Scientific Poster Session

n-lorem FOUNDATION

Nano-rare Patient Colloquium 2025

Monday, October 20 | 5:15 – 6:15 pm EST

iPSC Strategies to Reduce Time and Cost in Disease Modeling

This work describes the establishment of an optimized iPSC-derived neuronal differentiation platform to streamline disease modeling for ASO screening. By utilizing patient-specific iPSCs, this approach offers a scalable, robust, and cost-effective solution for high-throughput ASO screening, significantly reducing timelines and costs in the preclinical discovery pipeline.

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Hosted by:

Biogen

Introduction

Efficient antisense oligonucleotide (ASO) discovery screening is critical to any drug discovery program, and this is especially true for n-of-1 (nano-rare) therapeutic development. At n-Lorem, this process **must be both cost-effective and time-efficient** to meet the urgent **needs of our patients**.

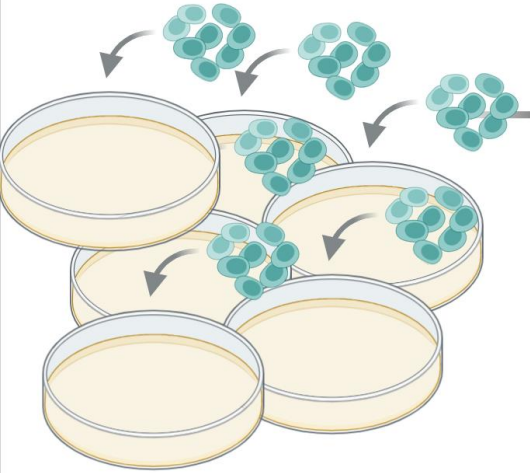
For certain central nervous system (CNS) indications, screening requires the use of **mature neurons** because the target gene is only expressed at this stage of neuronal development.

Traditional Organizations

n-Lorem and other biotech organizations have relied on **Sendai virus–mediated differentiation** of induced pluripotent stem cells (iPSCs) to generate these neurons. However, this approach presents significant challenges

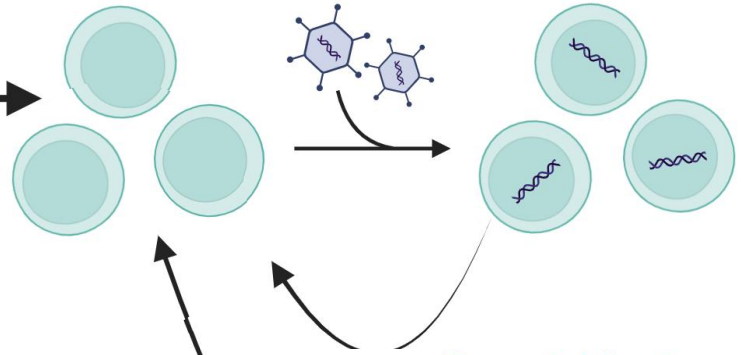
- **Extended generation timelines (up to 8 months)**
- **High cost (~USD 3,000 per ASO plate)**
- **Labor-intensive workflows**
- **Variable neuronal yields**
- **Need for multiple rounds of neuron generation**
- **Limited scalability for high-throughput screening**

1 *Significant iPSC Plating Event*



Sendai Virus (SeV) Transduction

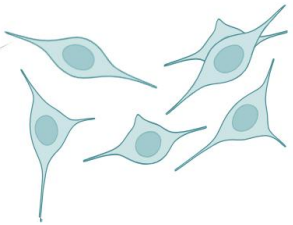
2 *SeV very sensitive to stress*



Initial differentiation

3 *DIV3 split determines neuron yield*

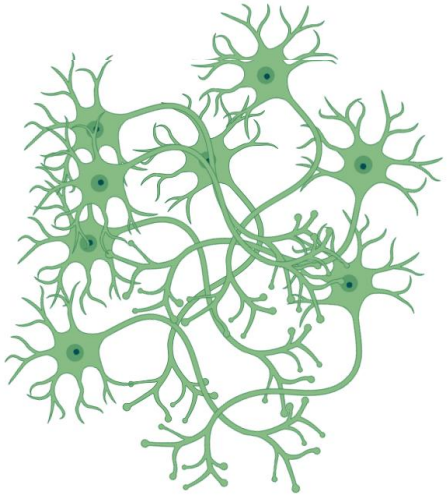
(extremely variable)



