Morning Plenary

Biogen 2015 R&D Day

Advancing the Next Wave of Potential Therapies

November 3, 2015

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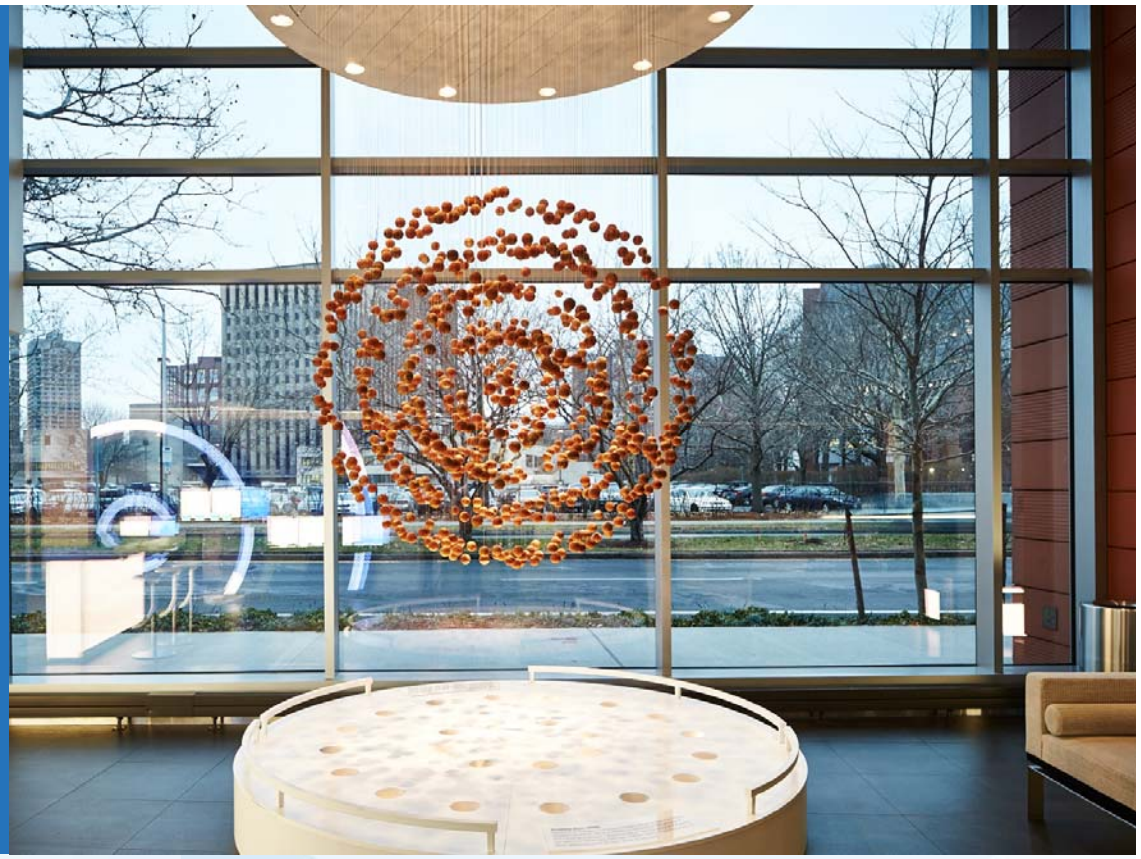
Welcome to Biogen's 2015 R&D Day

George Scangos, Ph.D.
Chief Executive Officer



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Forward-looking statements

These presentations contain forward-looking statements, including statements relating to: clinical trials; potential safety and clinical effects of research and development programs; and pipeline potential and progress. These forward-looking statements may be accompanied by such words as “anticipate,” “believe,” “could,” “estimate,” “expect,” “forecast,” “intend,” “may,” “plan,” “potential,” “project,” “target,” “will” and other words and terms of similar meaning. You should not place undue reliance on these statements.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including: risks associated with clinical trials, including our ability to adequately manage clinical activities, unexpected concerns that may arise from additional data or analysis obtained during clinical trials, regulatory authorities may require additional information or further studies or may fail to approve or may delay approval of our drug candidates; the risk that positive results in a clinical trial may not be replicated in subsequent or confirmatory trials or success in early stage clinical trials may not be predictive of results in later stage or large scale clinical trials or trials in other potential indications; the occurrence of adverse safety events, restrictions on use with our products or product liability claims; our dependence on collaborators and other third parties for the development and commercialization of products and other aspects of our business, which are outside of our control; and the other risks and uncertainties that are described in the Risk Factors section of our most recent annual or quarterly report and in other reports we have filed with the SEC. These statements are based on our current beliefs and expectations and speak only as of the date of these presentations. We do not undertake any obligation to publicly update any forward-looking statements.

