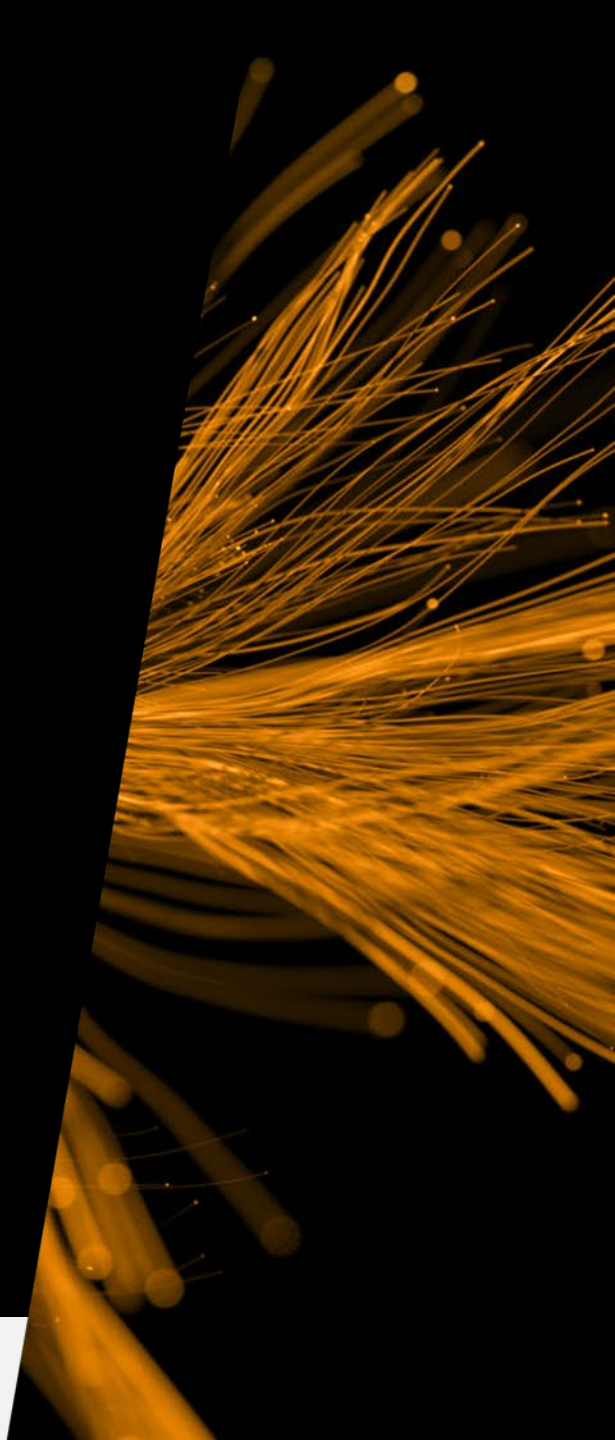


Progress Toward the Discovery of an ASO for Therapeutic Upregulation of SYNGAP1

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This presentation may contain “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 relating to our business and operations, including but not limited to express or implied statements regarding the current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results and other future conditions. Any forward-looking statements in this presentation are based on management’s current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this presentation, including, without limitation, risks relating to: (i) the success and timing of our ongoing clinical trials, (ii) the success and timing of our product development activities and initiating clinical trials, (iii) the success and timing of our collaboration partners’ product development activities, (iv) the timing of and our ability to obtain and maintain regulatory approval of any of our product candidates, (v) our plans to research, discover and develop additional product candidates, (vi) our ability to enter into collaborations for the development of new product candidates, (vii) our ability to establish manufacturing capabilities, and our and our collaboration partners’ abilities to manufacture our product candidates and scale production, (viii) our ability to meet any specific milestones set forth herein, and (ix) the potential addressable market sizes for product candidates. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements.

For further information regarding the risks, uncertainties and other factors that may cause differences between our expectations and actual results, you should review the “Risk Factors” section of our Annual Report on Form 10-K for the year ended December 31, 2022, our Quarterly Reports on Form 10-Q and other filings with the Securities and Exchange Commission.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and make no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

Our mission at Praxis



To help patients by delivering life-altering treatments faster and more effectively than has ever been done before —
and to do it again and again.



