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Research: Building the Pipeline of the Future

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R&D Day
September 21, 2021

Biogen

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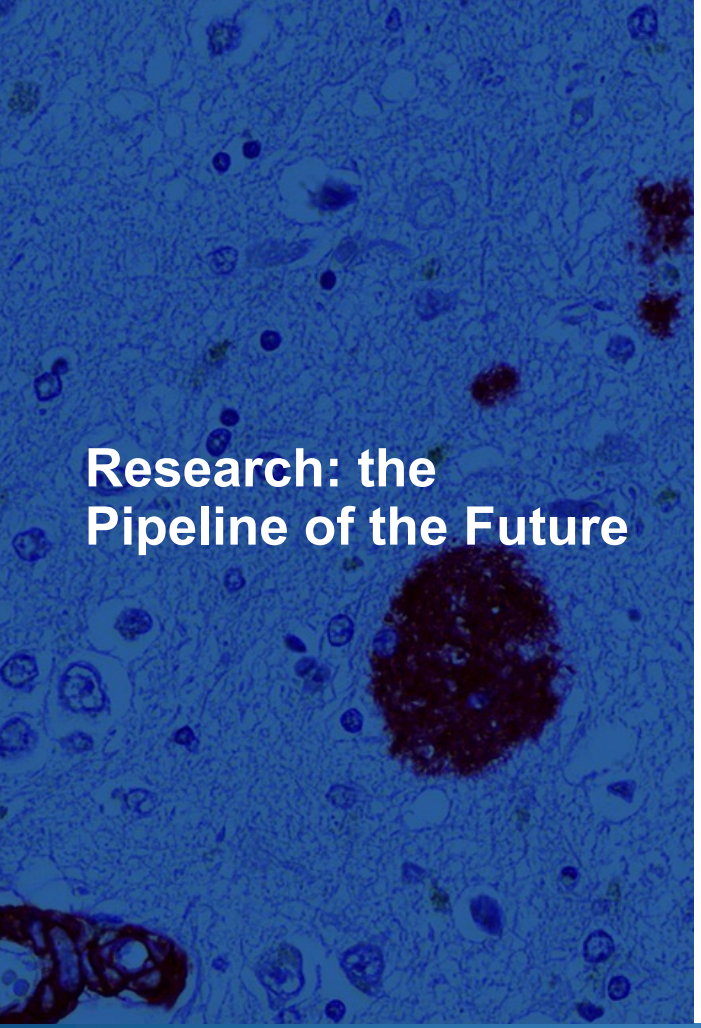


Research: the Pipeline of the Future

01 **Going deep in neuroscience**
Growing from core areas to strategic adjacencies

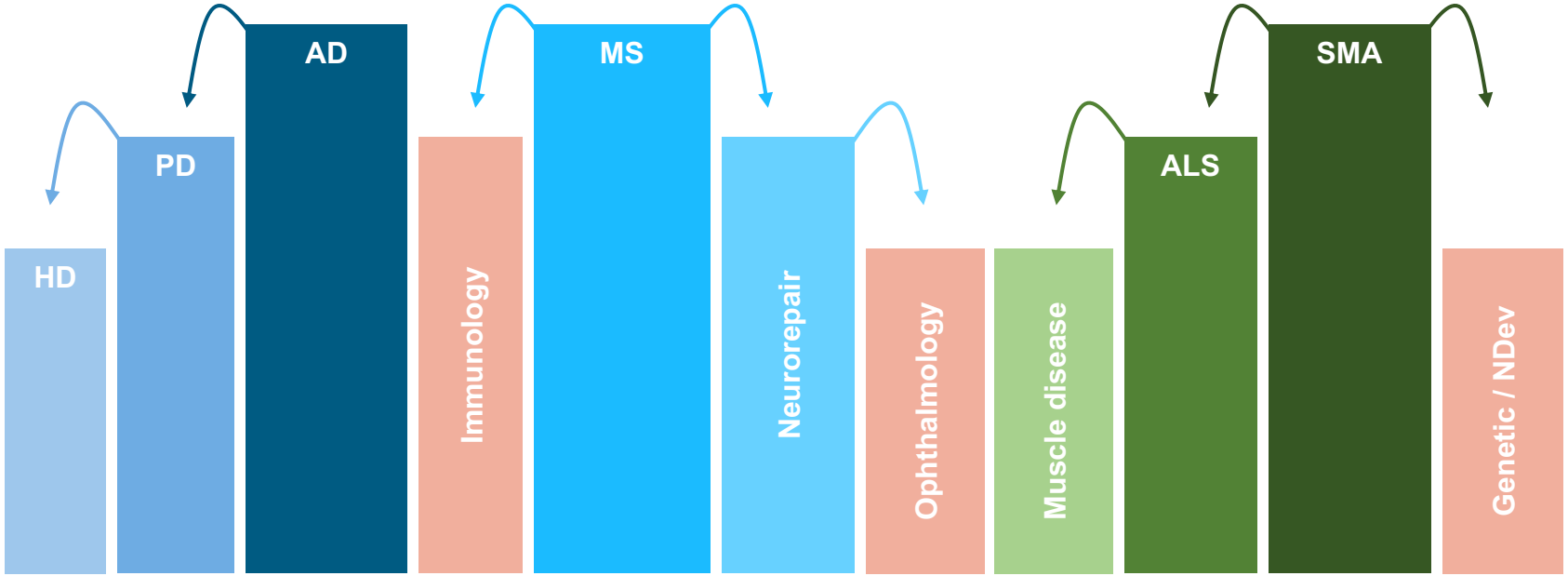
02 **Synergies across disease areas strengthened by neuroscience focus**
Shared biologies & technology, multi-modality optionality

