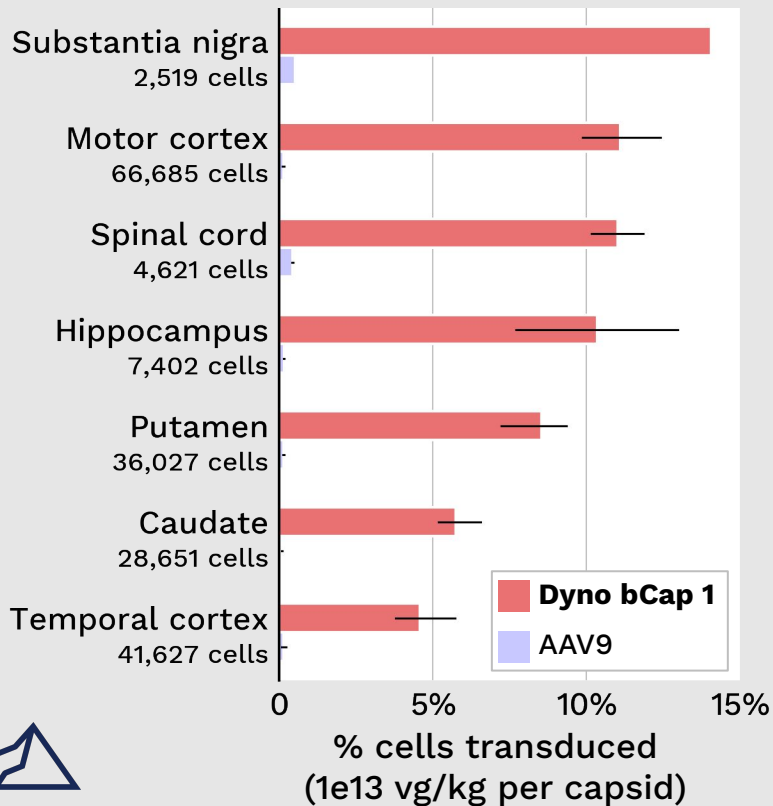




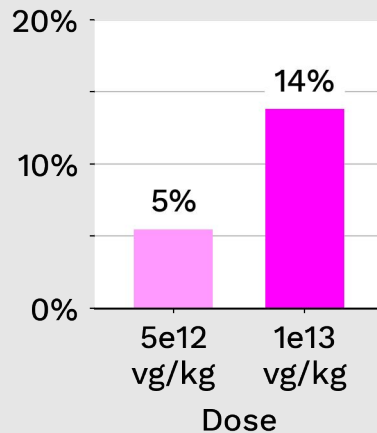
Motor cortex: **minimal AAV9 transduction**



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

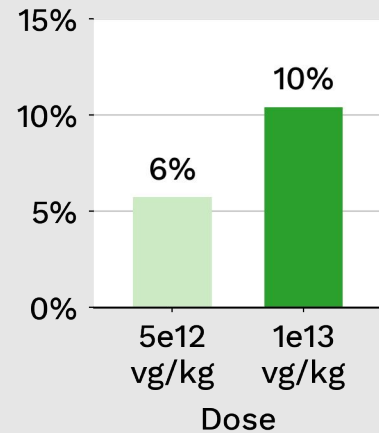


% transduced upper motor neurons (VGLUT1+)



24551 43560
Total counted VGLUT1+ cells

% transduced medium spiny neurons, putamen (VGAT+)



21957 30255
Total counted VGAT+ cells



Dyno **b**Cap 1 delivery

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

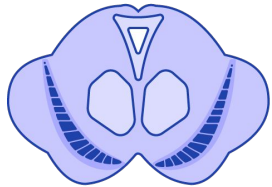
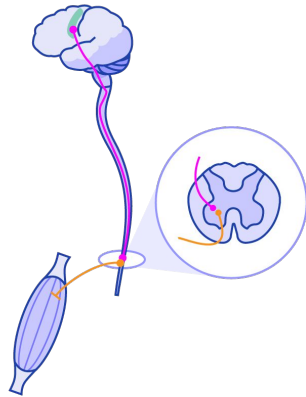
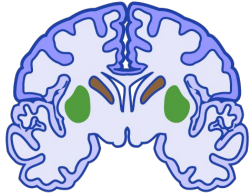
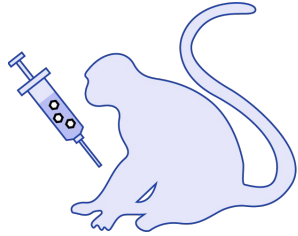
1x production vs AAV9

10x liver detargeting vs AAV9

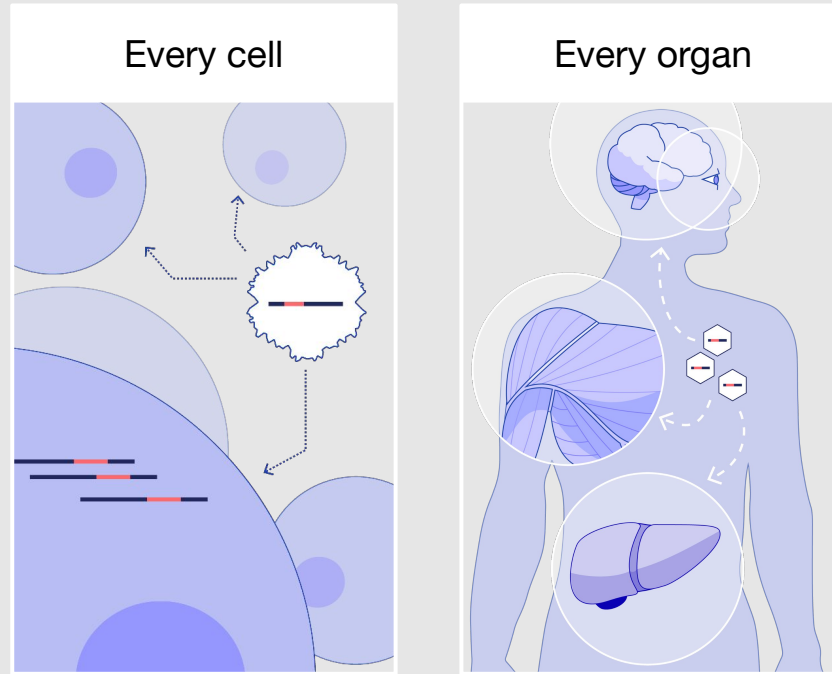
100x brain transduction vs AAV9

Transduces **neurons** and other
therapeutically relevant cell-types

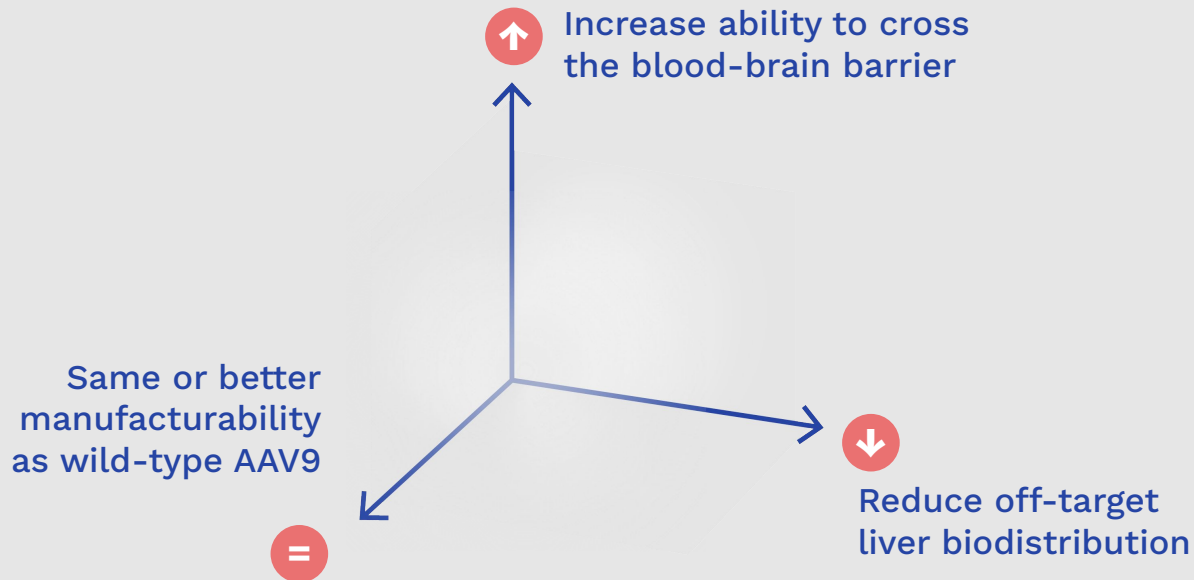
Transduction patterns relevant for **ALS**,
Huntington's & Parkinson's Disease, ...