Repeatable steps often required - depending on yield

4

Neurons ready for use



Differentiation into mature neurons

Methodology

NGN2 (Neurogenin-2), is a proneural transcription factor that drives **rapid differentiation** of pluripotent stem cells into neurons. We package the NGN2 plasmid using a high-titer lentiviral packaging service. NGN2 is a:

- **Master regulator of neurogenesis**
- **Fast and reproducible neuronal induction**
- **Generates cortical-like neurons**
- **Scalable for disease modeling and screening**

iPSCs

Generation of NGN2 iPSCs

Timeline : 6 to 8 weeks

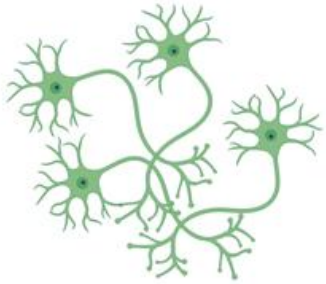
NPCs

Large scale NPC generation and banking

Timeline : 1.5 weeks

nL00713: ~**250 Millions** (140 Mil, **1.8x**)
nL01121: ~**600 Millions** (160 Mil, **3.75x**)
nL00314: ~**325 Millions** (165 Mil, **2x**)
nL01505: ~**300 Millions** (155 Mil, **2x**)
nL00645: ~**300 Millions** (25Mil, **6X**)

Neurons



Small scale, single dose and dose response screening in neurons

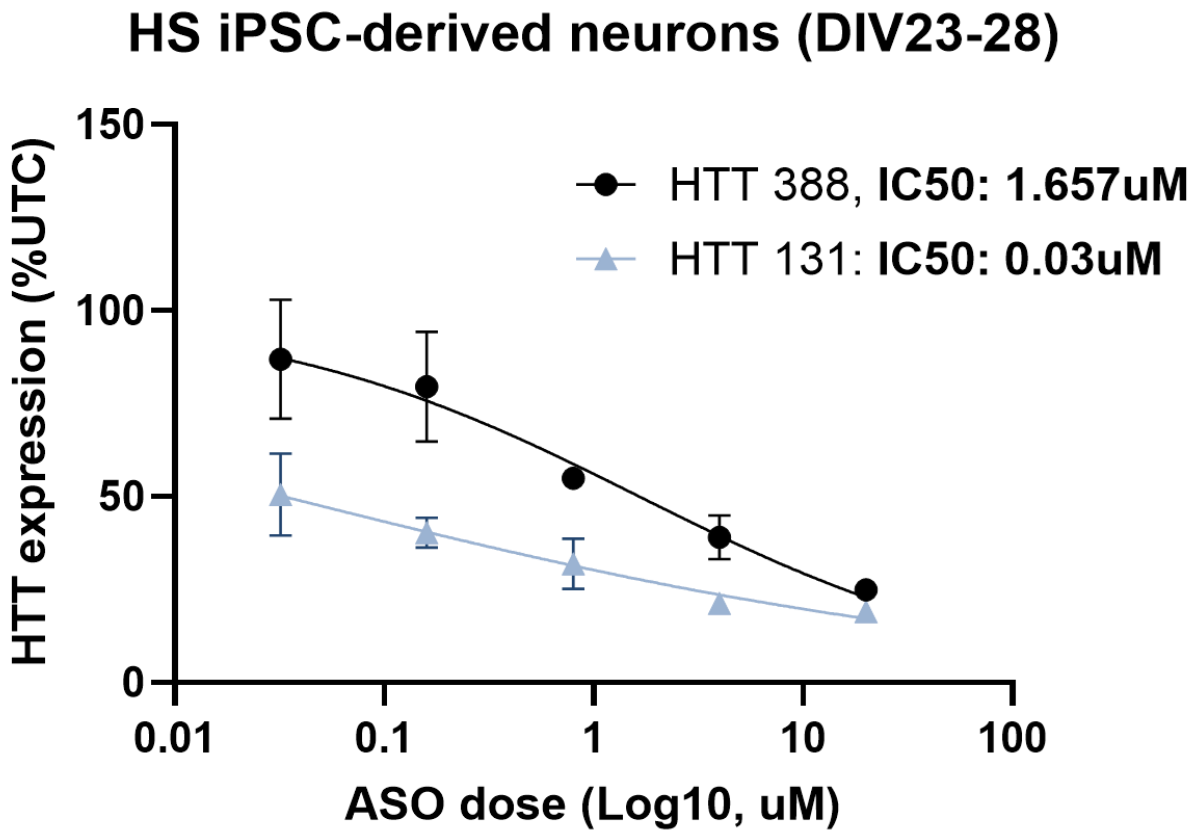
Timeline:
Small scale diff: **4 weeks**
Single dose and DRC: **9 weeks**