03 **A "human-first" drug discovery pipeline**
Research contributes human data from early discovery to clinical development, to increase probability of success

04 **Combining internal & external capabilities**
Academic and industry collaborators enrich pipeline through new targets, modalities and technologies

Going deep in neuroscience

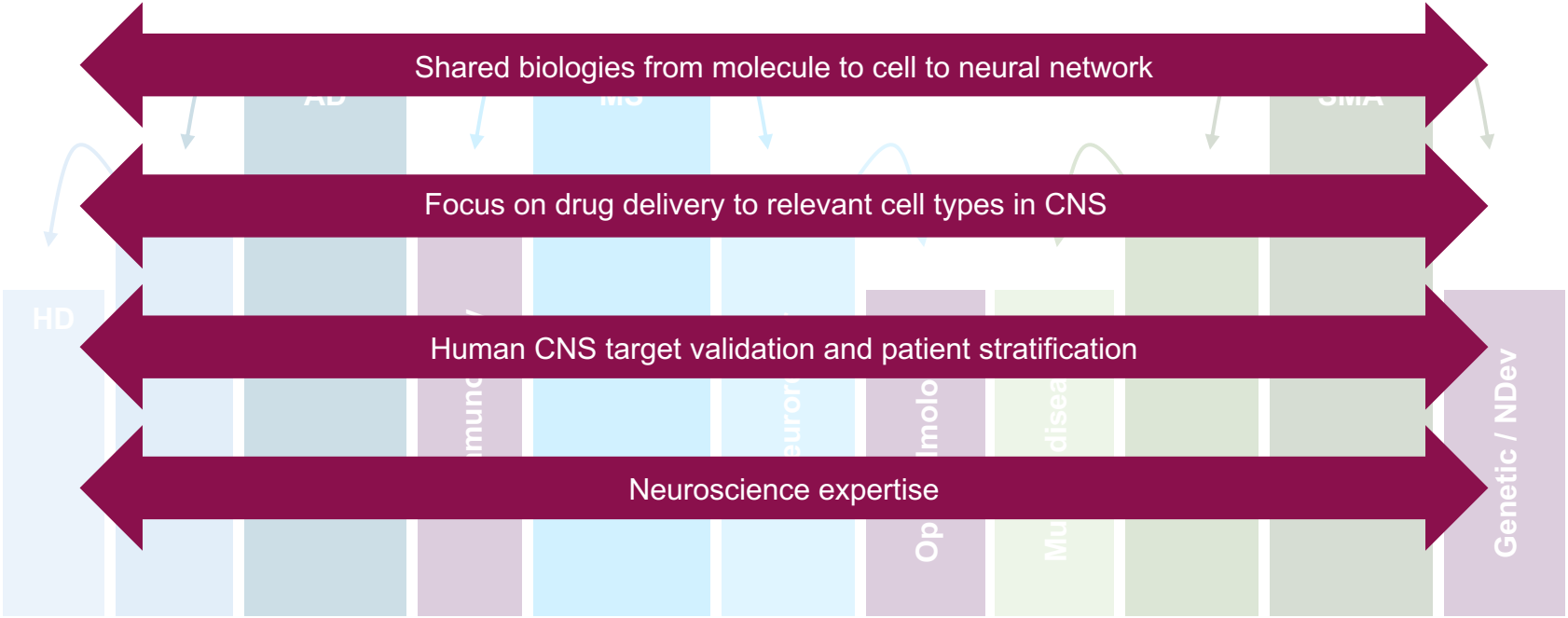
Growth into synergistic adjacencies to established areas may reduce innovation risk and potentially lower incremental investment for each new program