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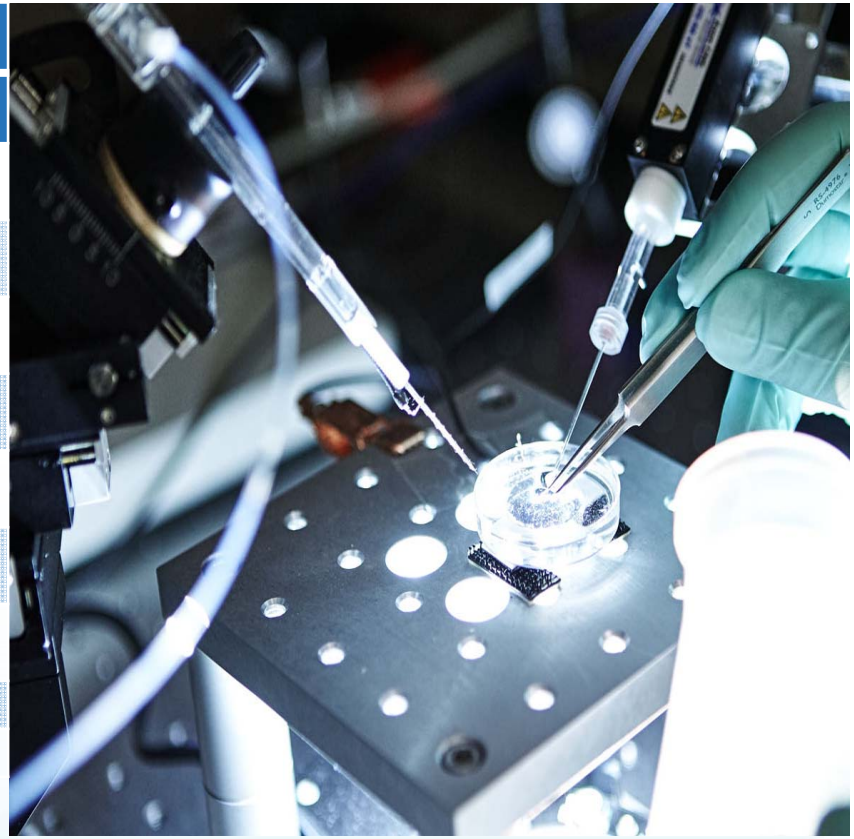
Biogen 2015 R&D Day Agenda

Agenda: Morning Session		
Time	**Topic**	**Speaker**
10-10:05am	Introduction	**George Scangos, PhD** Chief Executive Officer
10:05-10:25am	Biogen R&D strategy and capabilities	**Al Sandrock, MD, PhD** Chief Medical Officer
10:25-10:40am	MS remyelinating programs: Anti-LINGO-1 and BIIB061	**Diego Cadavid, MD** Senior Medical Director
10:40-10:55am	Alzheimer's disease strategy including E2609 and BAN2401	**Samantha Budd Haeberlein, PhD** VP Clinical Development
10:55-11:10am	Aducanumab for early Alzheimer's disease	**Jeff Sevigny, MD** Senior Medical Director
11:10-11:25am	SMA and nusinersen (SMN_{Rx}) program update	**Wildon Farwell, MD** Senior Medical Director
11:25-11:40am	MT-1303 for autoimmune diseases	**Jeff Bornstein, MD** Senior Medical Director
11:40-12:15pm	Q&A	
12:15-12:45pm	Lunch	



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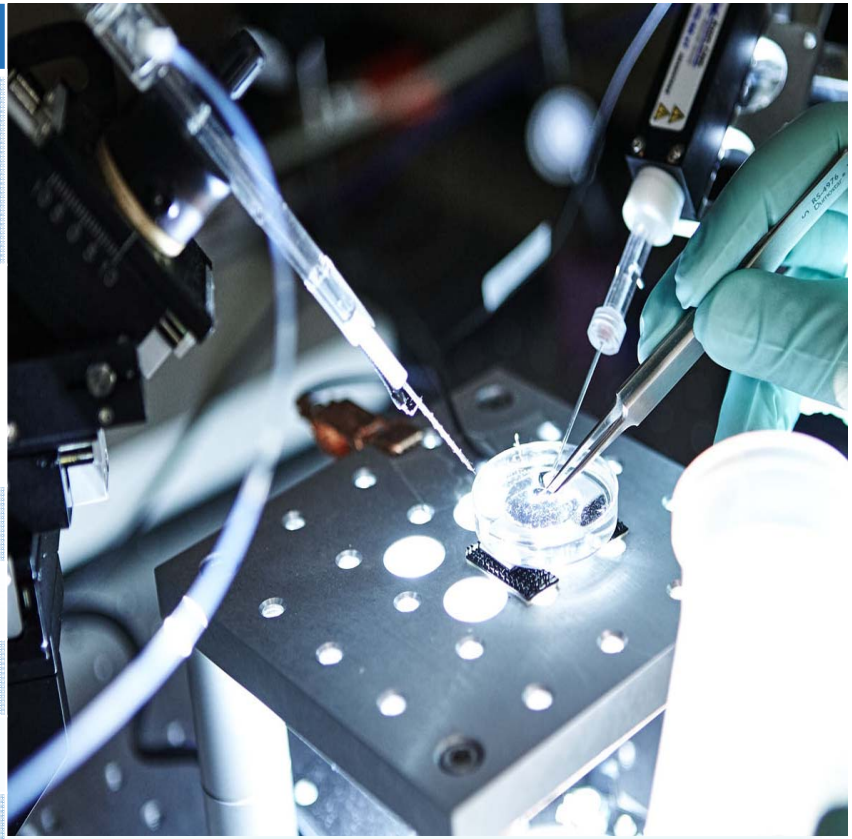
Biogen 2015 R&D Day Agenda (continued)