Timeline for neuronal screens (good quality iPSCs to end of screening)
21 -23 weeks (5.25 – 6 months)

6

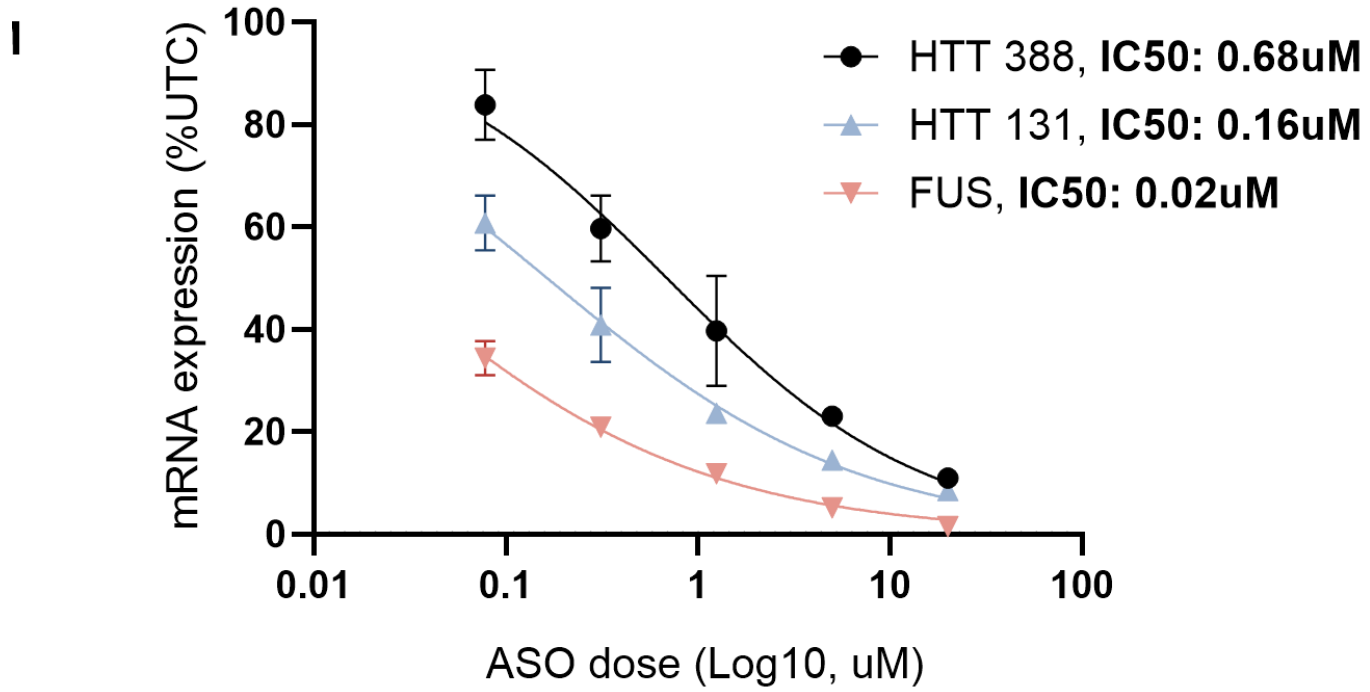
NGN2 differentiated neurons are required to uptake ASOs in a similar manner to Sendai virus method. Control ASOs were dosed via free uptake for 5 days and compared to previously generated Sendai data