AD = Alzheimer's disease; ALS = amyotrophic lateral sclerosis; HD = Huntington's disease; MS = multiple sclerosis; Ndev = neurodevelopmental; PD = Parkinson's disease; SMA=spinal muscular atrophy

Leveraging our focused neuroscience discovery engine

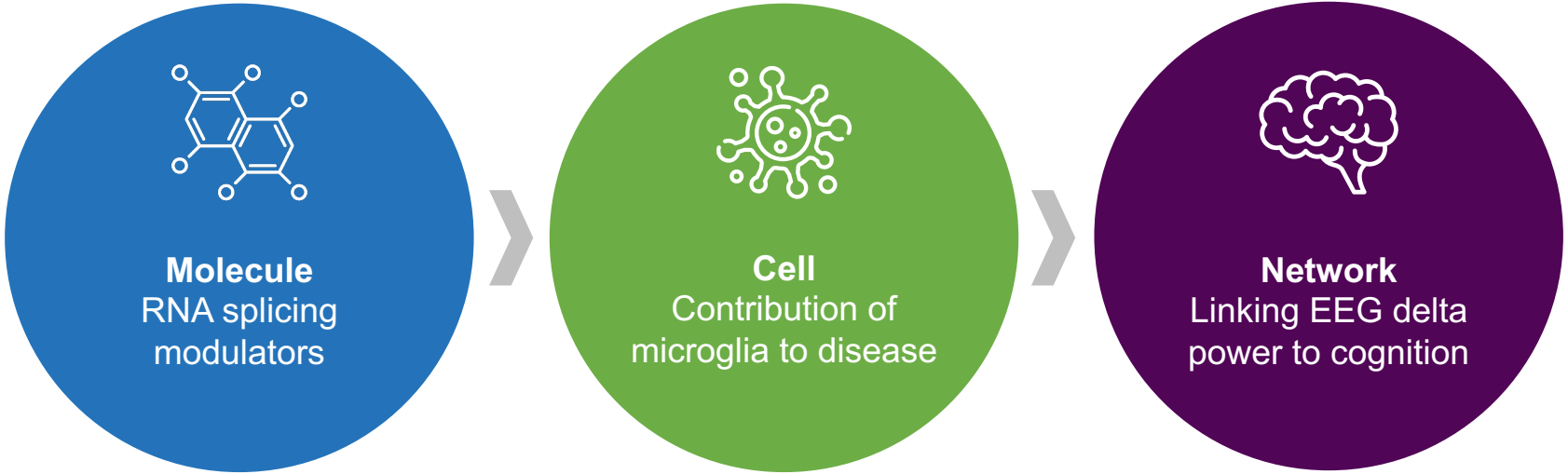
Although distinct, chosen pathologies share biologic and technological features we are exploiting



CNS = central nervous system

Shared biologies: from molecule to cell to neural network

Research in disease-relevant biologies generates and validates innovative therapeutic targets, and may provide experimental proof-of-concept for outcome measures to be used in human