Leveraging genetics to efficiently translate insights into therapies



GENETICS

Focus on therapeutic targets identified through human genetics



TRANSLATIONAL TOOLS

Translational tools validate potential of target and product candidate and can provide early proof of biology



EFFICIENT & RIGOROUS

Efficient, rigorous clinical development paths to proof-of-concept in humans

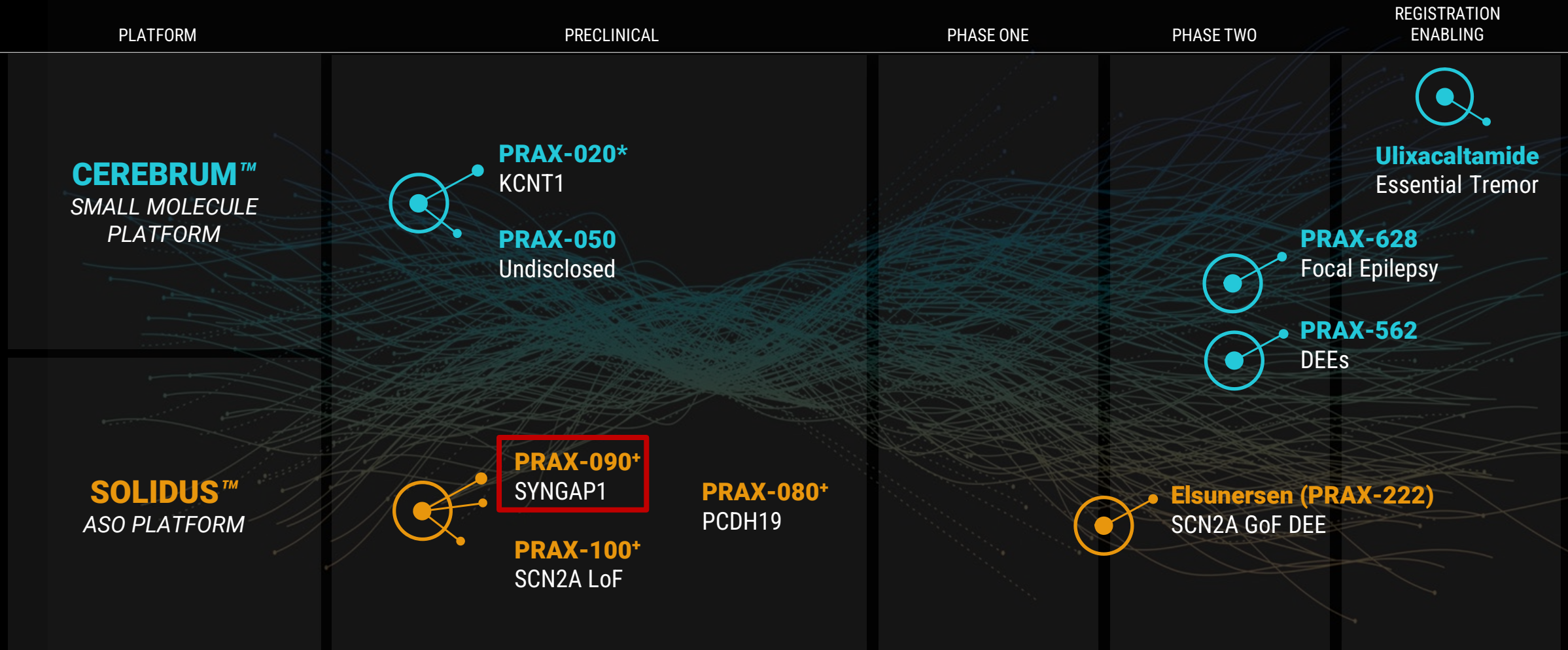


PATIENT-GUIDED

Patient-guided development strategies to deliver on what patients actually need