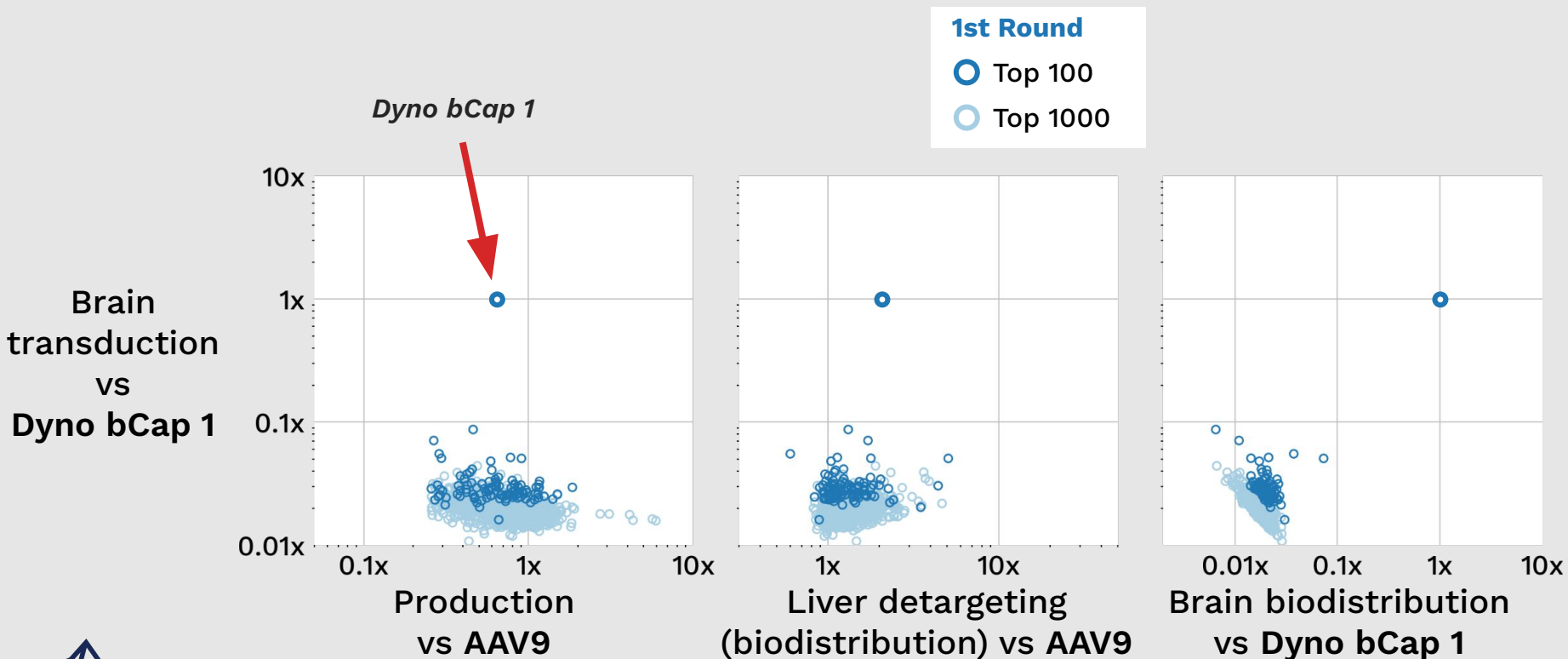
Expanding the reach of gene therapy



We optimize capsids across multiple properties



Each high-throughput round improves multiple capsid properties



Each high-throughput round improves multiple capsid properties

1st Round

2nd Round

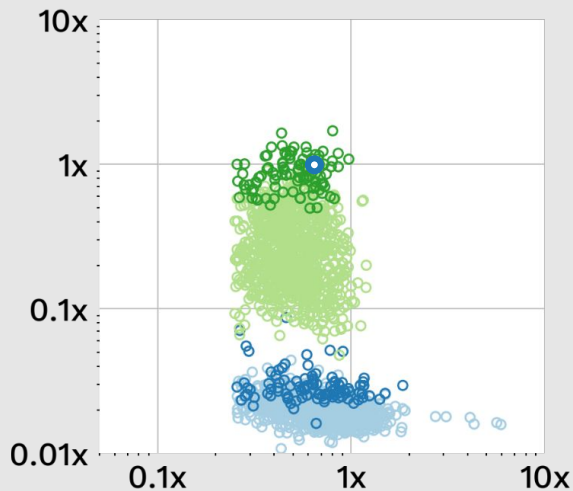
○ Top 100

○ Top 100

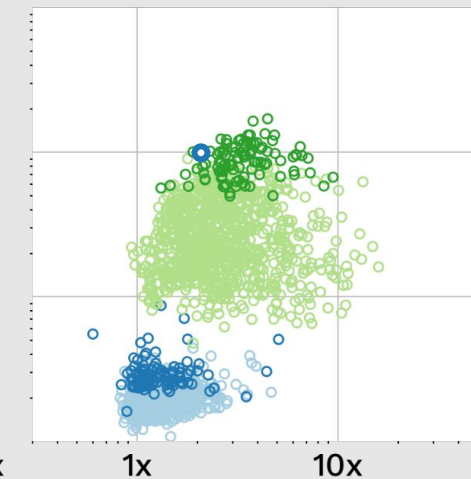
○ Top 1000

○ Top 1000

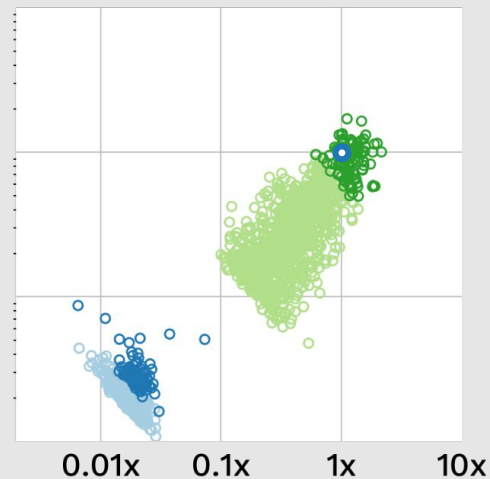
Brain
transduction
vs
Dyno bCap 1



Production
vs AAV9



Liver detargeting
(biodistribution) vs AAV9



Brain biodistribution
vs Dyno bCap 1



Each high-throughput round improves multiple capsid properties

1st Round

2nd Round

3rd Round

● Top 100

● Top 100

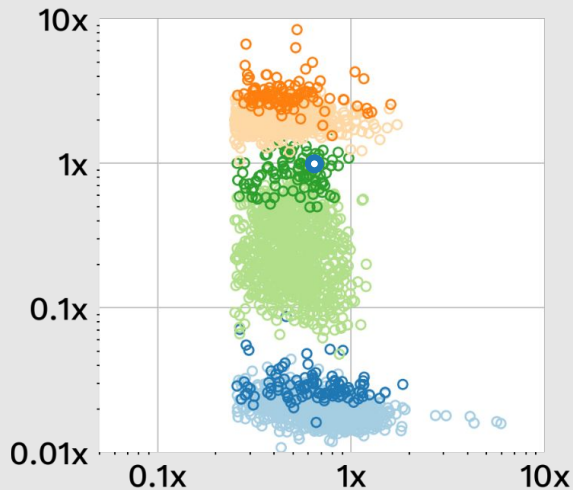
● Top 100

○ Top 1000

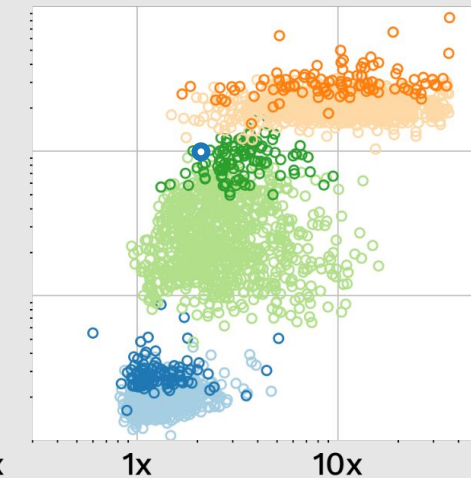
○ Top 1000

○ Top 1000

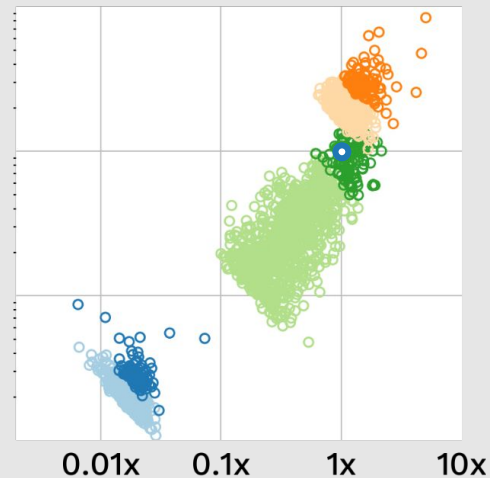
Brain transduction vs Dyno bCap 1



Production vs AAV9



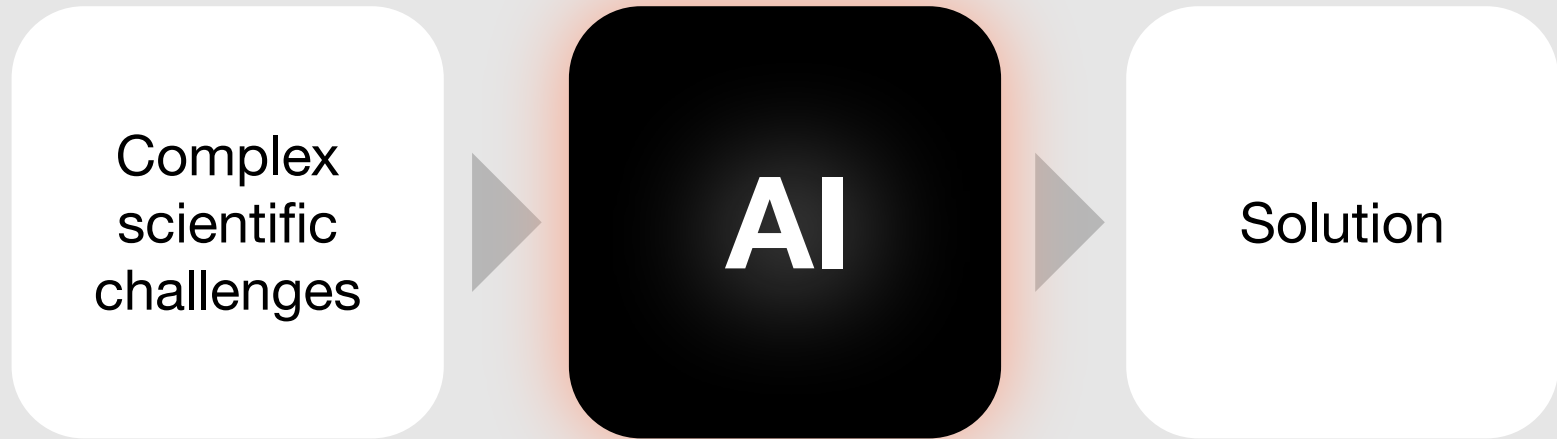
Liver detargeting (biodistribution) vs AAV9



Brain biodistribution vs Dyno bCap 1



The challenge of designing for high-performance



One does not simply ... apply AI



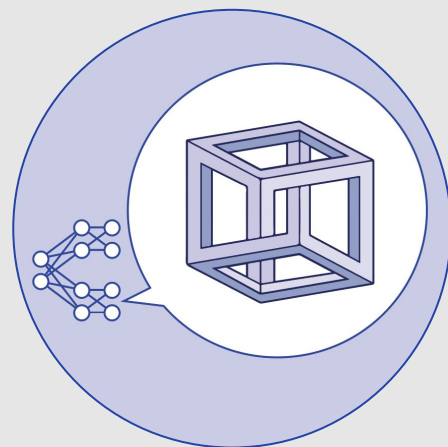
When hype faces reality



Mice
lie



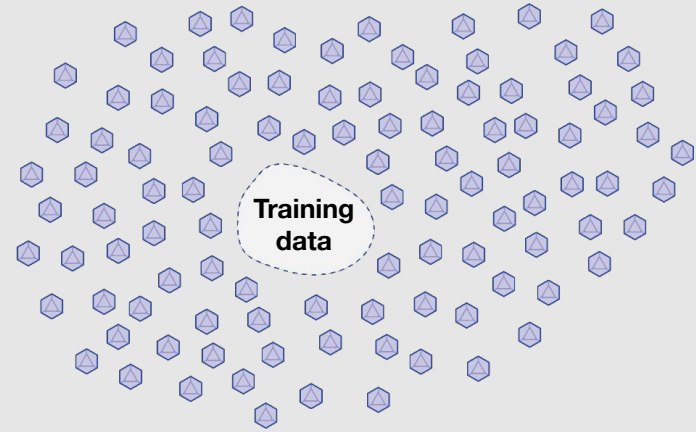
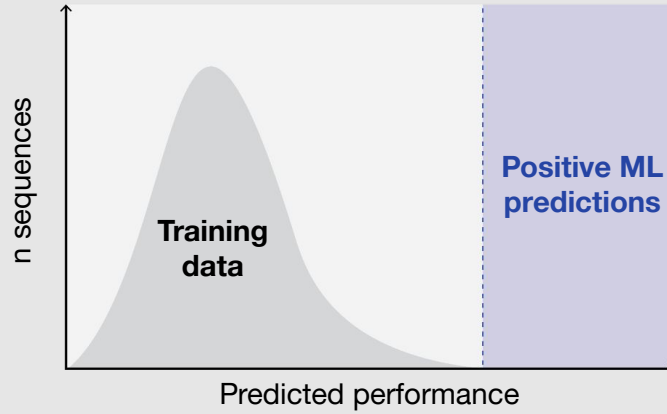
Monkeys
exaggerate