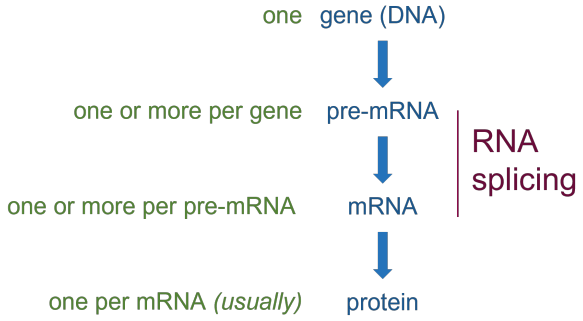


EEG = electroencephalogram; RNA = ribonucleic acid

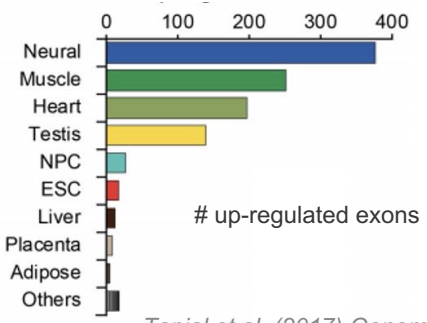
RNA splicing: a key molecular event in health and disease

A gene encodes protein through multiple steps, which can be defective in disease but also provide opportunities for potential therapeutic interventions

Defects at any level can cause disease



In humans, tissue-specific splicing is most intensive in brain



Tapial et al. (2017) Genome Res

Reasons to focus on RNA splicing

Correction of mis-spliced disease gene shows benefit

- SMA (SPINRAZA, Evrysdi)

CNS disorders associated with RNA splicing changes

- Parkinson's disease, Alzheimer's disease, aging*
- SMA, ALS, frontotemporal dementia
- Inherited retinal disorders et al.

Experimental alteration of splicing in upstream genes

- May upregulate or activate target genes/proteins
- May downregulate or inactivate target genes/proteins

Importance of appropriate splice form

- Gene replacement strategies in gene therapy

**Raj et al. (2019) Nature Genetics*

mRNA = messenger RNA

RNA splicing underlies multiple potential therapeutic strategies

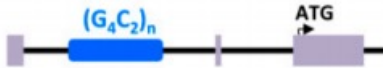
Neuromuscular Disorders provide some examples of multi-modality potential

SMA — **SMN2 exon 7**

Stable SMN protein

SPINRAZA (nusinersen) injection 12 mg/5 mL

ALS — **C9ORF72 exon 1a/1b**



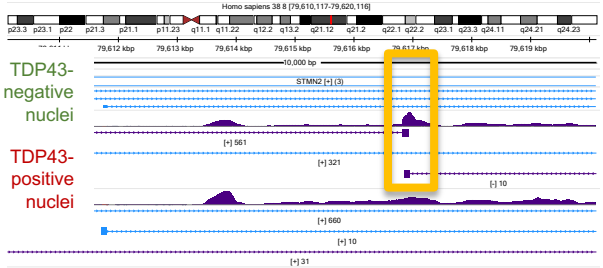
exon 1a → *toxic repeats* | exon 1b → *repeats excluded*

Selectively degrade exon 1a transcripts

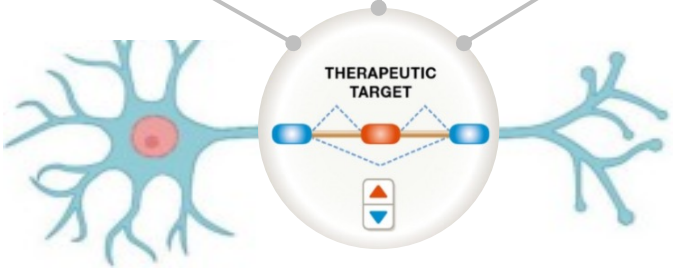
ALS — **Mis-splicing downstream of TDP43**

- Normal TDP-43 excludes “cryptic exons” from key RNAs
- In ALS, this function is lost, leading to protein disruption

Correct TDP43-dependent splicing events



Liu et al. Cell Reports 2019



Multiple potential modalities

- Antisense oligonucleotides (ASOs) — IONIS
- Small-molecule RNA modulators — SKYHAWK THERAPEUTICS
- AAV gene therapy