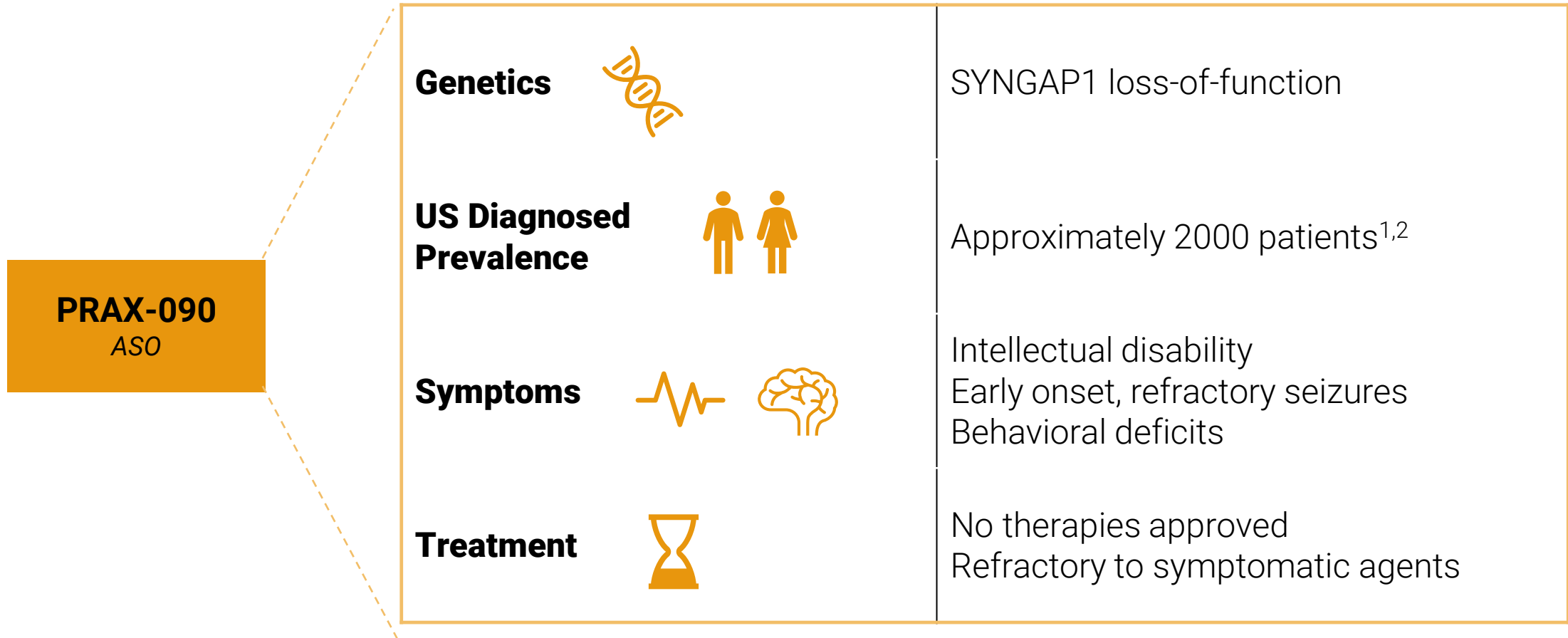
Targeting epilepsies & movement disorders connected by neuronal imbalance



*PRAX-020 (KCNT1) is a research collaboration with UCB

+PRAX-080 (PCDH19), PRAX-090 (SYNGAP1) & PRAX-100 (SCN2A-LoF) ASOs are a collaboration with The Florey Institute of Neuroscience and Mental Health

SYNGAP1 ASO Background



SYNGAP1 (PRAX-090) ASO is a collaboration with The Florey Institute of Neuroscience and Mental Health.