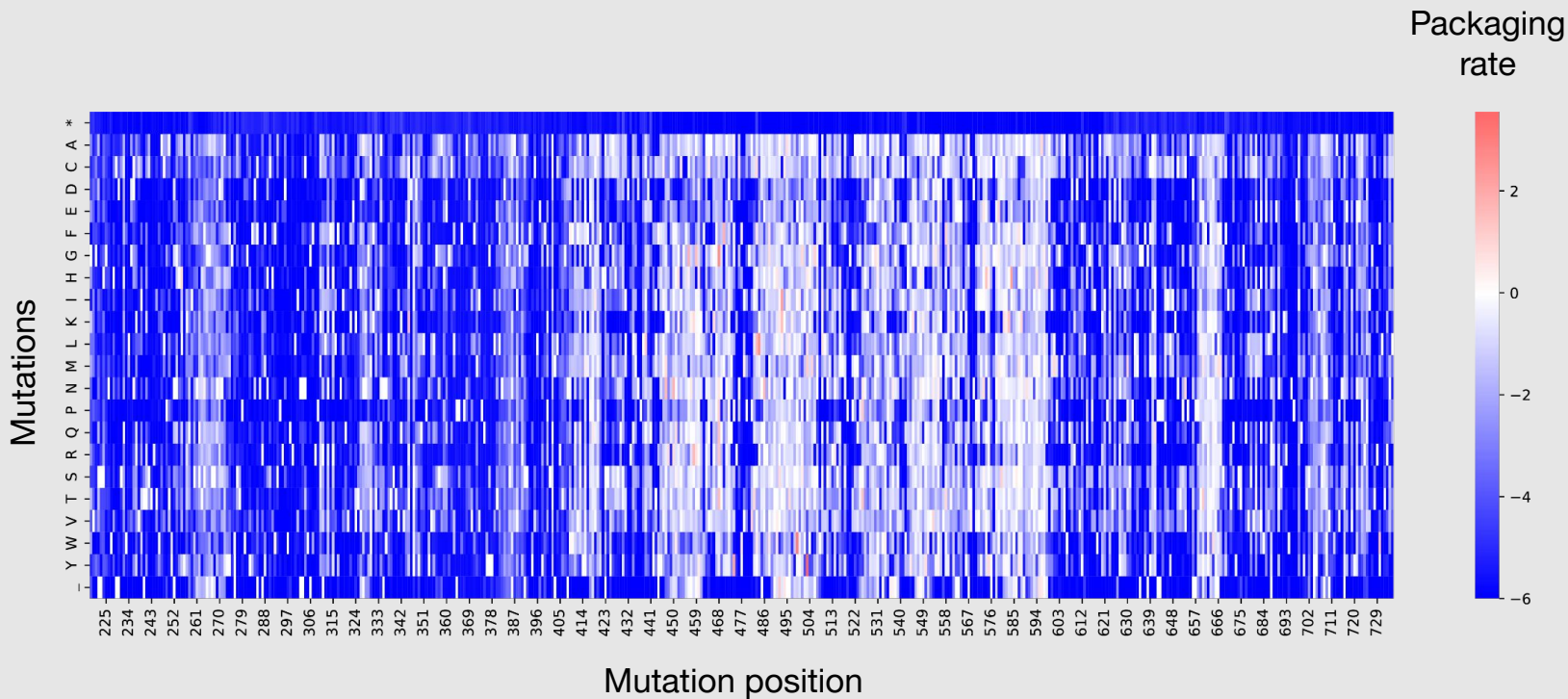
AI
hallucinate



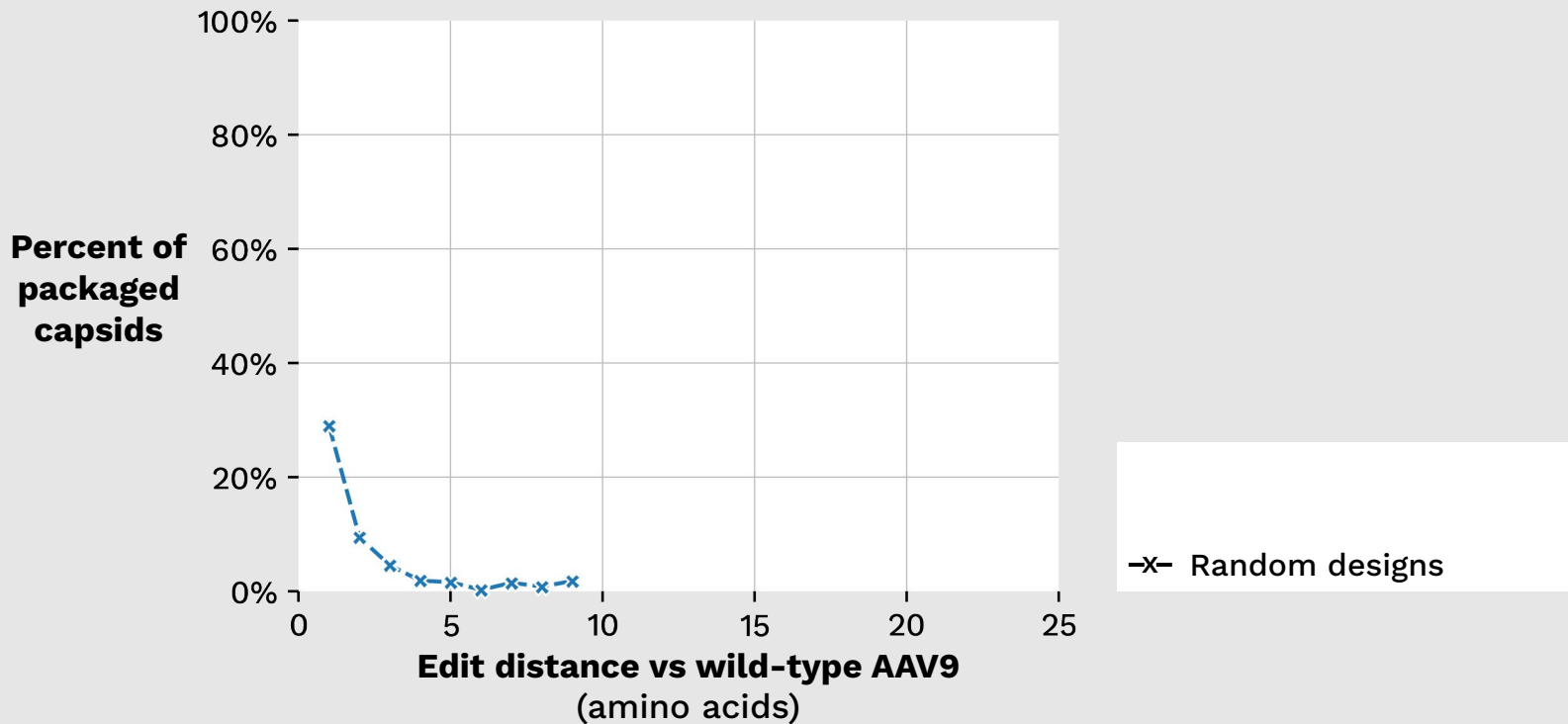
Aiming to predict performance beyond the training set



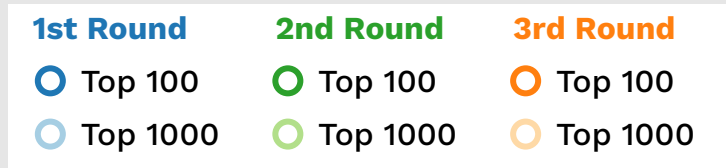
Most capsid mutations are deleterious



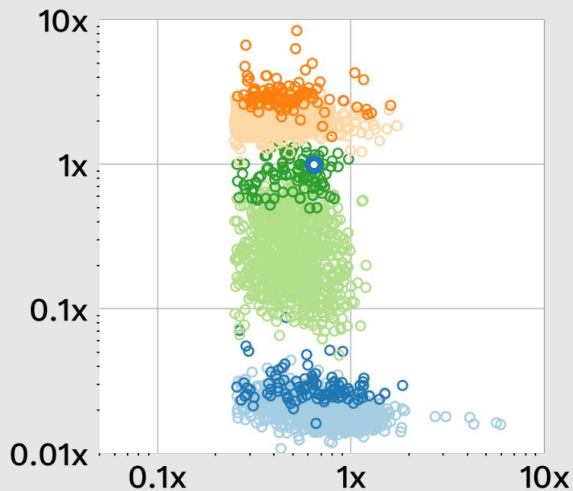
Most capsid mutations are deleterious



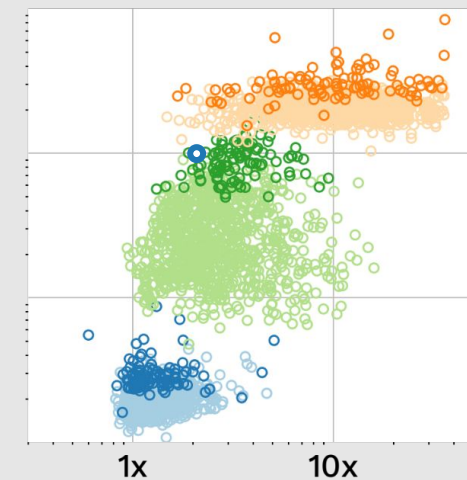
Prediction beyond the training set is challenging



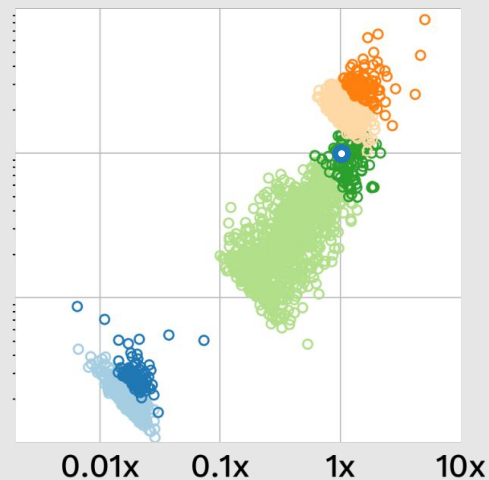
Brain transduction vs Dyno bCap 1



Production vs AAV9



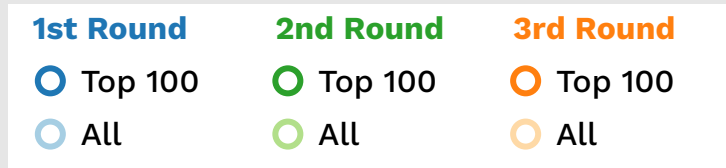
Liver detargeting (biodistribution) vs AAV9



