Research: Building the Pipeline of the Future

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R&D Day
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These statements are based on our current beliefs and expectations and speak only as of the date of this presentation. We do not undertake any obligation to publicly update any forward-looking statements.
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

- Shared biologies from molecule to cell to neural network
- Focus on drug delivery to relevant cell types in CNS
- Human CNS target validation and patient stratification
- Neuroscience expertise

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

Molecule
RNA splicing modulators

Cell
Contribution of microglia to disease

Network
Linking EEG delta power to cognition

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.

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

Tapial et al. (2017) Genome Res

mRNA = messenger RNA
RNA splicing underlies multiple potential therapeutic strategies

Neuromuscular Disorders provide some examples of multi-modality potential

Multiple potential modalities
- Antisense oligonucleotides (ASOs)
- Small-molecule RNA modulators
- AAV gene therapy

**SMA**

<table>
<thead>
<tr>
<th>SMA</th>
<th>SMN2 exon 7</th>
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<tr>
<td>6</td>
<td>7</td>
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<td>8</td>
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**ALS**

**C9ORF72 exon 1a/1b**

- Increase inclusion
- 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

**Liu et al. Cell Reports 2019**

SMN = survival motor neuron; TDP-43 = TAR DNA binding protein 43
Discovering new potential RNA targets through AI/ML

**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

**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
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**

Microgliosis in mouse CNS is BTK-dependent

**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

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.

<table>
<thead>
<tr>
<th>SMA (monogenic)</th>
<th>SOD1 ALS (monogenic)</th>
<th>C9orf72 ALS (monogenic)</th>
<th>Two further monogenic disorders in preclinical pipeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPINRAZA</td>
<td>Tofersen</td>
<td>BIIB078</td>
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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

EEG Can Predict Cognitive Performance in Angelman Syndrome

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

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

Sidorov et al, 2017, J Neurodev Dis

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

**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.

**Human genetics are proven objective basis for drug discovery**

**Human databases to probe epidemiology**

**Natural history studies generate biomarkers and endpoints**

**Patient’s voice a reference from preclinical stages**

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

Biogen’s approach:

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

<table>
<thead>
<tr>
<th>Internal CoE</th>
<th>External*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Genetics, Genome Technologies</td>
<td>FinnGen, BioFinder, Envisagenics (AI/ML), UK Biobank, Pre-competitive industry collaborations</td>
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#### Models

<table>
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<th>Internal CoE</th>
<th>External*</th>
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<tbody>
<tr>
<td>Human Cell &amp; Molecular Biology</td>
<td>Harvard, UC Berkeley, Mayo Clinic, UPenn, Michael J. Fox Foundation, Jackson Labs</td>
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#### Modalities

<table>
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<th>Internal CoE</th>
<th>External*</th>
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<tr>
<td>Biotherapeutics &amp; Medicinal Sciences</td>
<td>ASOs/siRNAs (Ionis, Atalanta), Small molecules (C4T, Skyhawk), Gene therapy collaborators</td>
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#### Patients

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<th>Internal CoE</th>
<th>External*</th>
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<td>Seamless Research-Development interface</td>
<td>Platforms for natural history studies, Patient advocacy groups, Invitae (Behind the Seizure), BeaT-PD (Tel Aviv)</td>
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