Sendai Virus Protocol



NGN2 Protocol

HS iPSC-derived neurons (DIV24-29)



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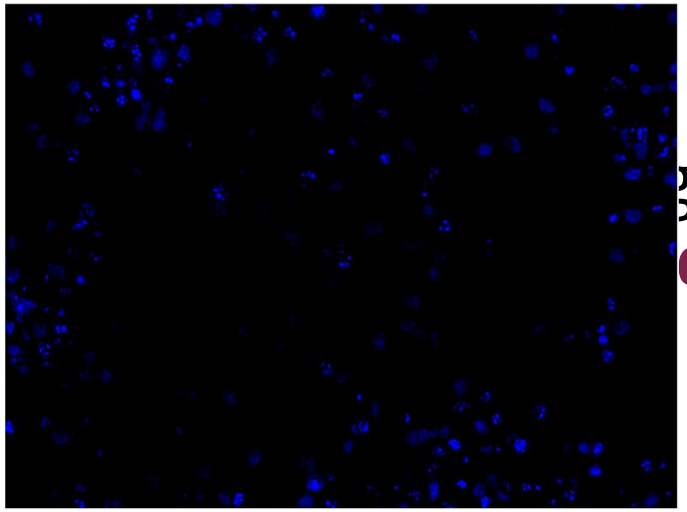
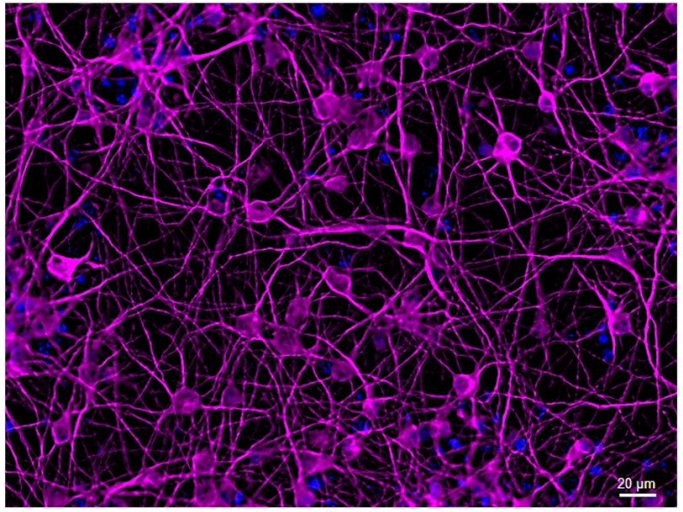
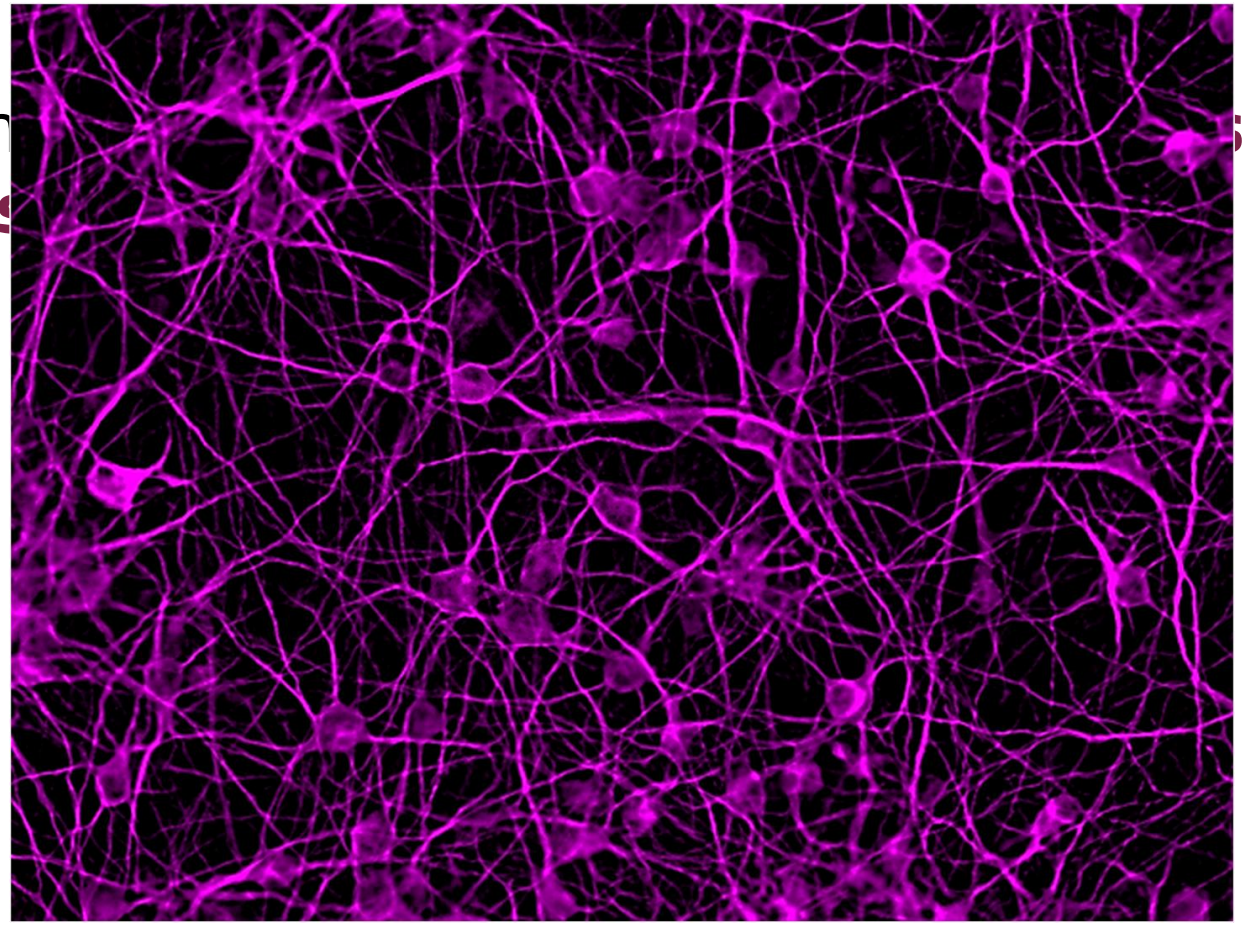
DAPI