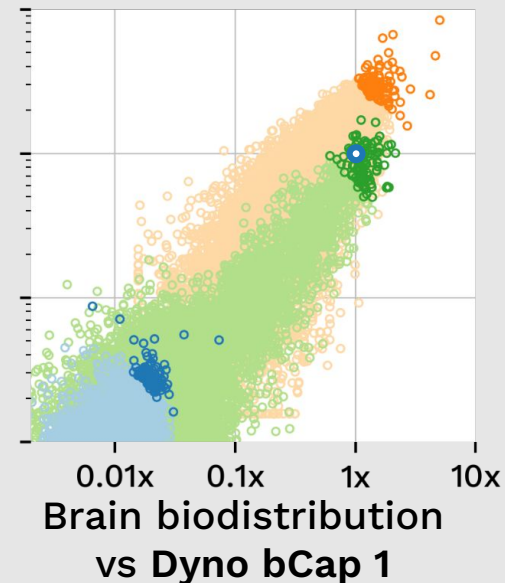
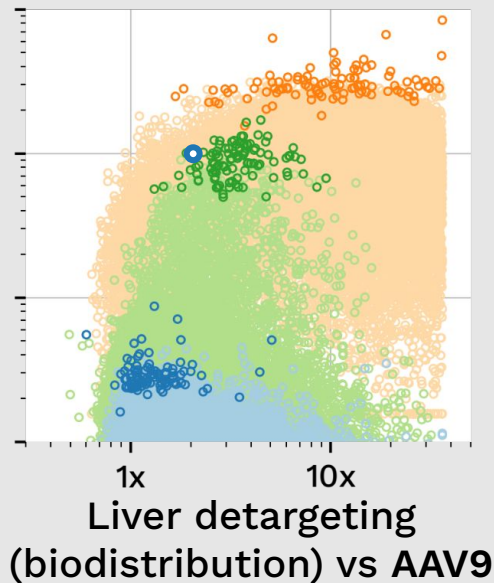
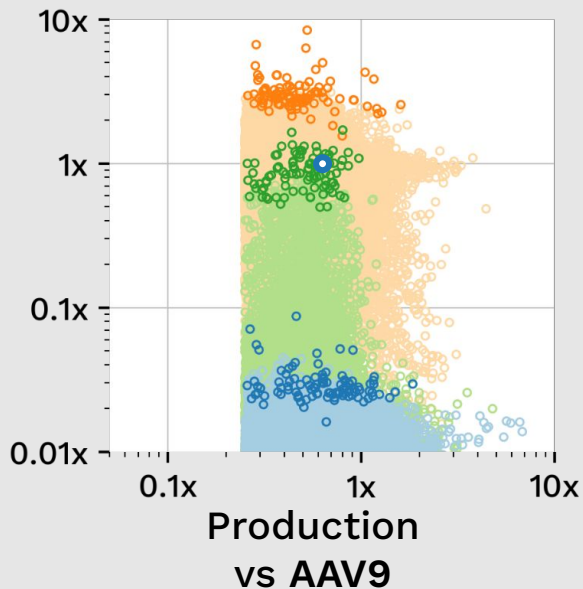
Brain biodistribution vs Dyno bCap 1



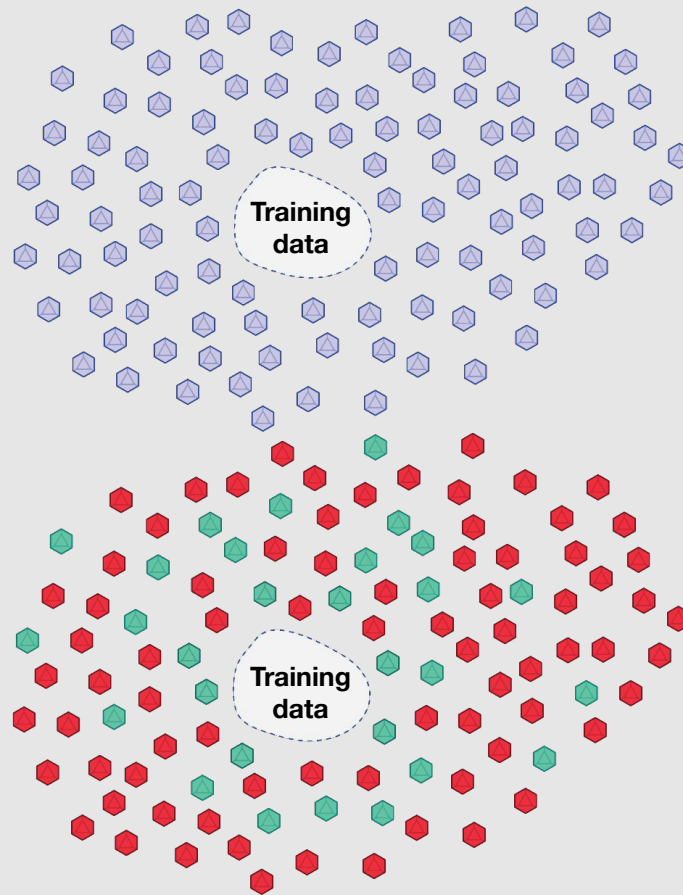
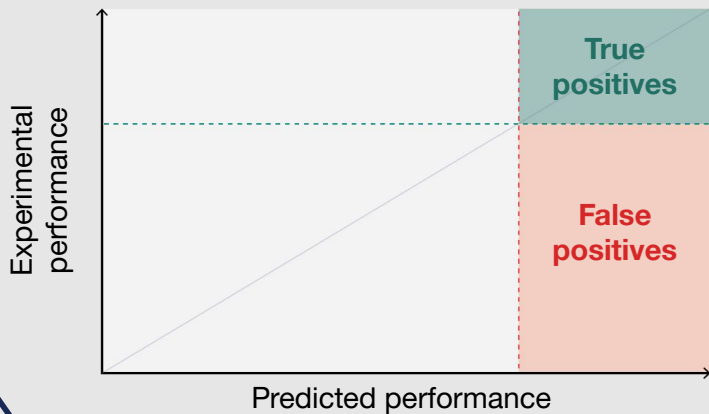
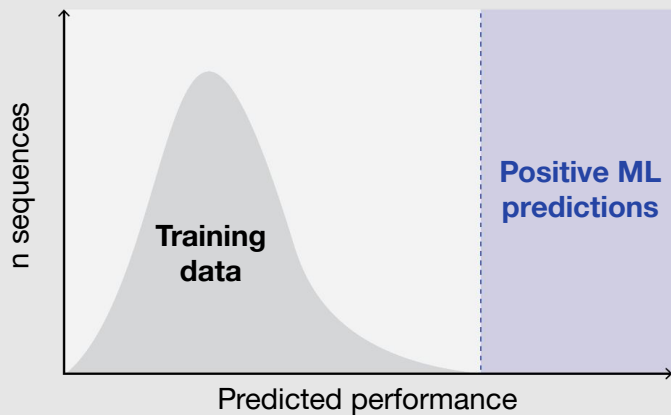
Prediction beyond the training set is challenging



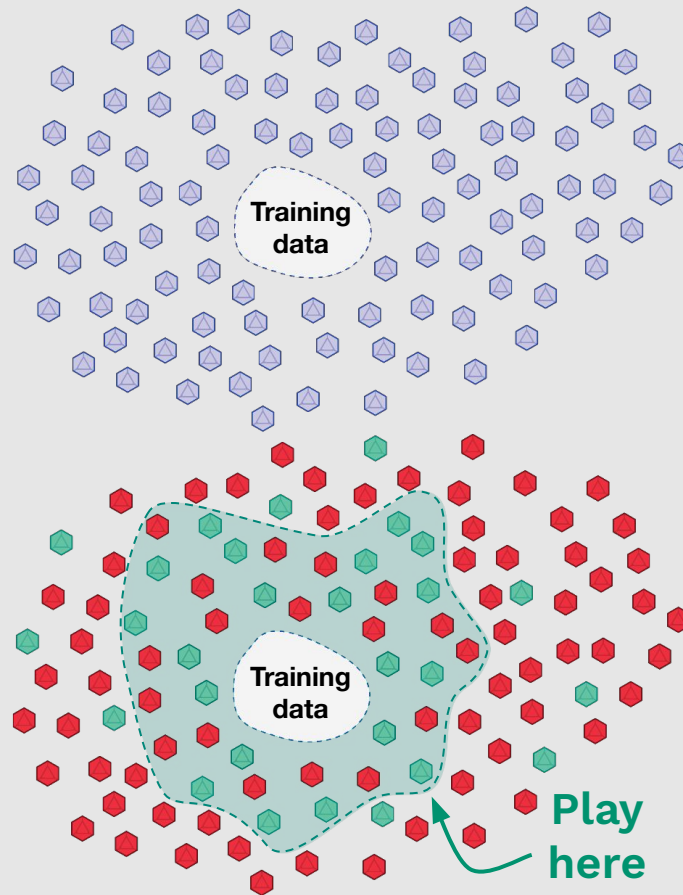
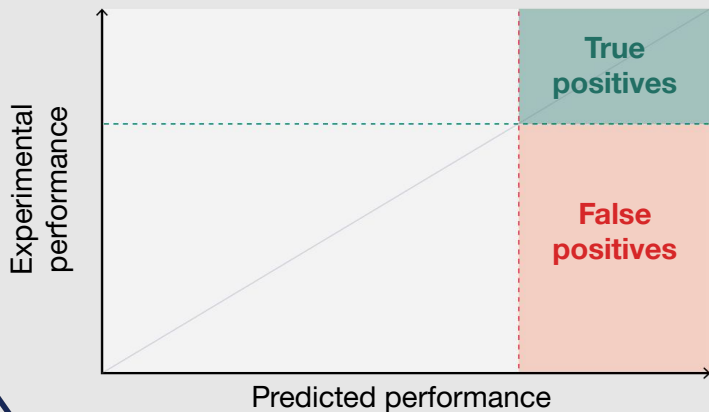
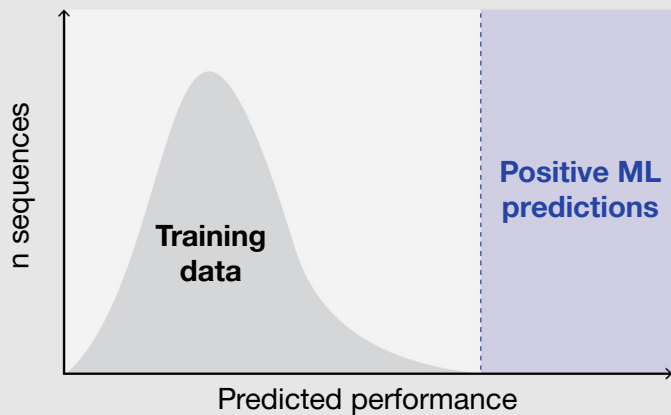
Brain transduction vs Dyno bCap 1