¹Source: Invitae Behind The Seizure Data; Ambit Genetic Testing and Claims Data Analysis

Pathway from ASO Discovery to Approval



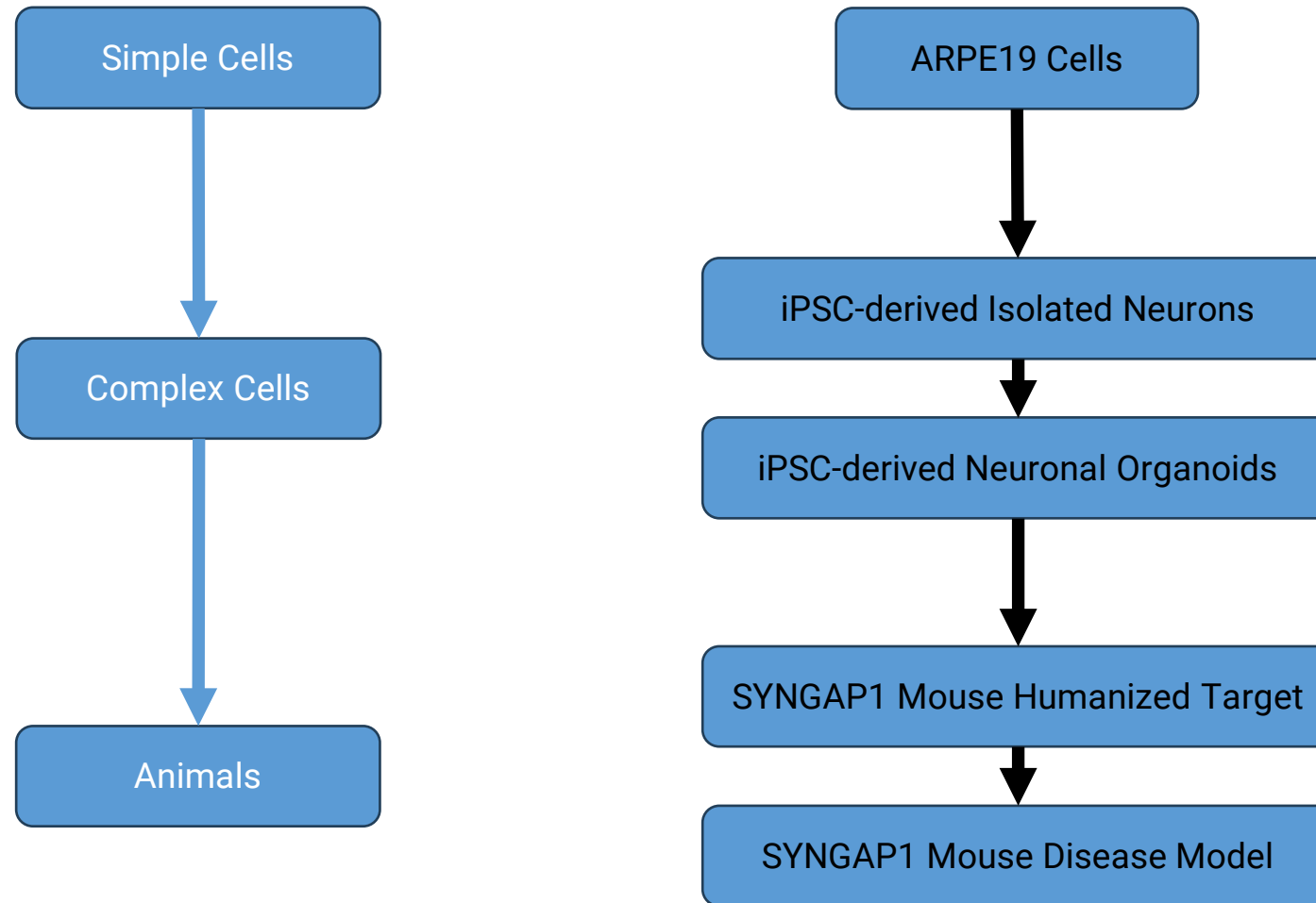
PRAX-090

- Program to discover an ASO to therapeutically upregulate SYNGAP1 mRNA and protein
- ASO candidates have shown potential to modify disease by increasing gene expression^{1, 2}

¹Florey/Praxis data on file

²Creson, T. K. *et al.* . *Elife* **8**, e46752 (2019)