Overlay



MAP2



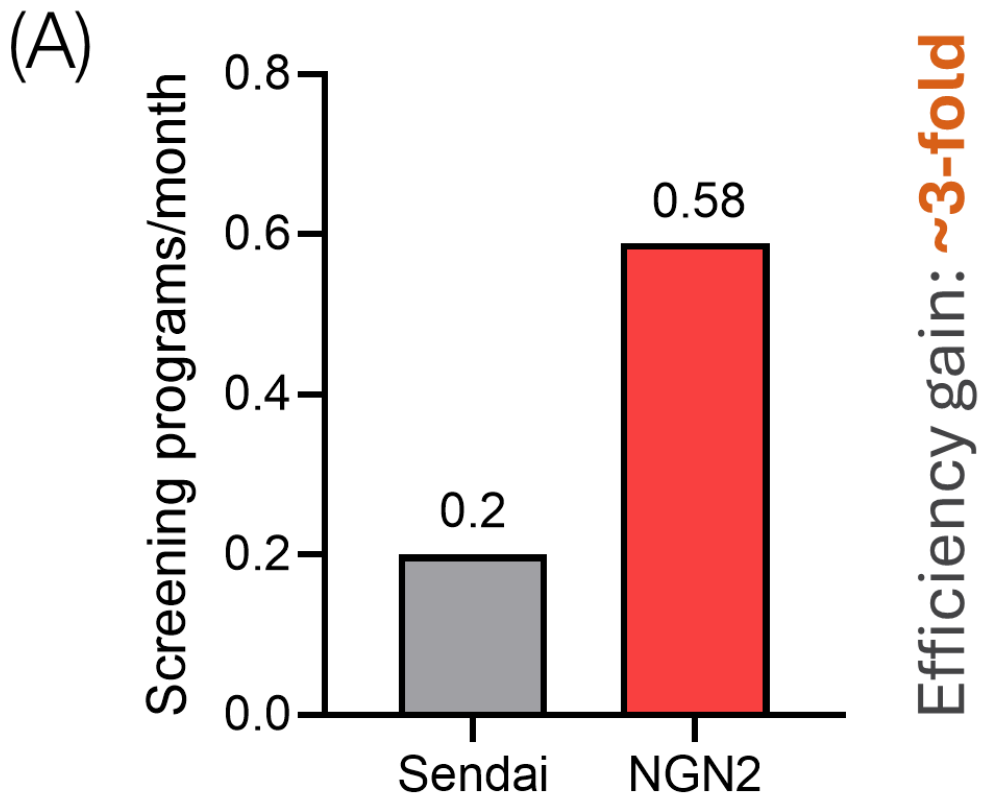
gen

es

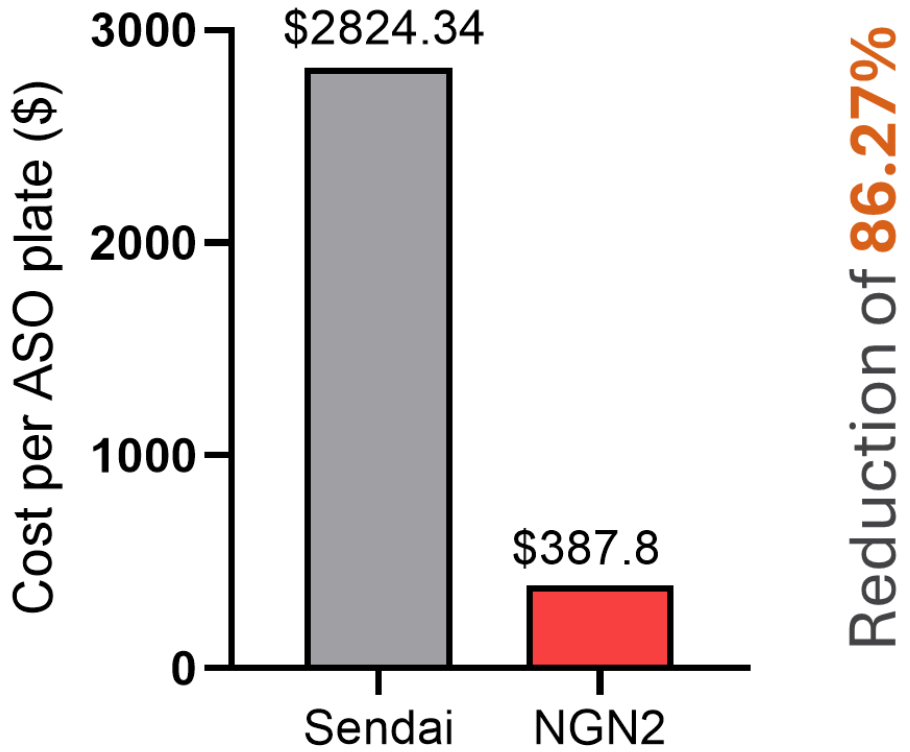
spread

NGN2 Protocol is time and cost effective – Allowing n-Lorem to increase output without sacrificing quality or standards.