	Agenda: Afternoon Session	
Breakout Session 1:00-2:00pm	**Track One:** • BIIB054 for Parkinson's disease • Amyotrophic lateral sclerosis • Gene therapy & gene editing	• **Jesse Cedarbaum, MD** VP Clinical Development • **Donald R. Johns, MD** VP Clinical Development • **Olivier Danos, PhD** SVP Cell & Gene Therapy
Breakout Session 1:00-2:00pm	**Track Two:** • The future of SMARTER drug development with biomarkers • Value based medicine	• **Richard Hargreaves, PhD** VP Neuropharmacology and Biomarkers **Ajay Verma, MD, PhD** VP Experimental Medicine • **Richard A. Rudick, MD** VP Development Sciences
2:15-2:30pm	Raxatrigine in neuropathic pain	**Simon Tate, PhD** VP Pain Research Therapeutic Area
2:30-2:45pm	Tysabri in stroke	**Jake Elkins, MD** Senior Medical Director
2:45-2:55pm	Research in Biogen: Why and how	**Spyros Artavanis-Tsakonas, PhD** Chief Scientific Officer
2:55-3:10pm	The new neurology at Biogen	**Chris Henderson, PhD** VP Neurology Research
3:10-3:25pm	Vision for neuroimmunology in neurodegeneration	**Richard M. Ransohoff, MD** Senior Research Fellow & VP Neuroimmunology
3:25-3:55pm	Q&A	



Biogen R&D strategy and capabilities

Alfred Sandrock, MD, PhD
EVP, Neurology Discovery and Development
Chief Medical Officer

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Organize for long-term success

Three focus areas

Specialty medicines

- Multiple Sclerosis
- Inflammatory Bowel Disease (IBD)

Neurodegeneration

- Alzheimer's Disease
- Parkinson's
- ALS
- Neuroimmunology

Rare diseases

- Hemophilia
- Spinal Muscular Atrophy (SMA)
- Neuropathic Pain

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The right people: World-class researchers

Internal (recent) Hires

- **Ransohoff** (Neuroimmunology, Cleveland Clinic)
- **Henderson** (Neurobiology/ALS, Columbia U.)
- **Artavanis-Tsakonas** (Dev. Genetics/Neurodeg, Harvard.)
- **Muskavitch** (Neuro-Epigenetics, BC/Indiana)
- **Duffield** (Dev. Biology/Stress Pathways, U. Washington)
- **Danos** (Gene Therapy, UCL/CNRS)
- **Rudick** (Mellen MS center, Cleveland Clinic)
- **Johns** (ALS, Harvard/Novartis)
- **Cedarbaum** (Parkinson's, Cornell)
- **Hargreaves** (Biomarkers, Merck)
- **Verma** (Experimental medicine, US Military/Pfizer)
- **Fisher** (Biomedical imaging, Cleveland Clinic)
- ***Sanes** (Neuro-Ophthalmology, Harvard)
- ***Kirchhausen** (Membrane traffic, Harvard).
- ***Walz** (Structure/Cryo EM, Rockefeller)

* Part time Academic experts

Right People

External Collaborations

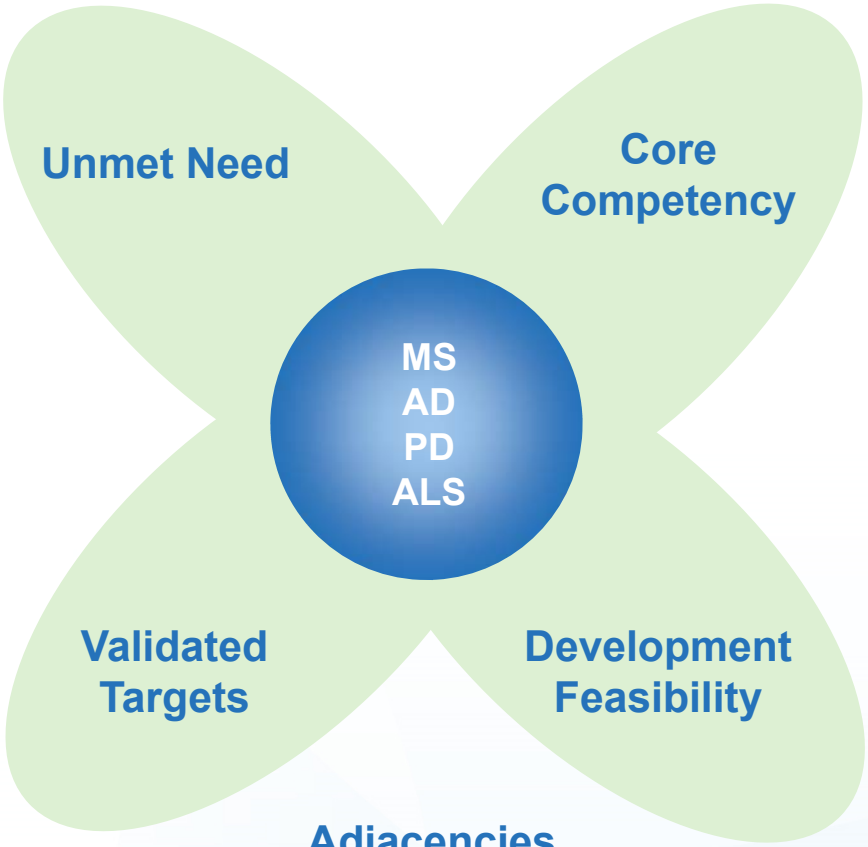
Penn · MAYO CLINIC · HARVARD MEDICAL SCHOOL · MIT · The Rockefeller University · HHMI HOWARD HUGHES MEDICAL INSTITUTE · YALE

Academic Consortia:

ALS, Myelination, PML, Epigenetics, Sickle Cell

Human Proteome, Retromere

What



Adjacencies

- Ophthalmology
- Neuropathic pain

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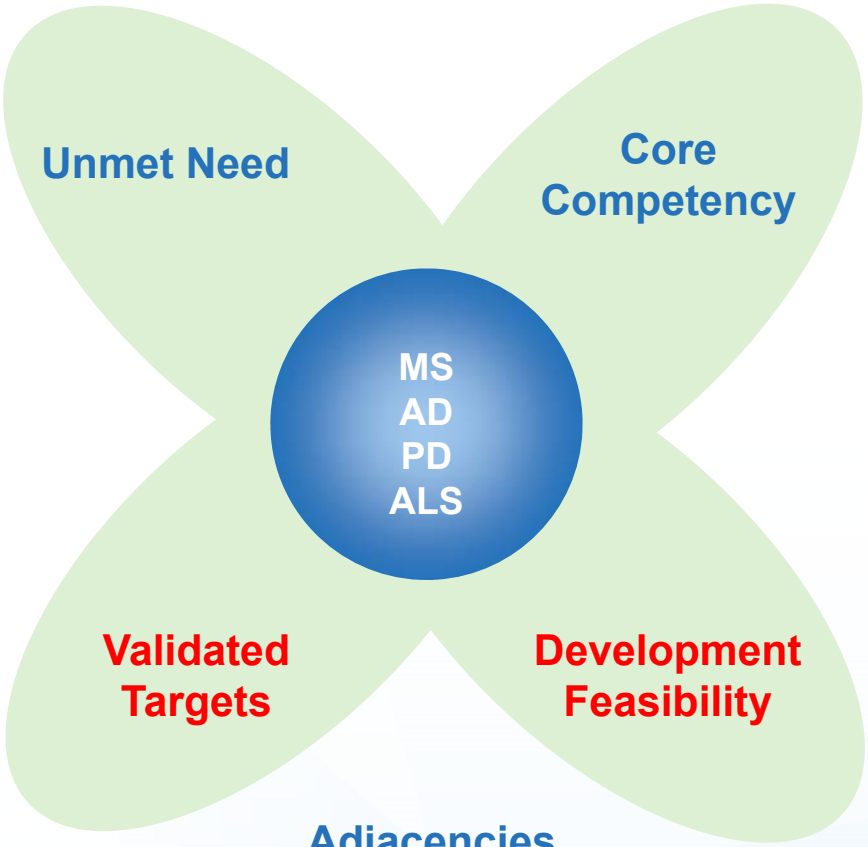
What



Adjacencies

- Ophthalmology
- Neuropathic pain

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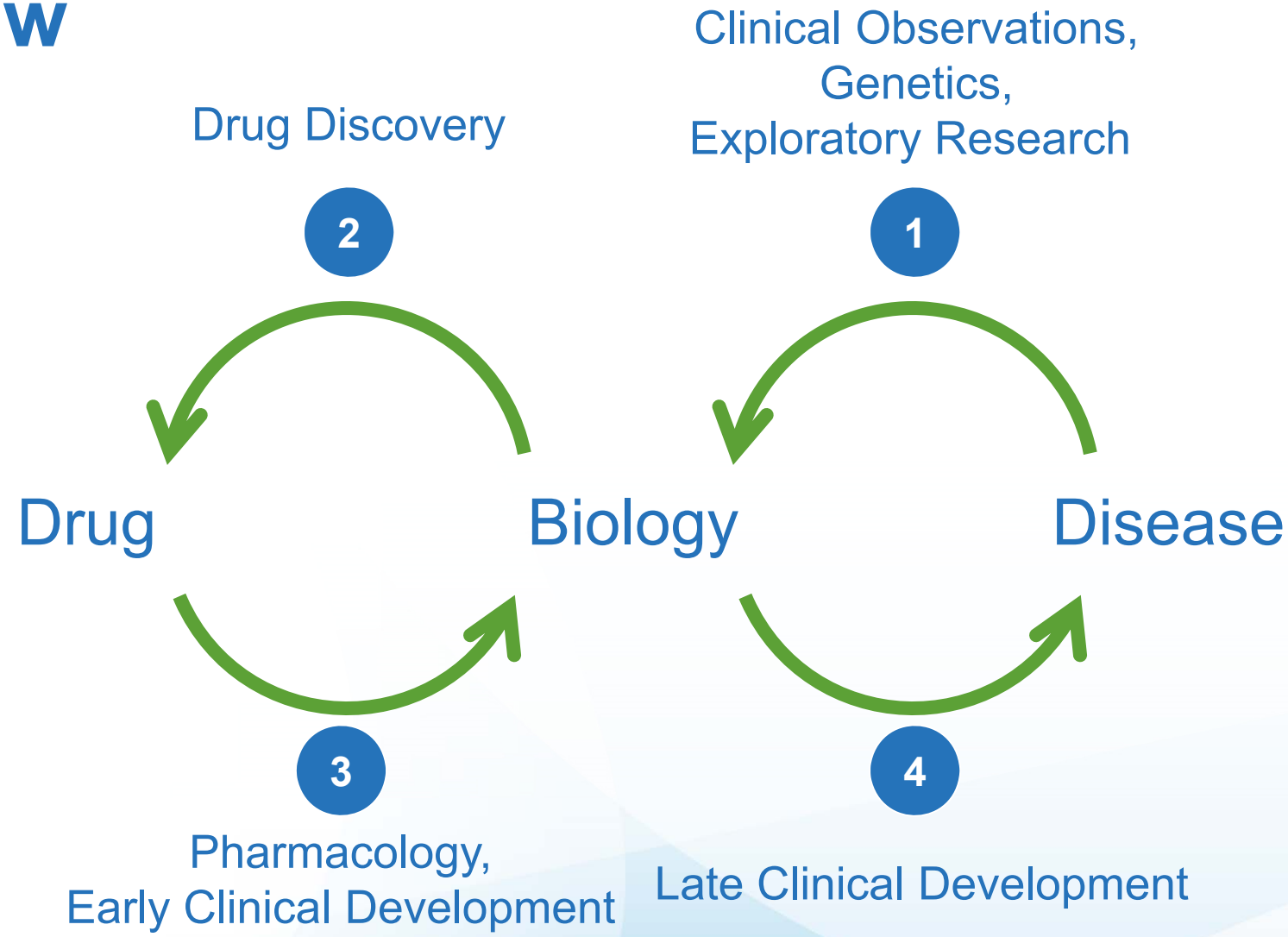
How