SMN = survival motor neuron; TDP-43 = TAR DNA binding protein 43

Discovering new potential RNA targets through AI/ML

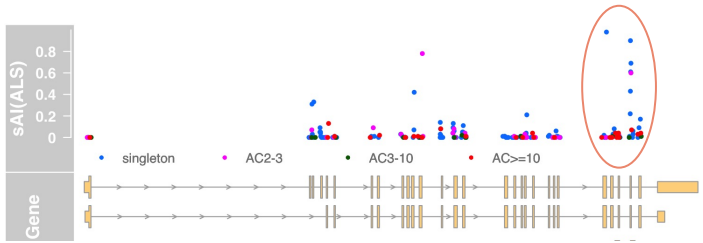
project MinE

DNA from 1000s of people with ALS, as well as control subjects

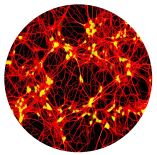
PI: Jan Veldink

SpliceAI

Confirm splice-altering variants in *KIF5A* that increase risk for ALS



Nicolas *et al.* (2018) *Neuron*



Biogen iPSC-derived neurons

ENVISAGENICS

In human neurons, aim to identify:

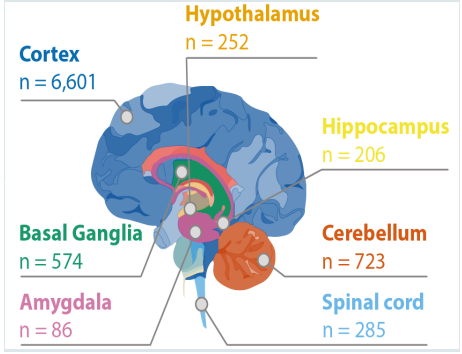
(a) **Non-functional RNA isoforms**

(b) **Splicing events that regulate targets**

MetaBrain

university of groningen

15 datasets, **6,518** individuals
8,727 RNA-seq samples



Identify splicing genetic biomarkers (sQTLs)

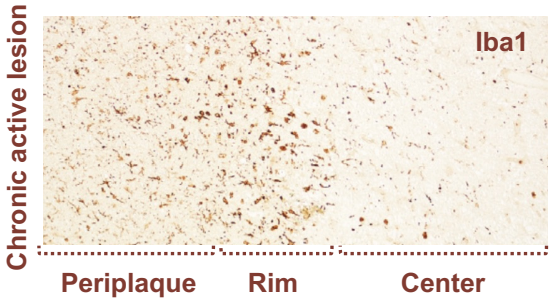
Prioritize targets where human genetics predicts RNA isoforms linked to risk of CNS disease

AI = artificial intelligence; iPSC = induced pluripotent stem cell; ML = machine learning

Microgliosis in mouse CNS is BTK-dependent

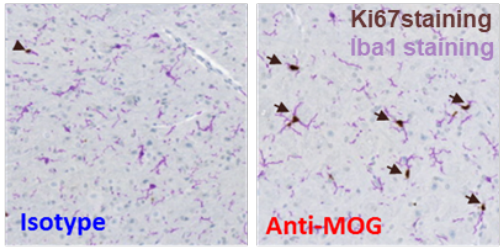
Microglial activation is a common feature across neurological diseases, and some key genes linked to human disease are selectively expressed in microglia

MS as example: Microgliosis is a cardinal feature of active and chronic active lesions



Lassmann et al., Cold Spring Harb Perspect Med 2018

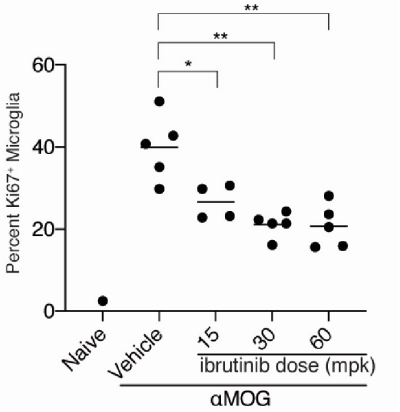
Anti-MOG autoantibodies trigger a FcR-dependent microgliosis reaction



- Anti-MOG antibodies injected IP at 30 mg/kg twice daily for 3 days
- Effect not seen using antibodies modified to block interaction with microglial Fc receptor *(not shown)*