- **3-Fold Efficiency Gain**
- **Over 85% REDUCTION IN COST**


(A)
Screening programs/month
0.8
0.6
0.4
0.2
0.0
0.2
0.58
Sendai
NGN2
Efficiency gain: ~3-fold

(B)


3000
2000
1000
0
Cost per ASO plate ($)
$2824.34
$387.8
Sendai
NGN2
Reduction of 86.27%

(C)

Case	Sendai	NGN2
nL00713 (SS, SD, DRC)	39540.87928	5429.2868
nL01121 (SS, SD)	29655.65946	4071.9651
nL00314 (SS, SD)	29655.65946	4071.9651
nL01505 (SS)	1412.17426	193.9031
nL00645 (SS, DRC)	5648.69704	775.6124
	105913.0695	14542.7325

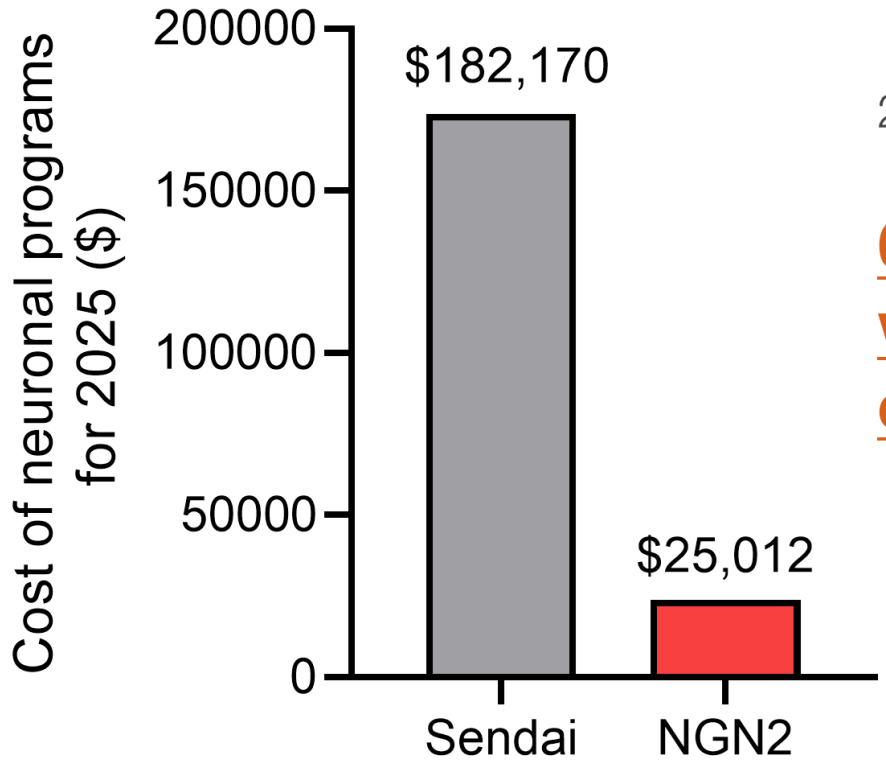
SS – Small scale differentiation; SD – Single dose; DRC – Dose response

Savings of **$91,370.34**

Conclusion

All the described methodology encompasses a **continuous, diligent and data-driven attempt to optimize** our processes to help more **NANO-RARE PATIENTS TODAY**

Conclusion



2025 Savings: **$157,157**

6.28 x more patients we can help for cost equivalent

Acknowledgements

We would like to thank the **Yeo Lab** at **UCSD** for a portion of the initial NGN2 plasmids provided at the beginning of the study. As well as the **Gleeson Lab UCSD/Rady** for a modified protocol of the current NGN2 presented.

Thank you

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