Clinical Observations,
Genetics,
Exploratory Research
Drug Discovery
2
1
Drug
Biology
Disease
3
4
Pharmacology,
Early Clinical Development
Late Clinical Development

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Drug development:
How to increase probability of success

- **Begin with disease-relevant biology**
- **Obtain rapid, robust human proof of concept (POC)**
  - De-risk late stage development costs
  - Pursue anti-sense oligonucleotide (ASO) or antibody approaches if target is amenable
- **Develop biomarker capabilities to overcome key challenges**
  - Biological (genetic) heterogeneity
  - Clinical heterogeneity
  - Inability to measure target engagement or the desired biological response
  - Inadequate measurements of disease progression

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The example of aducanumab

- **Begin with disease-relevant biology that is in the causal pathway to disease**
  - Genetics and human pathology pointed to the amyloid hypothesis
- **If ASO or Ab treatment possible, pursue to human POC as efficiently as possible**
  - Found aducanumab at Neurimmune
- **Overcome drug development challenges**
  - Clinical heterogeneity: mild/prodromal, MMSE>20
  - Biological (Genetic) Heterogeneity
    - apoE status
    - Selection with amyloid imaging – AV45 PET positivity at baseline (60% rejection rate)
    - CSF evidence of protein abnormalities – hallmarks of disease
  - Inability to measure target engagement or targeted biological response
    - Amyloid AV45 PET imaging at 6 months, 12 months
    - CSF beta-amyloid 42 and tau – in progress
  - Inadequate measurements of disease progression: brain metabolism, cognition

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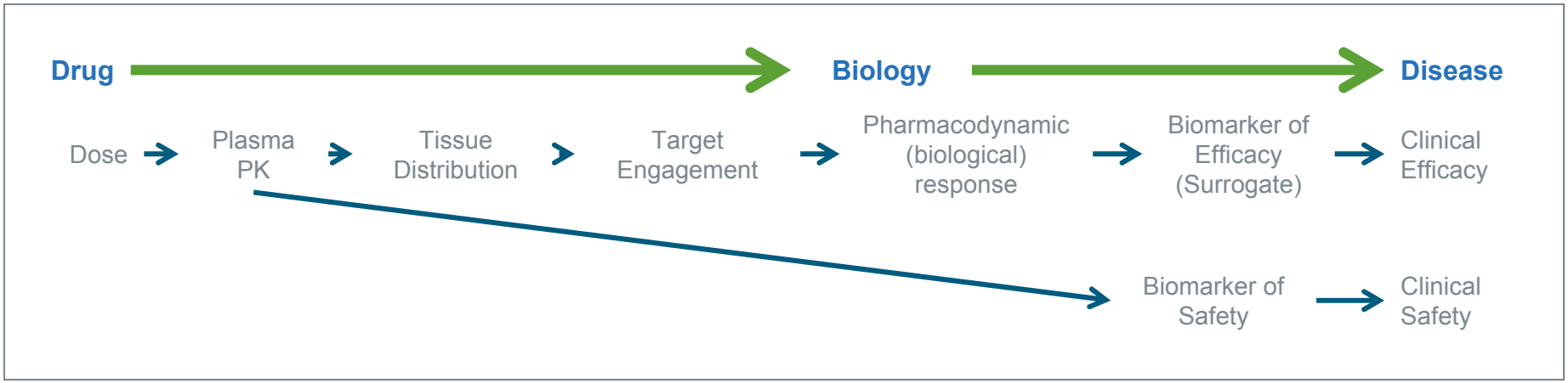
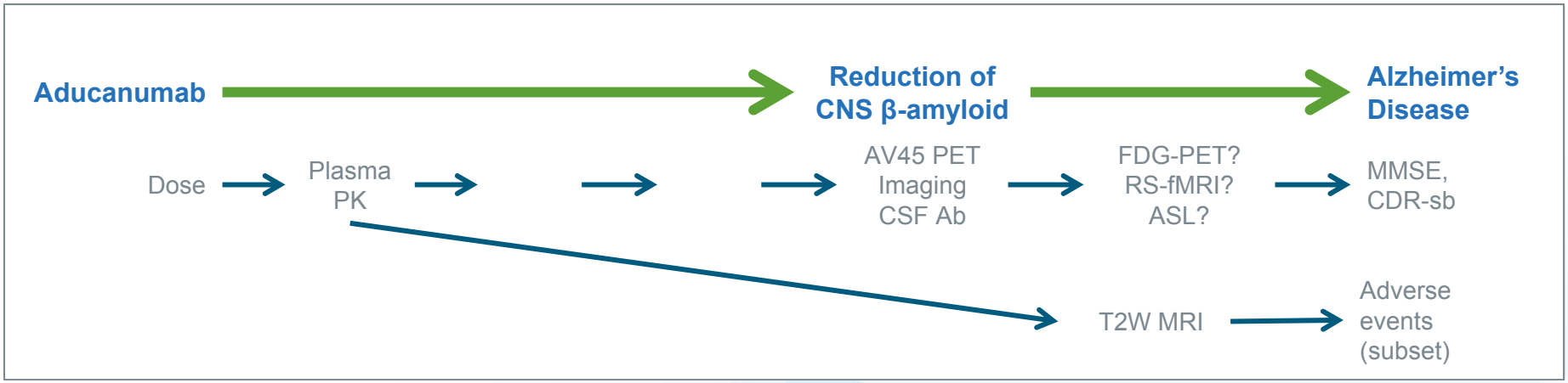
Learning from our aducanumab Phase 1b trial