MOG: myelin oligodendrocyte glycoprotein

CNS-penetrant BTKi blocks microgliosis induced by anti-MOG autoantibodies



BTKi: ibrutinib, oral inhibitor of Bruton's tyrosine kinase

2021-Pellerin et al. (Brain, Jun 18; online ahead of print)

See *MS Pipeline* by Jerome Hanna

BTK = Bruton's tyrosine kinase; FcR = Fc receptor; IP = intraperitoneal; MOG = myelin oligodendrocyte glycoprotein; FcR = Fc receptor

From neuromuscular to neurodevelopment

We plan to build on our learnings from both SMA and ALS through new programs that may help people living with other devastating genetic diseases

SMA (monogenic) › **SOD1 ALS (monogenic)** › **C9orf72 ALS (monogenic)** »» **Two further monogenic disorders in preclinical pipeline**

SPINRAZA | Tofersen | BIIB078

Programs with positive clinical trial data should benefit from SPINRAZA experience with:

- Pediatric neurology specialists
- Patient community links
- Rare disease launch

Angelman Syndrome
Delayed development, problems with speech and balance, intellectual disability and, in some cases, seizures

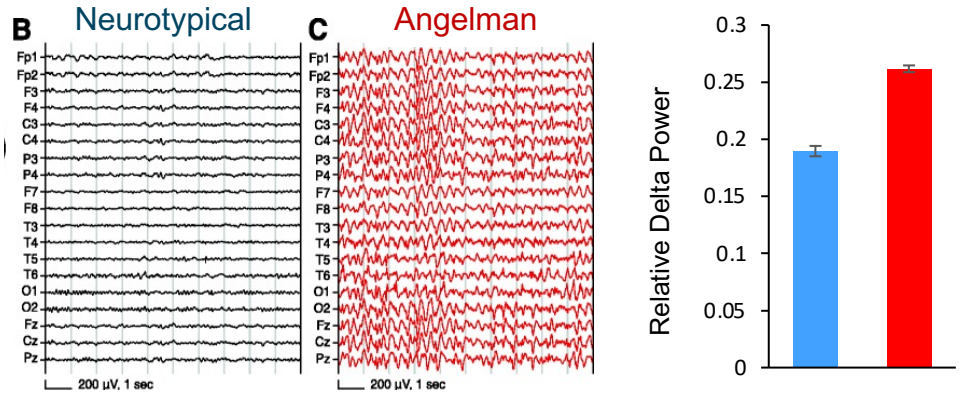
KCNT1 genetic epilepsy
Ranges from severe, infantile epileptic encephalopathy to frontal lobe epilepsy with additional psychiatric symptoms

Electroencephalography (EEG) abnormalities are shared across neurodevelopmental disorders and other diseases in the Biogen pipeline

See *ALS Update* by Toby Ferguson

Translational biomarker development: exploring brain delta wave activity by EEG as a functional measure

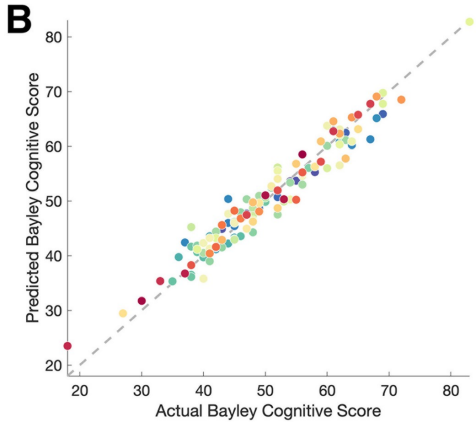
Delta (1-4Hz) Oscillations Are Elevated in Angelman patients



Data obtained from a large, multi-center Angelman Natural History Study that included concurrent EEG recordings and neurodevelopmental testing

Sidorov et al, 2017, J Neurodev Dis

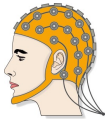
EEG Can Predict Cognitive Performance in Angelman Syndrome

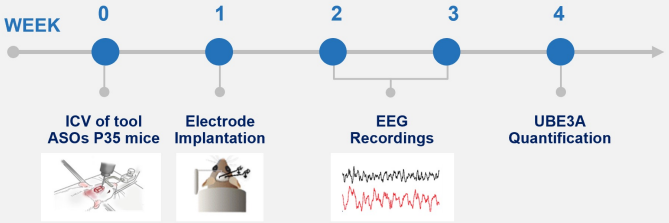


The Bayley Cognitive Score has been adjusted for a fixed age and genotype for visualization

Ostrowski et al, 2021, Ann. Clin. Transl. Neurol.