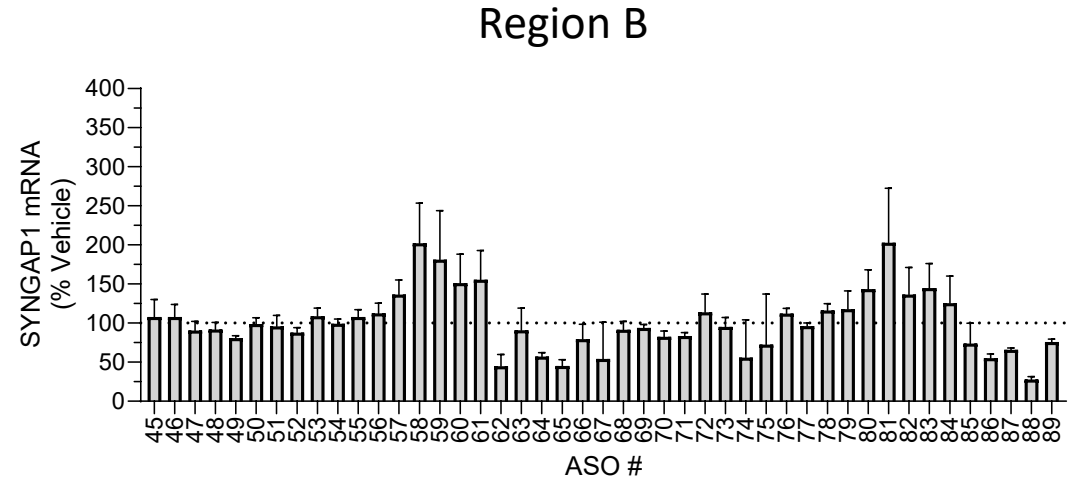
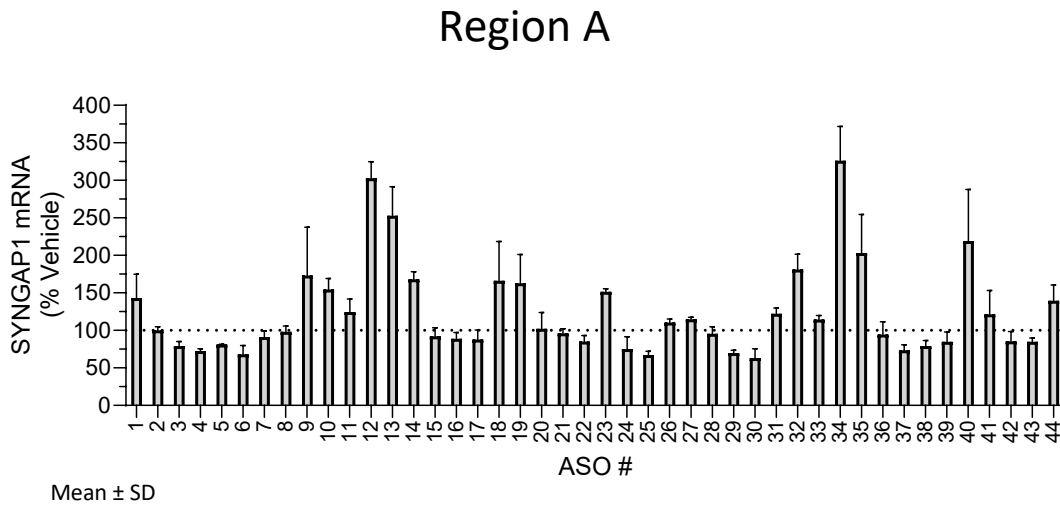
From Early Discovery to Efficacy Studies: Critical Steps for ASO Discovery





Recent Progress

Upregulation of SYNGAP1 mRNA in Cultured ARPE19 Neurons

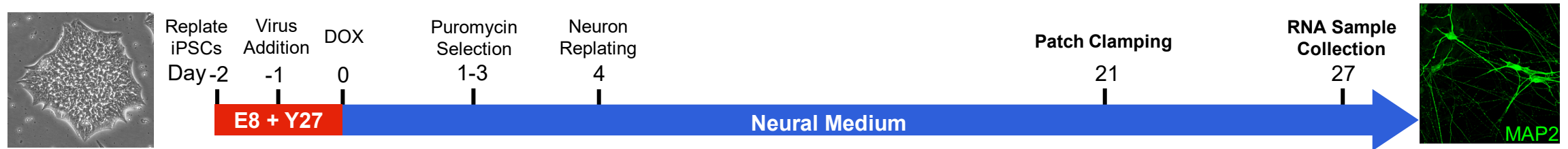


- Identified two targetable regions in human ARPE19 cultured neurons

Screening using cultured cells identifies multiple regions targets for upregulating SYNGAP1 mRNA