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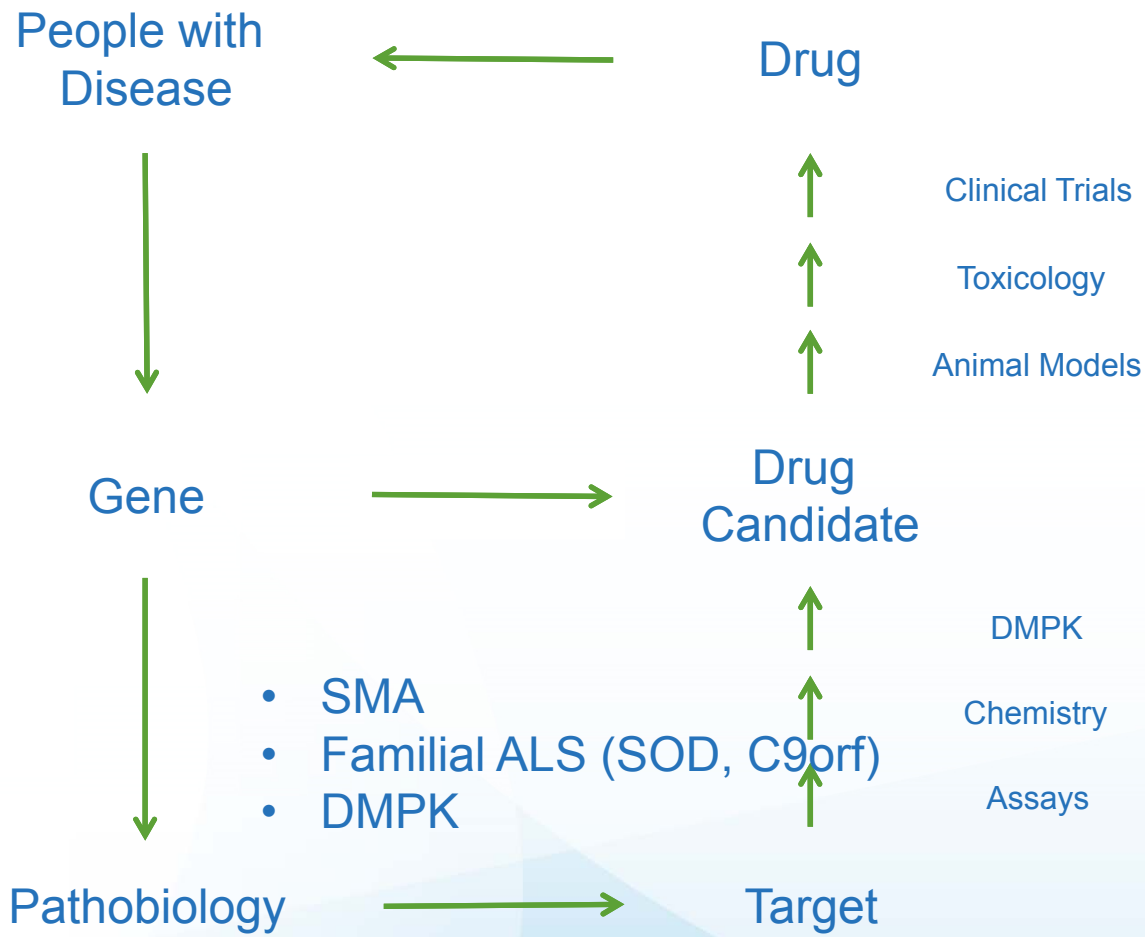
Our collaboration with ISIS allows us to take the shortest path from gene to drug

Use ASOs to target RNA



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R&D strategy

- **What**
  - Pursue programs with high unmet need that will make a meaningful impact on patients' lives; avoid incremental gain
  - Choose targets in biological pathways that are validated by human genetics or reliable clinical observations
  - Leverage biomarkers and ensure a clear regulatory pathway to approval
  - Choose diseases and therapeutic modalities to fit our core competencies or leverages our partners' capabilities
- **How**
  - De-risk as expediently as possible; take the shortest available path to robust clinical proof of concept
  - Once proof of concept is established, confirm benefit/risk with urgency; seek approval with superior labels in key territories globally
  - Don't forget the payors

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Conclusions

- Aided by genetics, we are in an era of potentially redefining neurologic diseases in actionable molecular pathophysiologic terms
- We believe we have the capability to make drug development tools that decrease the risk of drug development in neurology
- We have become better at measuring disease progression with sensitive outcome measures
- We have new therapeutic approaches that may allow us to go rapidly from gene to drug, e.g. with ASOs