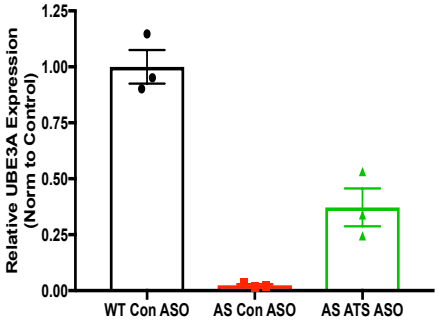
In Angelman Syndrome mice, an ASO targeting paternal antisense transcript *Ube3a-ats* lowers delta activity



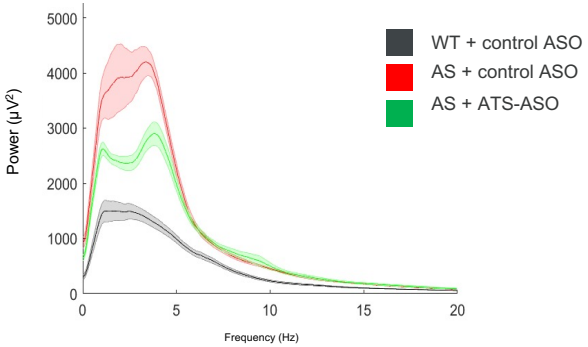


Treatment Groups:
Wild-Type (WT) + Control ASO
Ube3a$^{m-/p+}$ Het (AS) + Control ASO
Ube3a$^{m-/p+}$ Het (AS) + ATS-ASO

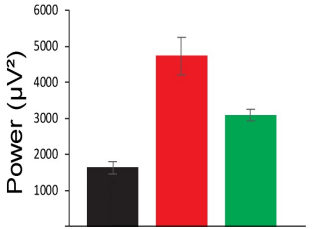
Ube3a mRNA levels



Power Spectral Densities



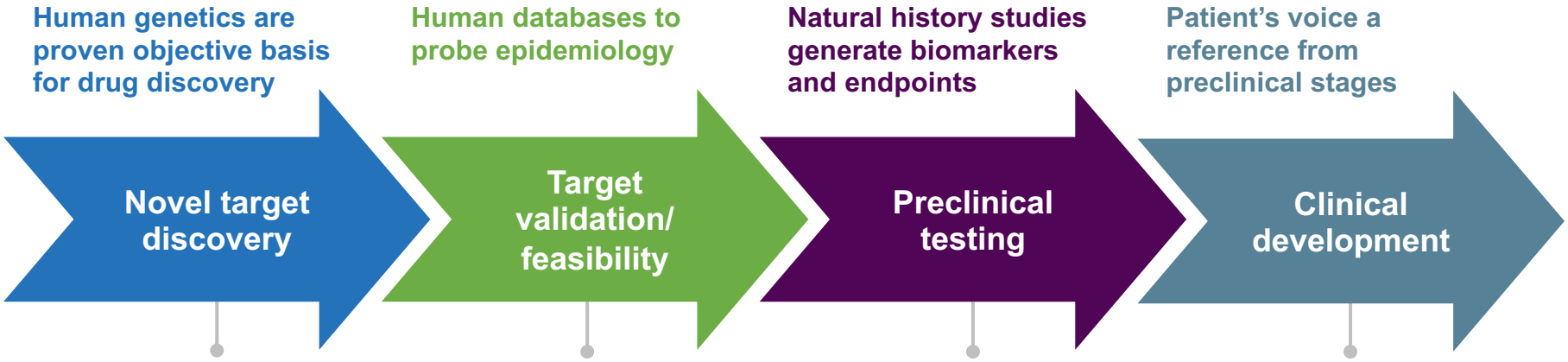
Delta (1 – 4 Hz) Power



Partial restoration of UBE3A results in partial correction of EEG abnormalities

Building a “human-first” discovery pipeline

Human data of all types inform programs well prior to entry into clinic, potentially increasing probability of success