Development of Patient iPSC-derived Neurons and CRISPR corrected Isogenic Controls

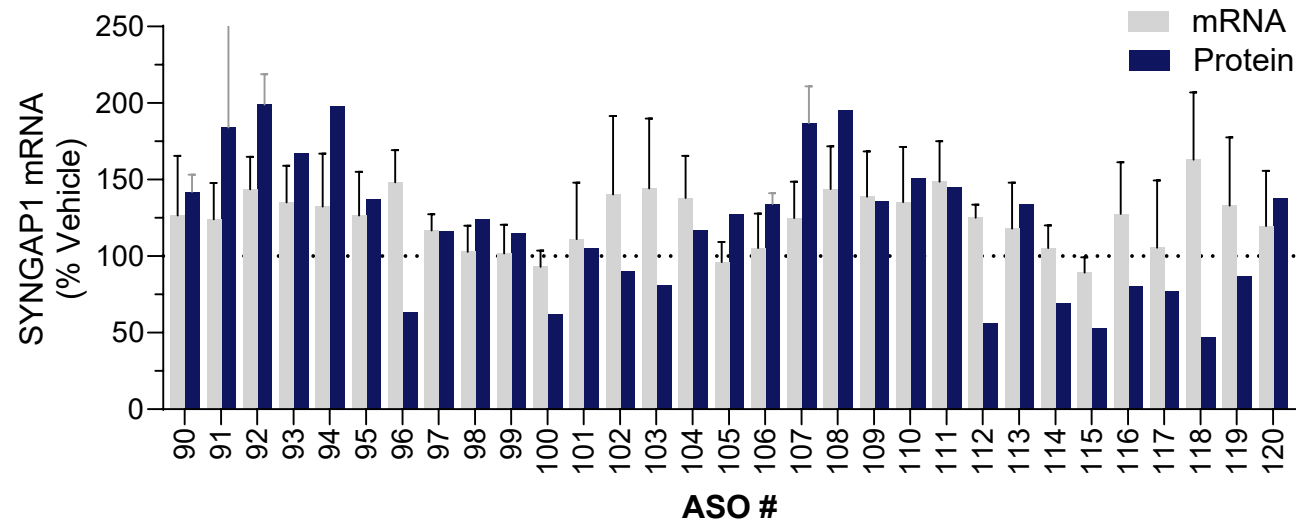
NGN2 Differentiation Protocol¹



- Neuronal expression system to measure ASO mediated upregulation of SYNGAP1 mRNA and protein
- Platform for identifying ASOs capable of rescuing cellular pathologies

¹Zhang, Y. *et al. Neuron* 5, P785-798 (2013)