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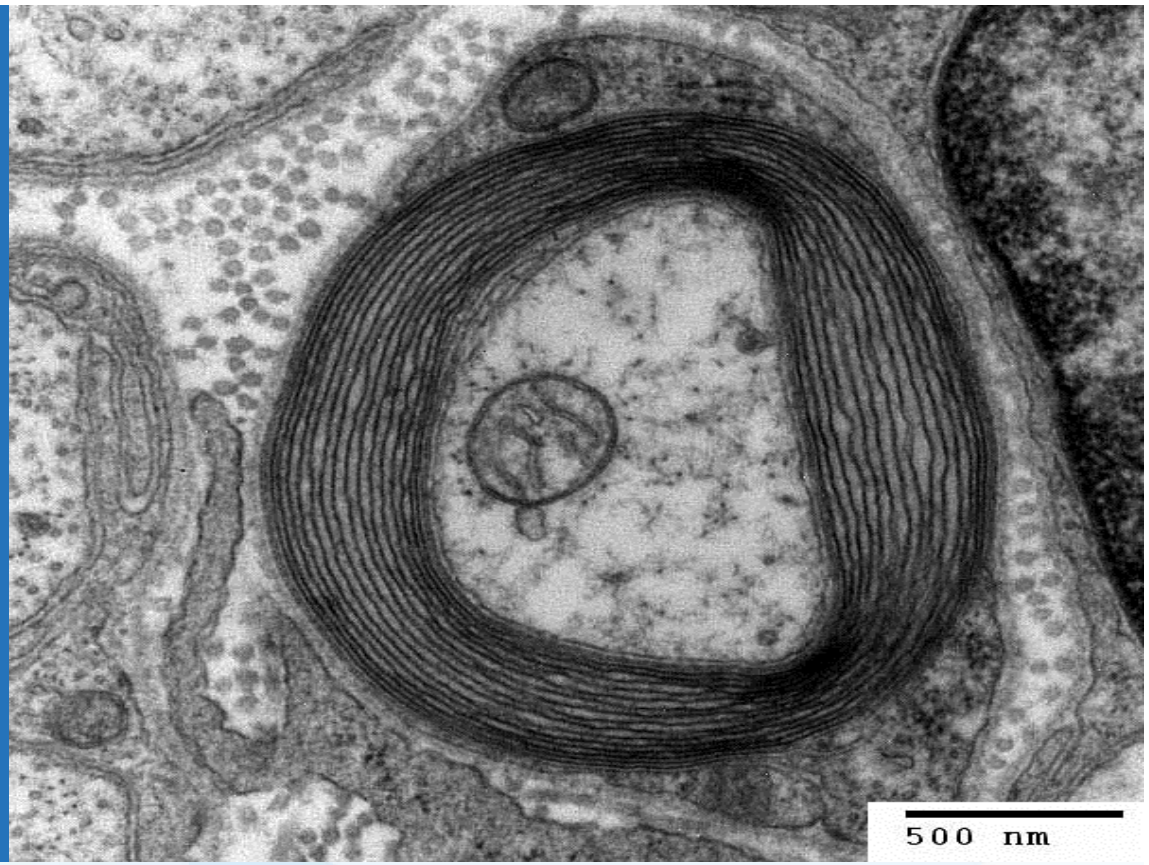
MS remyelinating programs: Anti-LINGO-1 and BIIB061

Diego Cadavid, MD
Senior Medical Director



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Headlines

- There is failure of remyelination in MS
- Potential for anti-LINGO-1 as first treatment for remyelination in MS
- Proof-of-biology study of anti-LINGO-1 in Acute Optic Neuritis recently completed
- Proof-of-concept study in MS is fully enrolled with readout mid-2016
- An oral remyelination compound is Phase 2 ready, BIIB061

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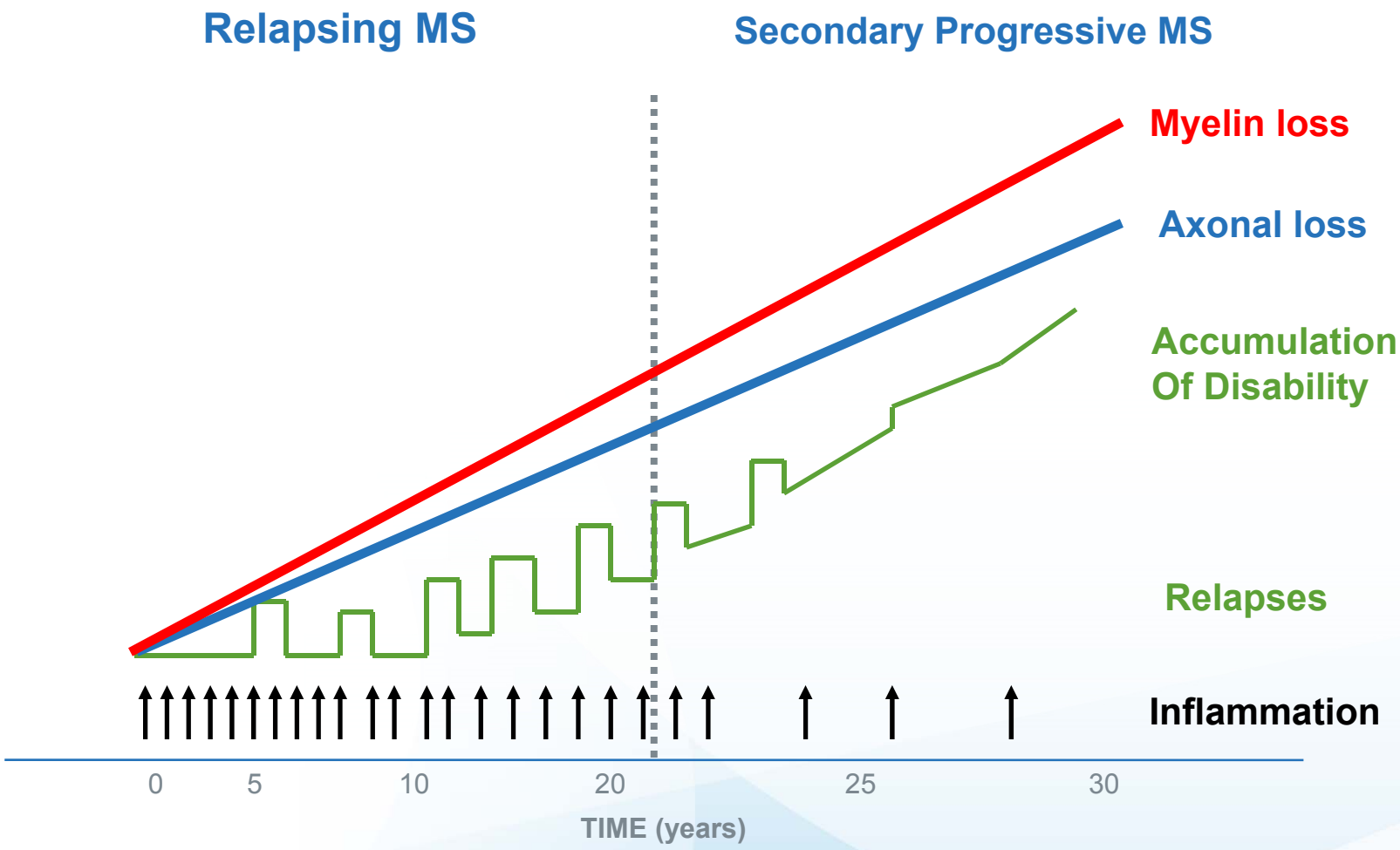
Key pathophysiology in relapsing multiple sclerosis