Improving the efficiency of high-performance prediction

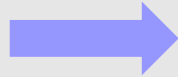


Improving the efficiency of high-performance prediction

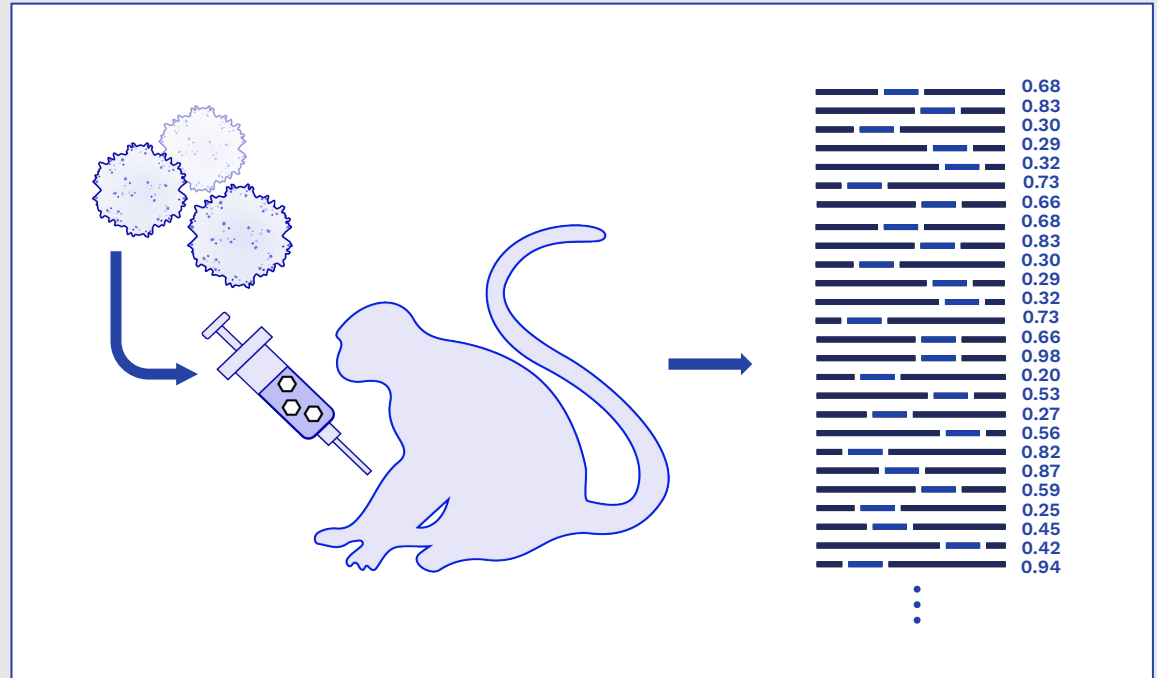


Improving the efficiency of high-performance prediction

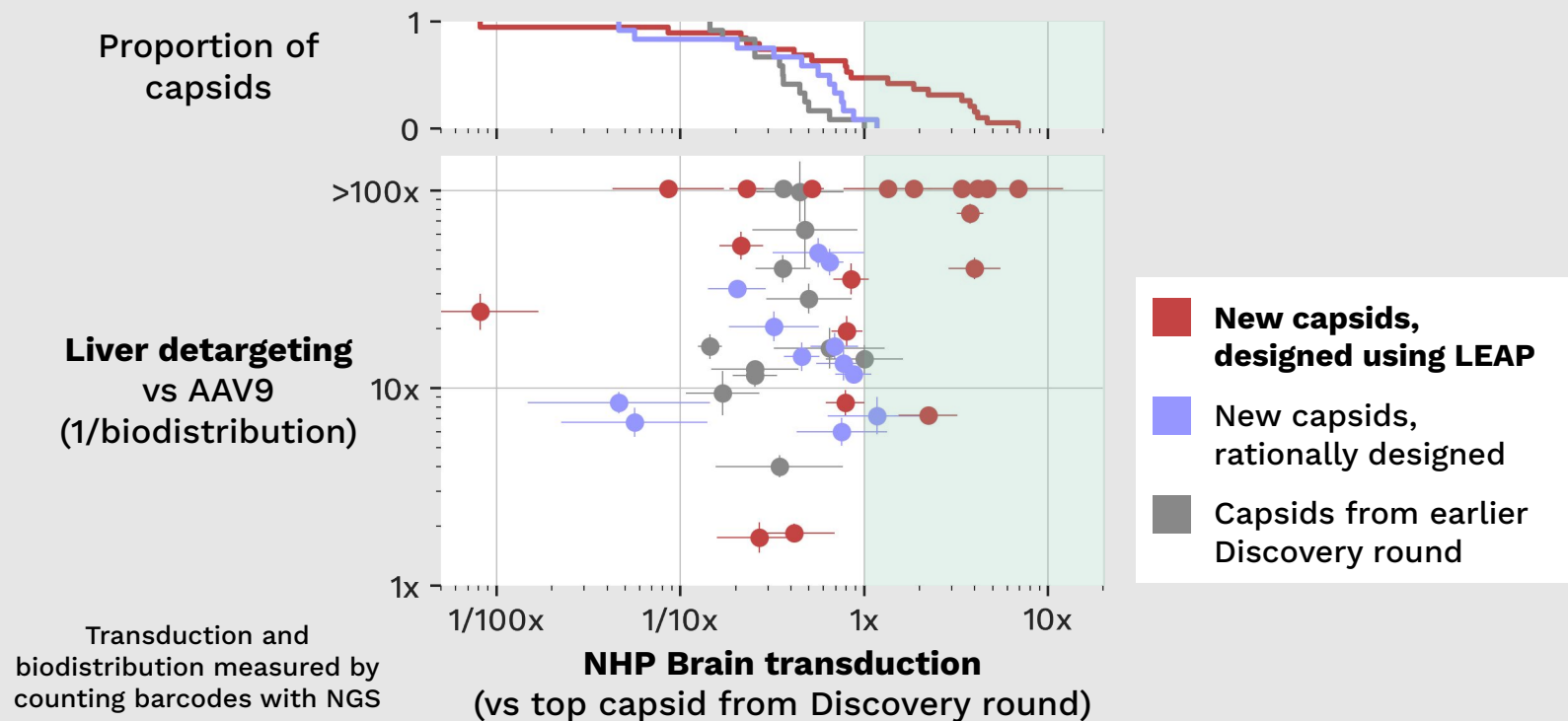
>20M capsid sequences



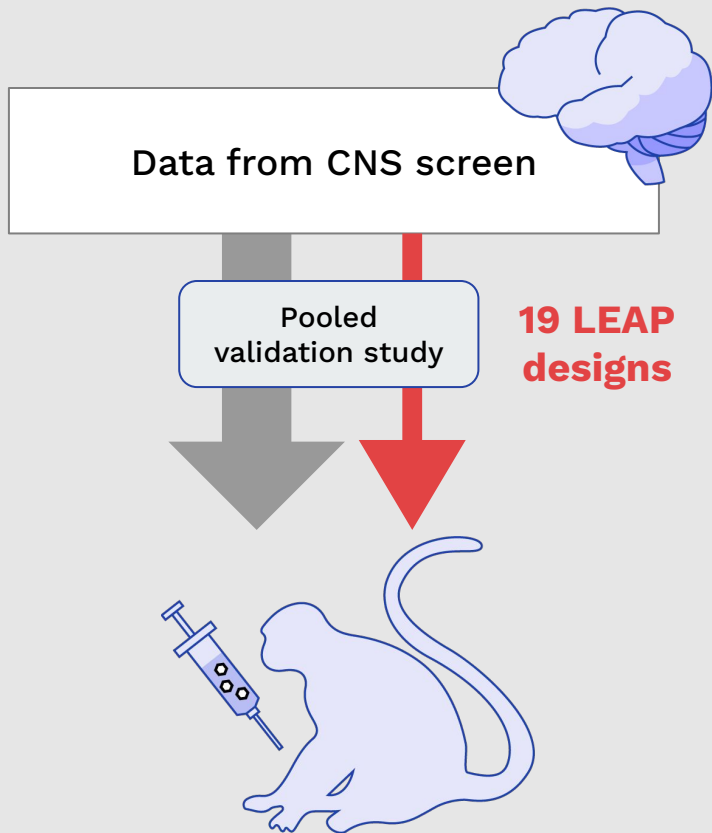
>25B in vivo measurements



Low-shot Efficient Accelerated Performance (LEAP)



Low-shot Efficient Accelerated Performance



90%

17 **packaged**
effectively

47%

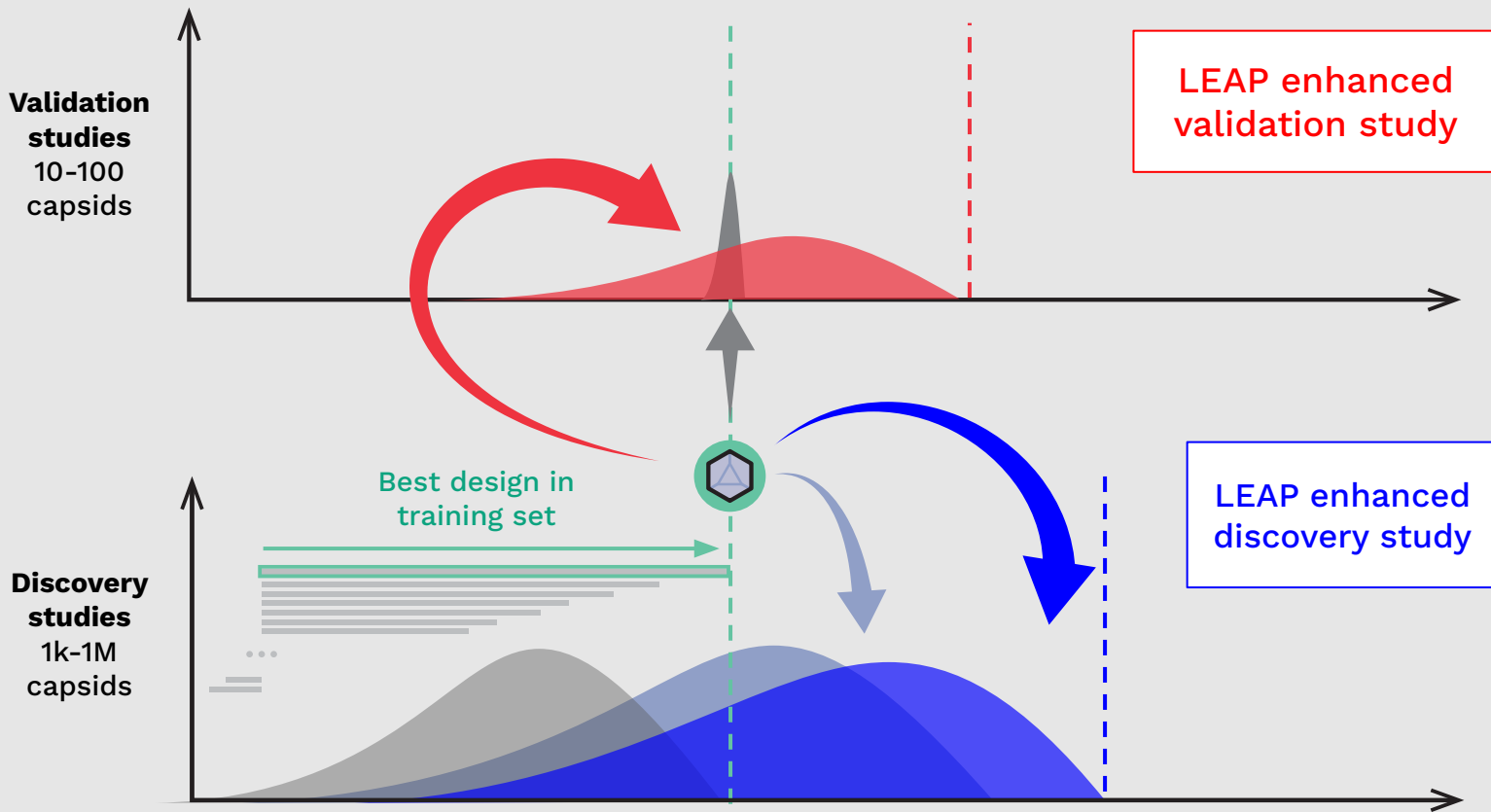
9 performed
better than anything we
had observed before