Upregulation of SYNGAP1 mRNA and Protein in Control iPSC-derived Neurons

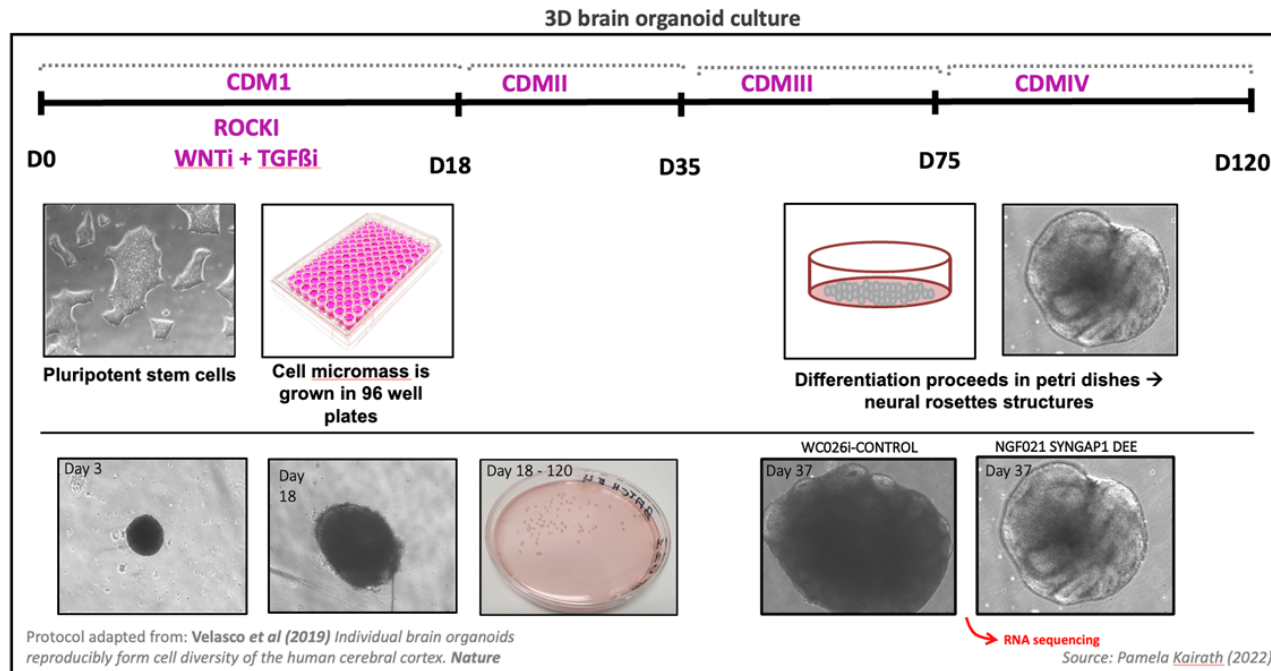


- Identified ASOs capable of increasing SYNGAP1 mRNA and protein in iPSC-derived neurons

Upregulation of neuronal SYNGAP1 mRNA can increase SYNGAP1 protein

Development of Patient iPSC-derived Organoids to Study 3D Architecture

Protocol for Producing Organoids¹



Molecular analysis

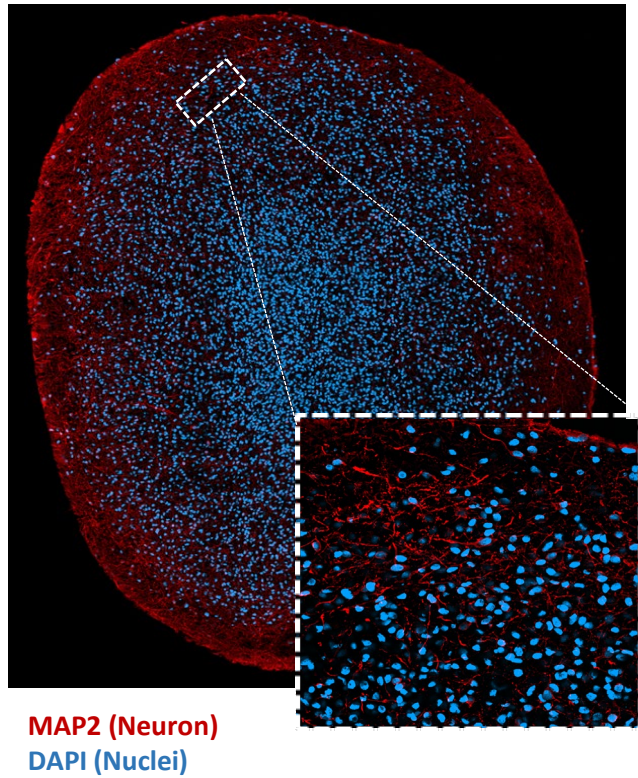
- Morphological analysis
- RNA sequencing and analysis
- Whole proteome sequencing

¹Velasco, S. et al. Nature 570 523-527 (2019)