Biogen’s approach:

Novel target discovery	Target validation/ feasibility	Preclinical testing	Clinical development
Integrated analysis of genetics with single-cell omics of patient tissue	Patient iPSC models test mechanisms and biomarkers (neurons, microglia, muscle)	Translatable functional outcome measures (excitability, RNA splicing) inform trial design	Human genetics drive patient ID and stratification (rapid progressors, genetic subsets)

See *Human Genetics* by Sally John, *Biomarkers* by John Beaver

Combining internal and external capabilities

Our internal centers of excellence (CoEs) provide an attractive basis for external experts to set up tight collaborations which amplify and extend our impact

Targets

Internal CoE

- Human Genetics, Genome Technologies

External*

- FinnGen
- BioFinder
- Envisagenics (AI/ML)
- UK Biobank
- Pre-competitive industry collaborations

Models

Internal CoE

- Human Cell & Molecular Biology

External*

- Harvard, UC Berkeley, Mayo Clinic, UPenn
- Michael J. Fox Foundation
- Jackson Labs

Modalities

Internal CoE

- Biotherapeutics & Medicinal Sciences

External*

- ASOs/siRNAs (Ionis, Atalanta)
- Small molecules (C4T, Skyhawk)
- Gene therapy collaborators

Patients

Internal CoE

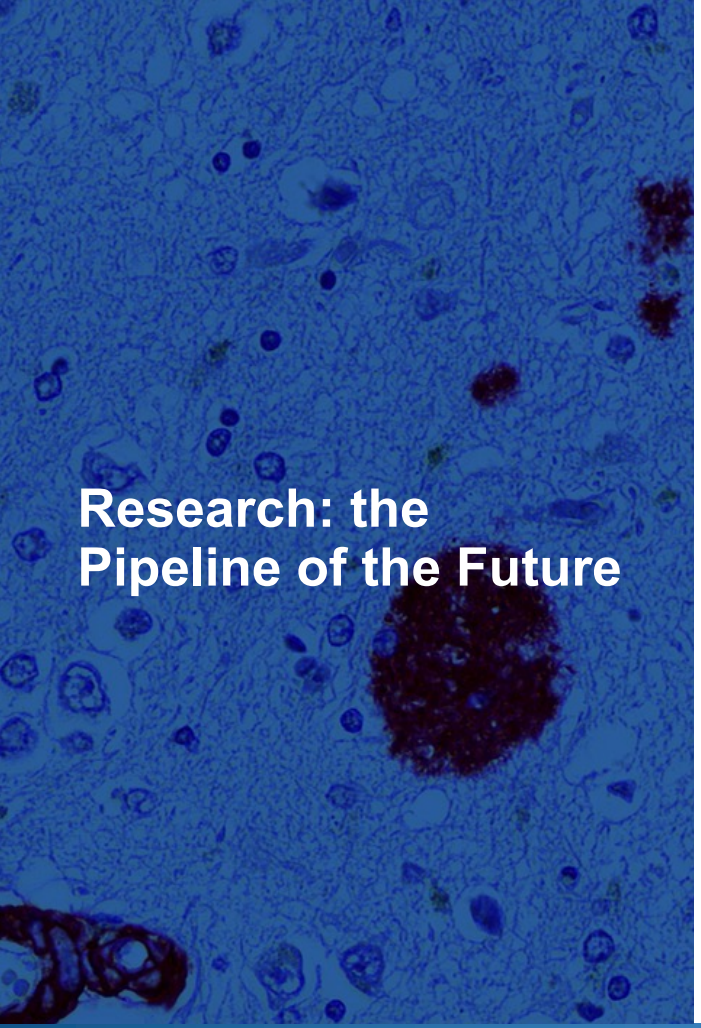
- Seamless Research-Development interface

External*

- Platforms for natural history studies
- Patient advocacy groups
- Invitae (Behind the Seizure)
- BeaT-PD (Tel Aviv)

See *Human Genetics* by Sally John, *Gene Therapy* by Junghae Suh, *Biotherapeutics and Medicinal Sciences* by Anabella Villalobos

*Selected examples



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