6x

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



LEAP enhances capsid validation



Validation studies
10-100 capsids

Discovery studies
1k-1M capsids

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**

LEAP enhanced validation study

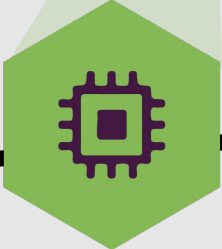
LEAP enhanced discovery study



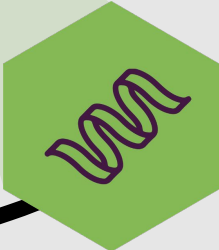
Scaling up AI-powered protein sequence design



nVIDIA®



DGX



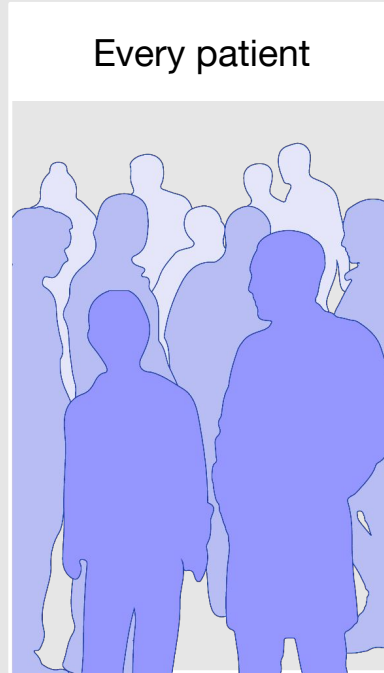
BioNeMO



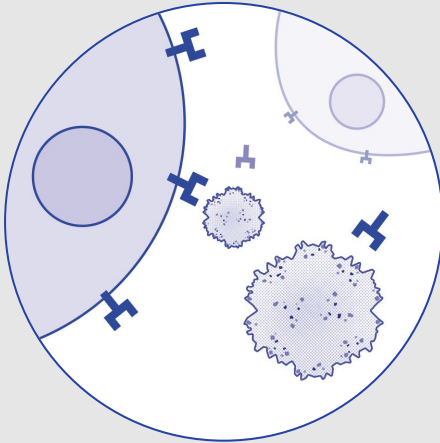
NIMS



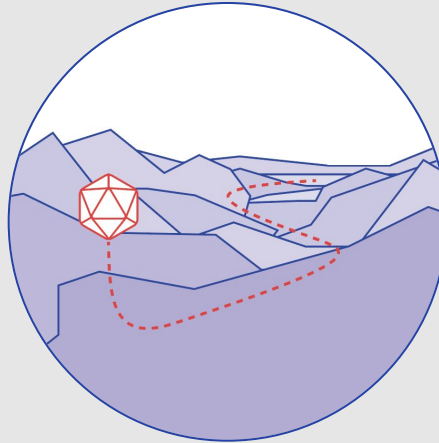
Expanding the reach of gene therapy



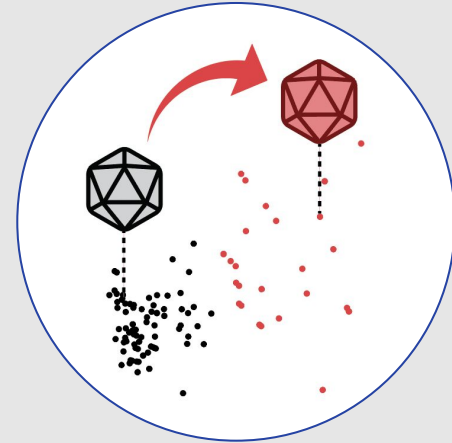
Expanding the reach of gene therapy



Problem



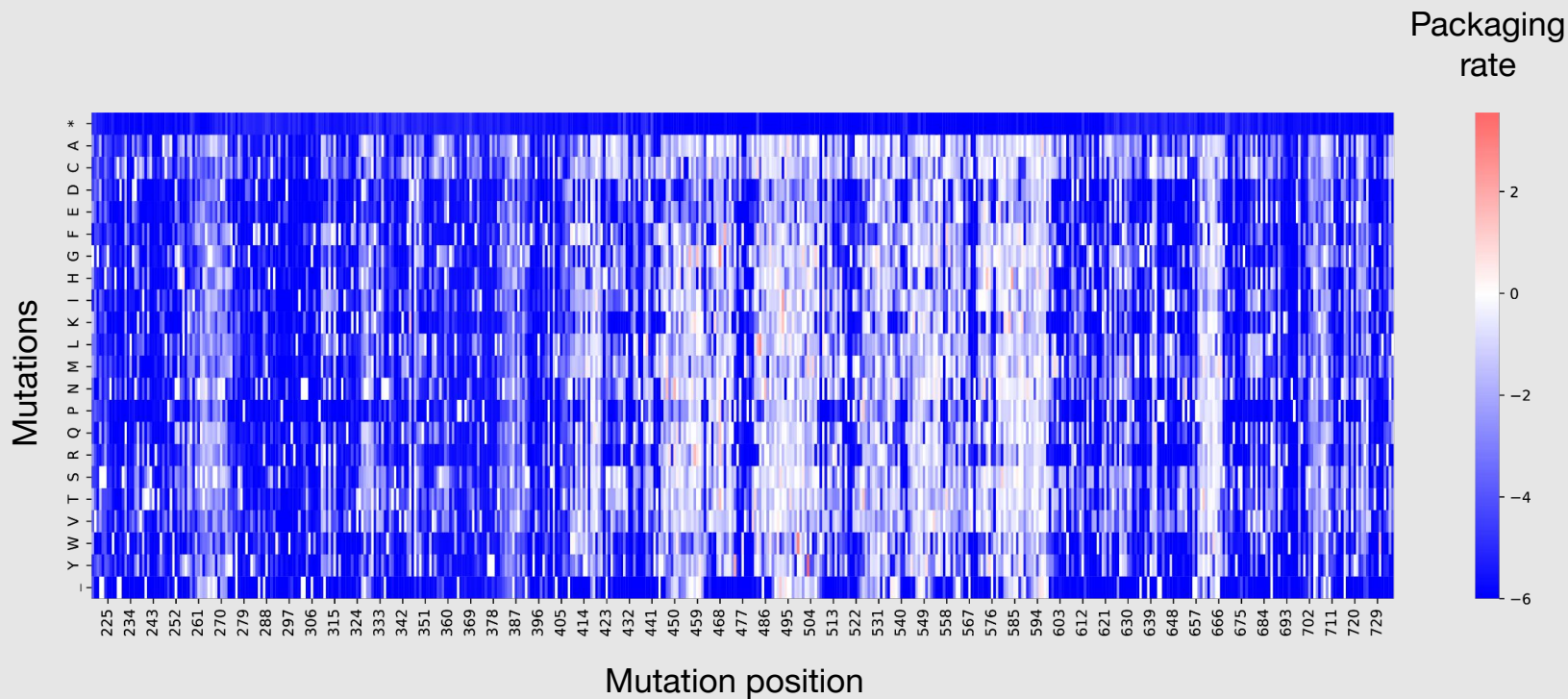
Challenge



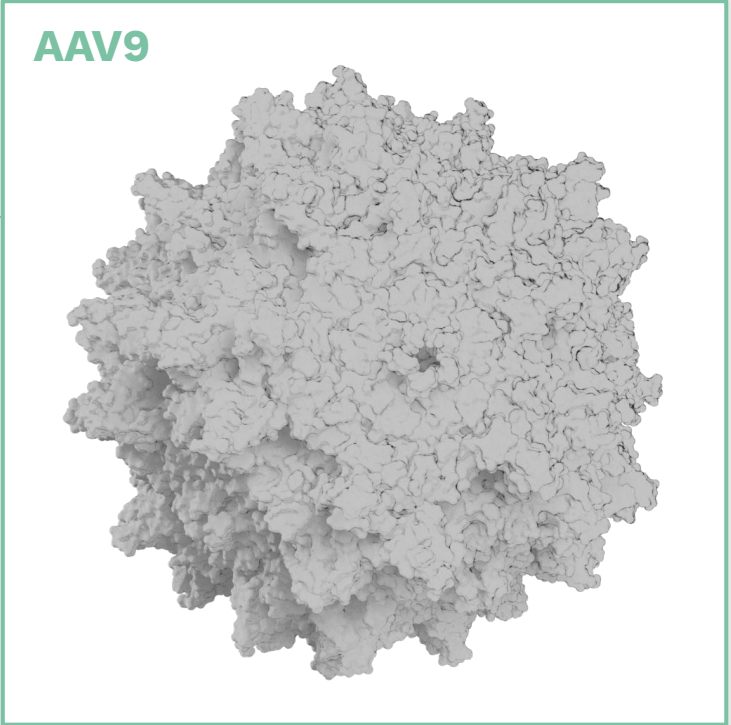
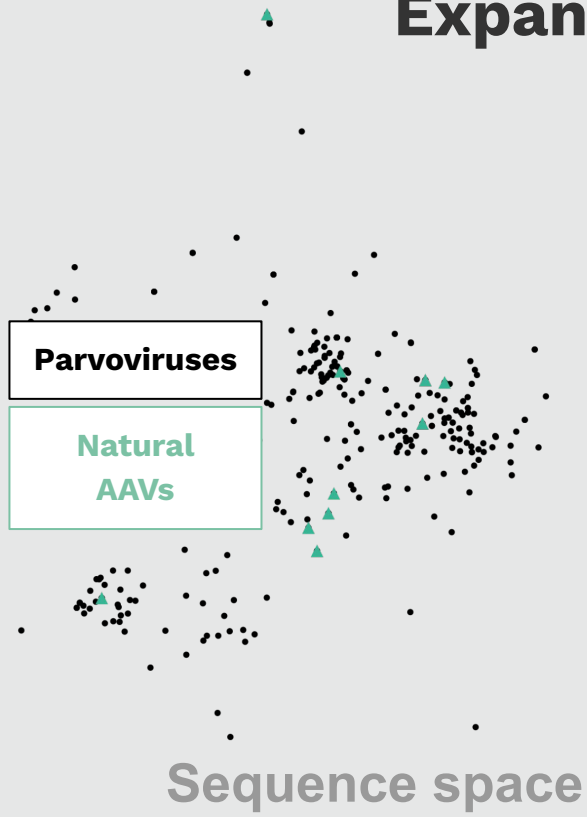
Solution