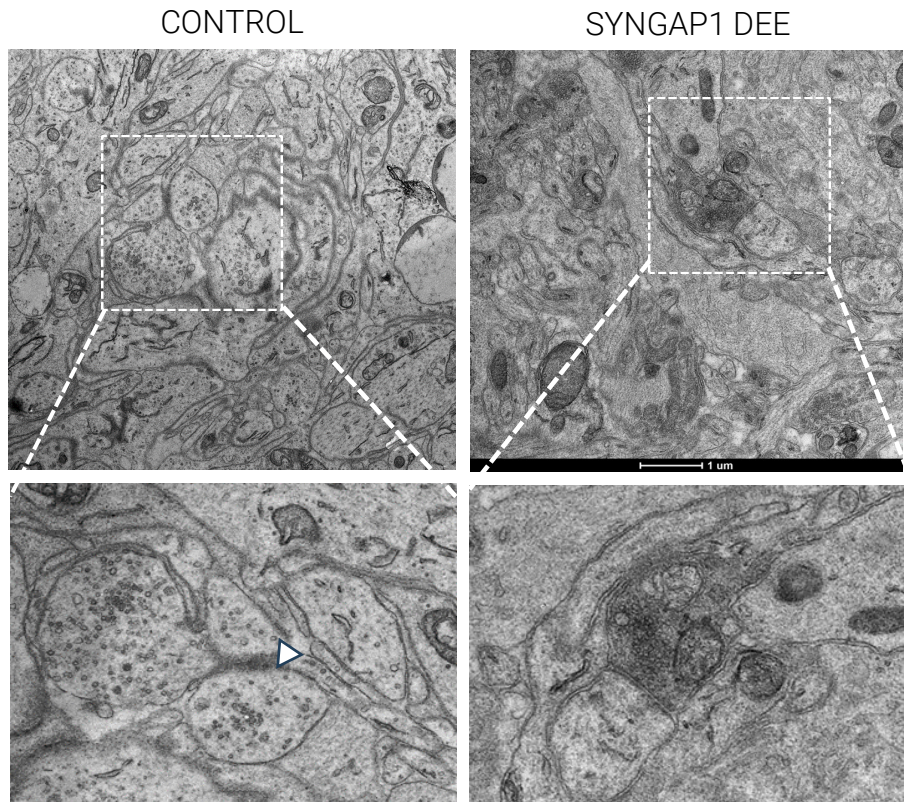
Neuronal organoids allow for the study of synapse formation and maintenance

Cytoarchitecture Exploration in SYNGAP1 Organoids

Imaging of Organoid Macrostructure



Imaging of Organoid Microstructure



Exploration of organoid cytoarchitectural pathology provides opportunity to assess potential for ASO mediated reversal of structural deficits



The Potential of ASOs in Rare Genetic Epilepsies

Praxis Proof of Concept



Potential to be First Disease-Modifying Treatment for SCN2A-DEE

Elsunersen

INTRATHECALLY-
ADMINISTERED
ASO for
SCN2A GoF DEE



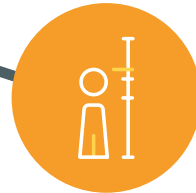
Precision targeting

“Knocked down” mRNA and protein in animal studies



Benefit potential

Showed significant seizure reduction in animal studies



Disease-modifying potential

Normalized developmental curve and significantly improved survival in animal studies

Early Clinical Experience: Unprecedented Clinical Efficacy and Tolerability



Elsunersen

INTRATHECALLY-
ADMINISTERED
ASO for
SCN2A GoF DEE

Significant and sustained seizure reduction at 1 mg dose levels

Unexpected benefits across all treated participants

Well-tolerated with no drug-related AEs

PRIME Designation from EMA for treatment of SCN2A GoF Developmental Epilepsies

Orphan Drug Designation (ODD) and Rare Pediatric Disease Designation from FDA, and ODD from EMA for the treatment of SCN2A-DEE

Next steps: Cohort extension planned for 1H2024; Praxis seeking regulatory advice on advancing development

Summary

- Screening prospective ASOs for the upregulation of SYNGAP1 mRNA in cell culture
- Promising ASOs upregulate SYNGAP1 mRNA and protein in iPSC-derived neurons
- Establishing platform for measuring potential therapeutic normalization of SYNGAP1 expression in response to ASO treatment in functional and structural domains

Acknowledgements

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- Jana Janaththani

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Questions?



contact@praxismedicines.com

How you can stay informed about
PRAX-090 for SYNGAP1?

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so we can update you