Most capsid mutations are deleterious



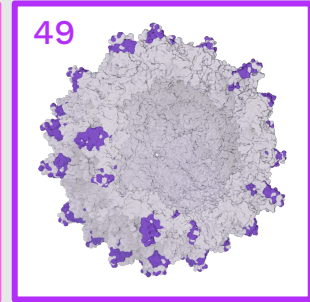
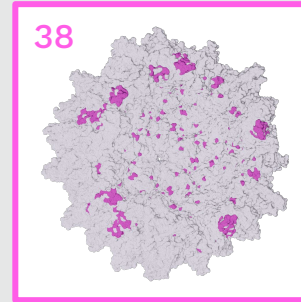
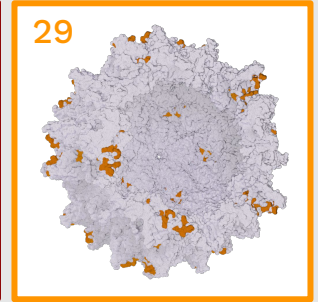
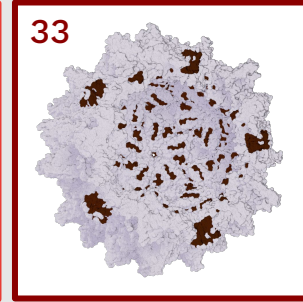
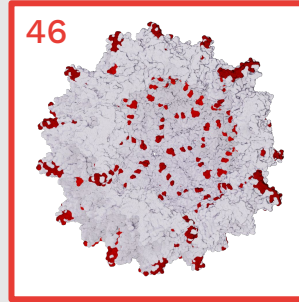
Expanding the Serotype Frontier



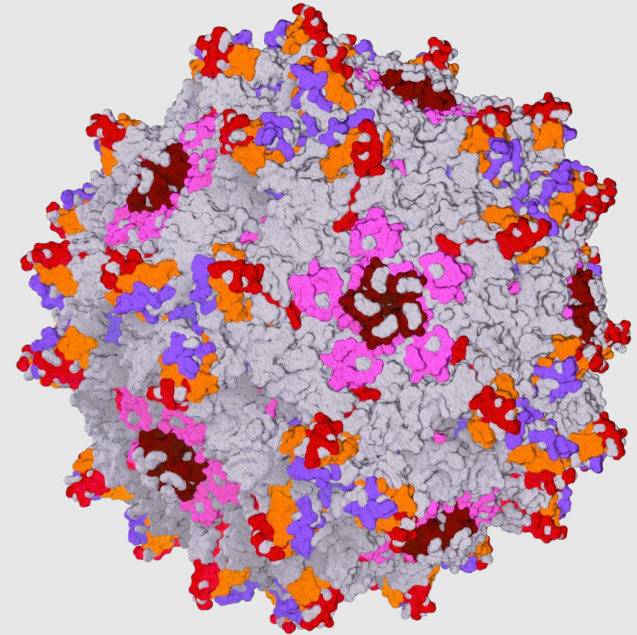
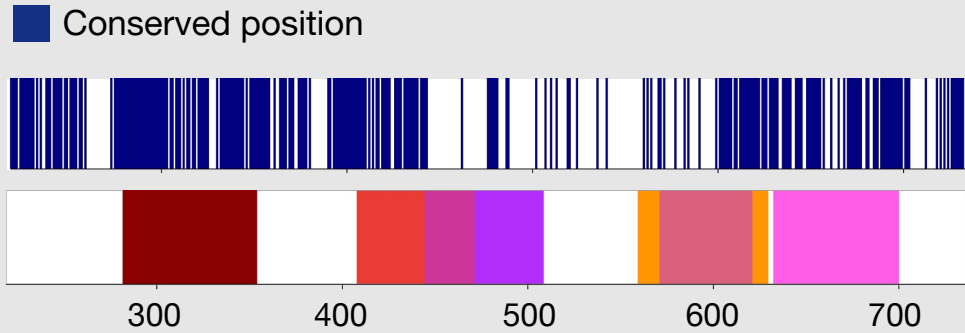
Expanding the Serotype Frontier

Dyno high edit
distance
serotypes

Sequence space

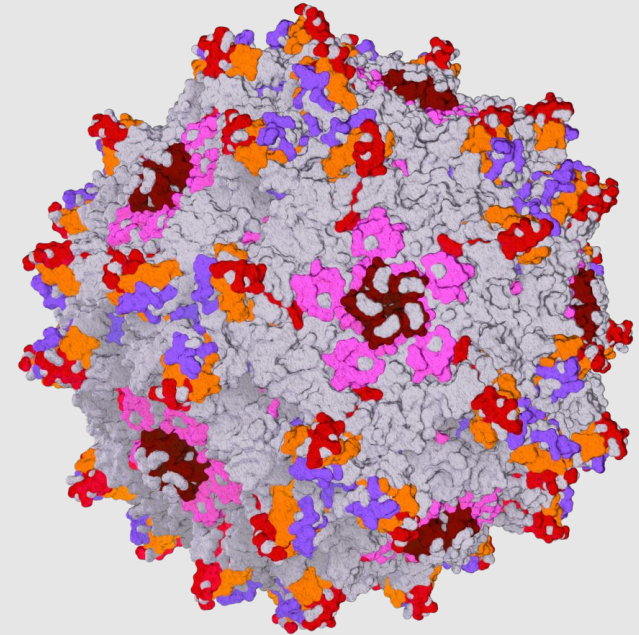
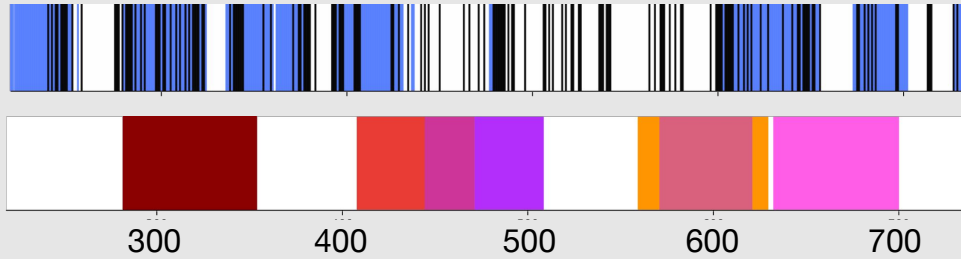


Modifying even conserved and buried regions



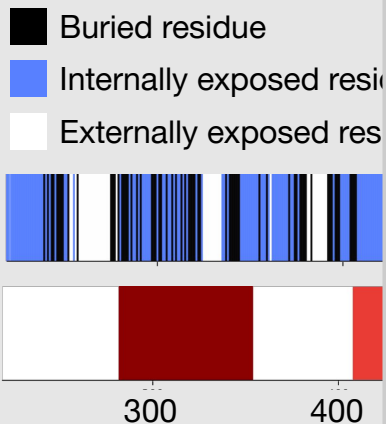
Modifying even conserved and buried regions

- Externally exposed residue
- Buried residue
- Internally exposed residue



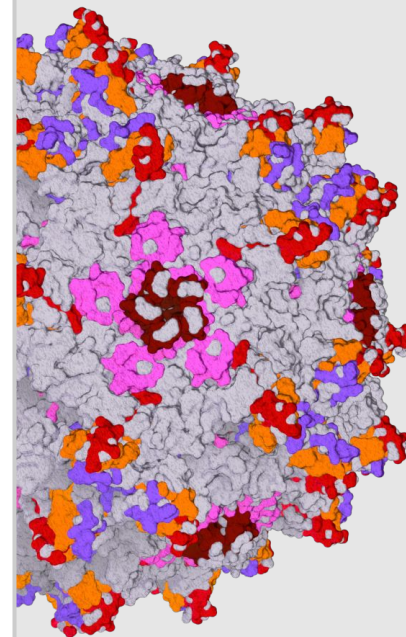
Modifyin

ed 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



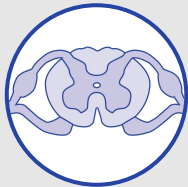
How can exponential change help more patients?

LUXTURNA
December 2017



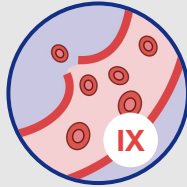
\$850,000

ZOLGENSMA
May 2019



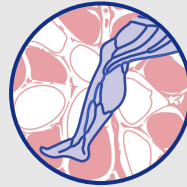
\$2.1 million

HEMGENIX
November 2022



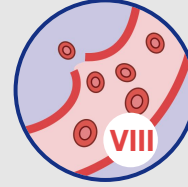
\$3.5 million

ELEVIDYS
June 2023



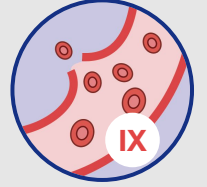
\$2.9 million

ROCTAVIAN
June 2023



\$2.9 million

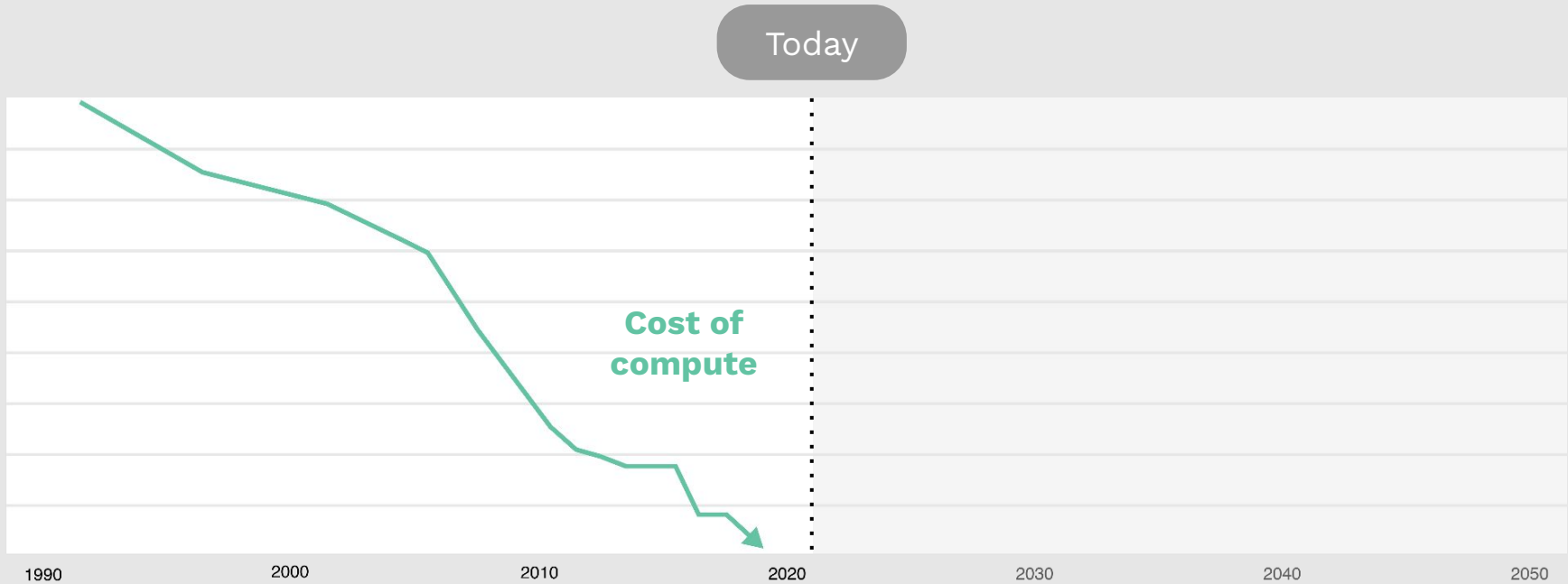
BEQVEZ
April 2024



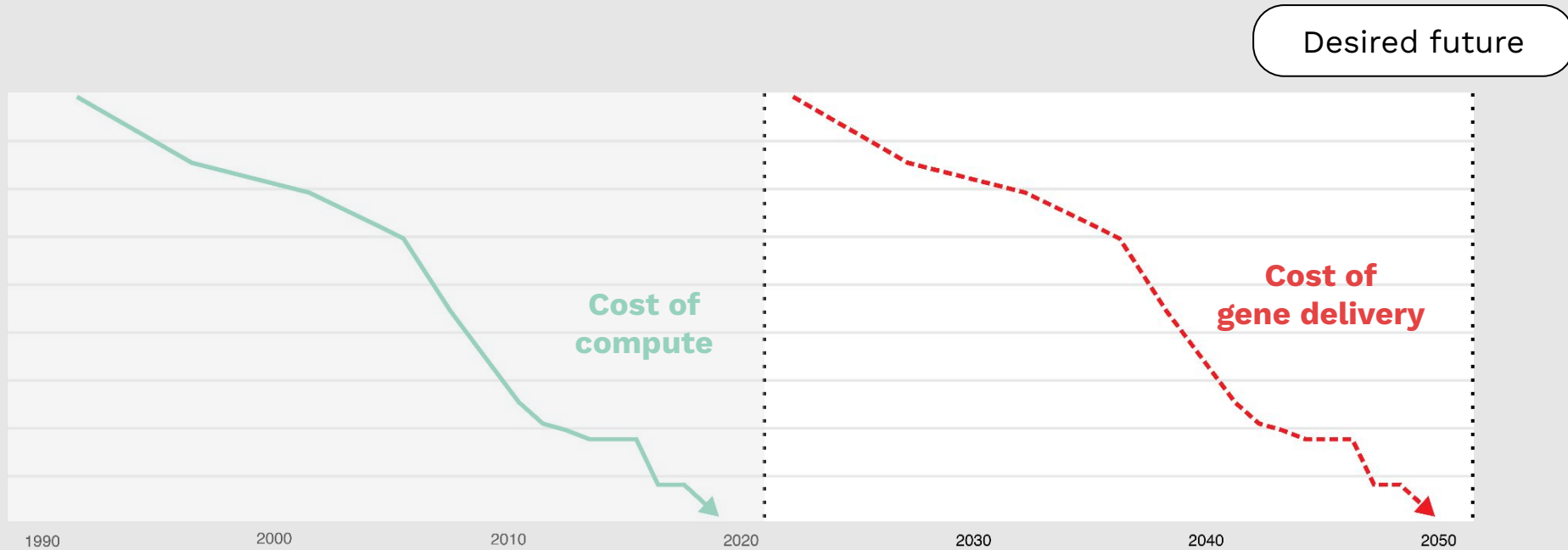
\$3.5 million



Bringing the cost of delivery down to zero



Bringing the cost of delivery down to zero



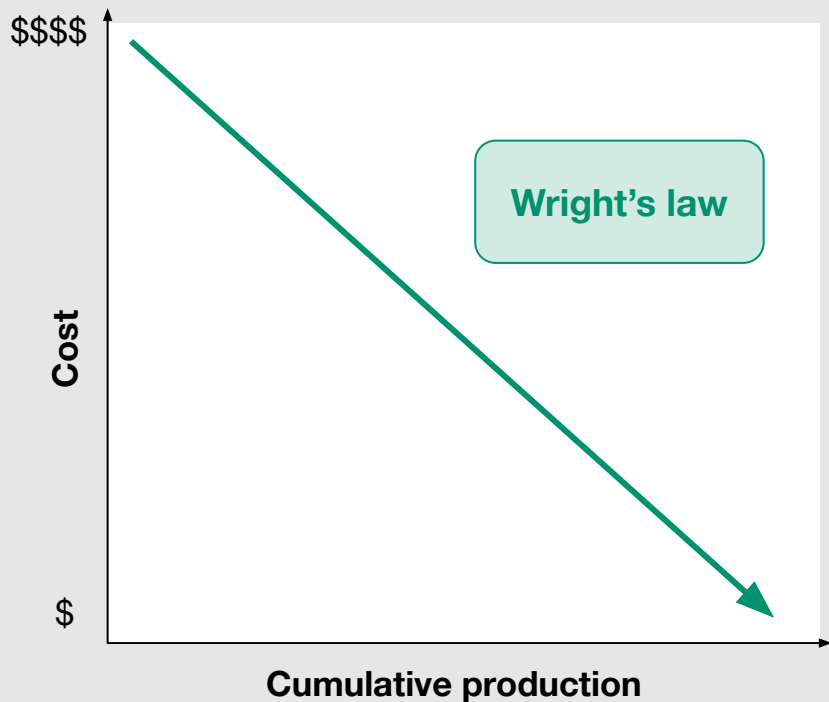


Entering an AI Era



via the Century of Biology

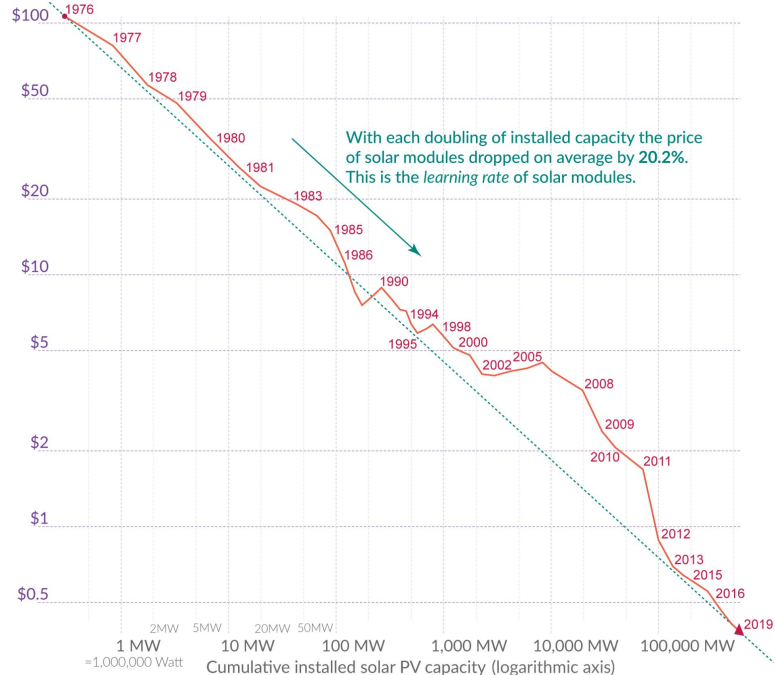
Cost falls as production increases



The price of solar modules declined by 99.6% since 1976

Our World in Data

Price per Watt of solar photovoltaics (PV) modules (logarithmic axis)
The prices are adjusted for inflation and presented in 2019 US-\$.
\$100 1976

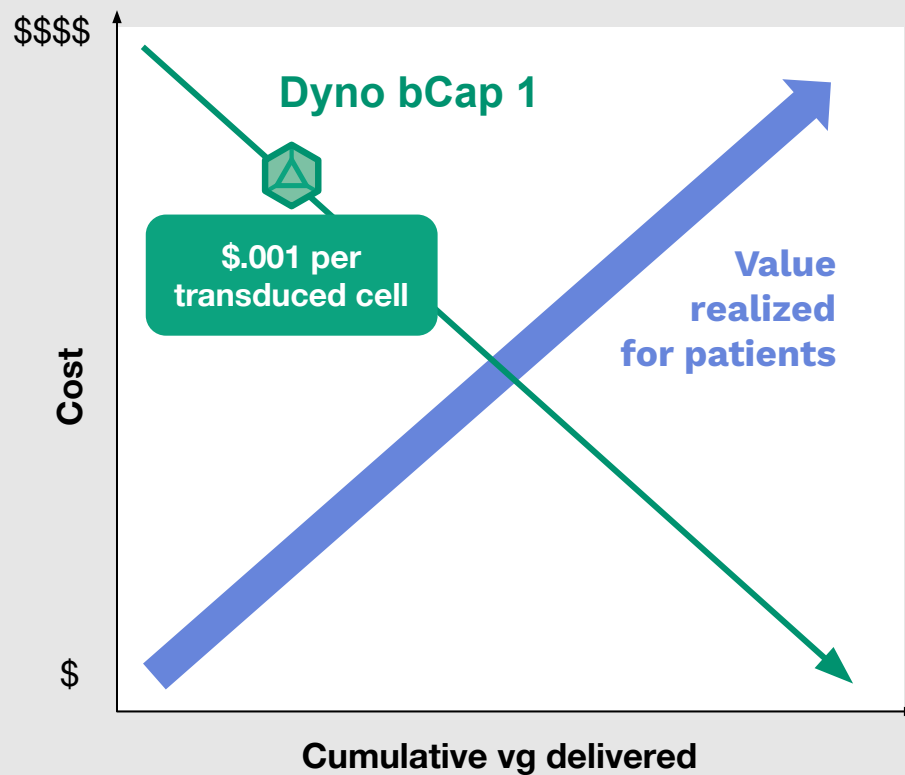


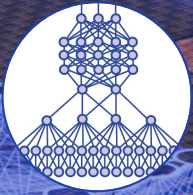
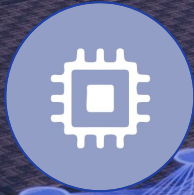
Data: Lafond et al. (2017) and IRENA Database; the reported learning rate is an average over several studies reported by de La Tour et al (2013) in Energy. The rate has remained very similar since then.
OurWorldinData.org - Research and data to make progress against the world's largest problems.

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The century of biology





Everyone can help