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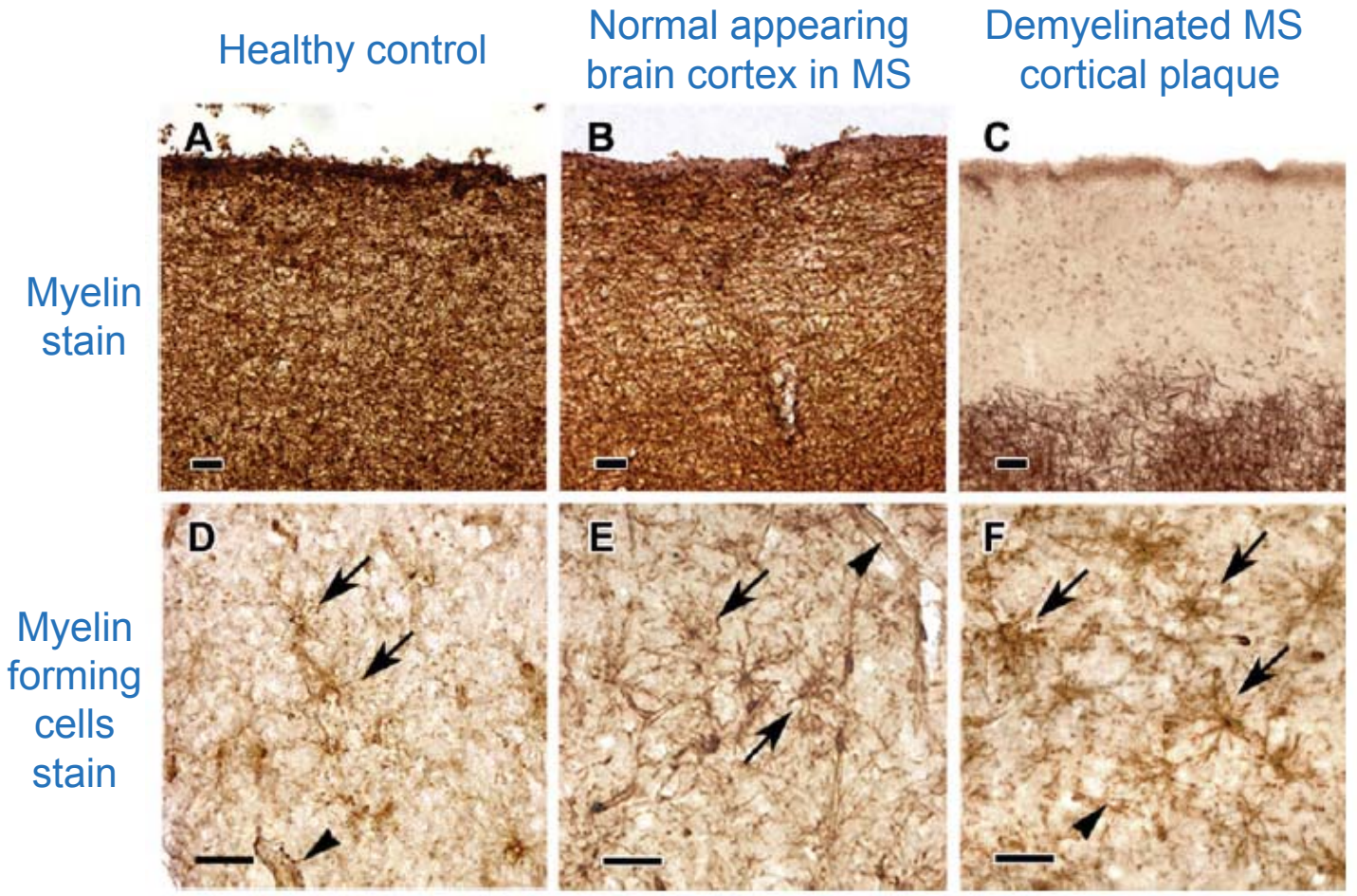
Demyelinated MS lesions have myelin forming cells



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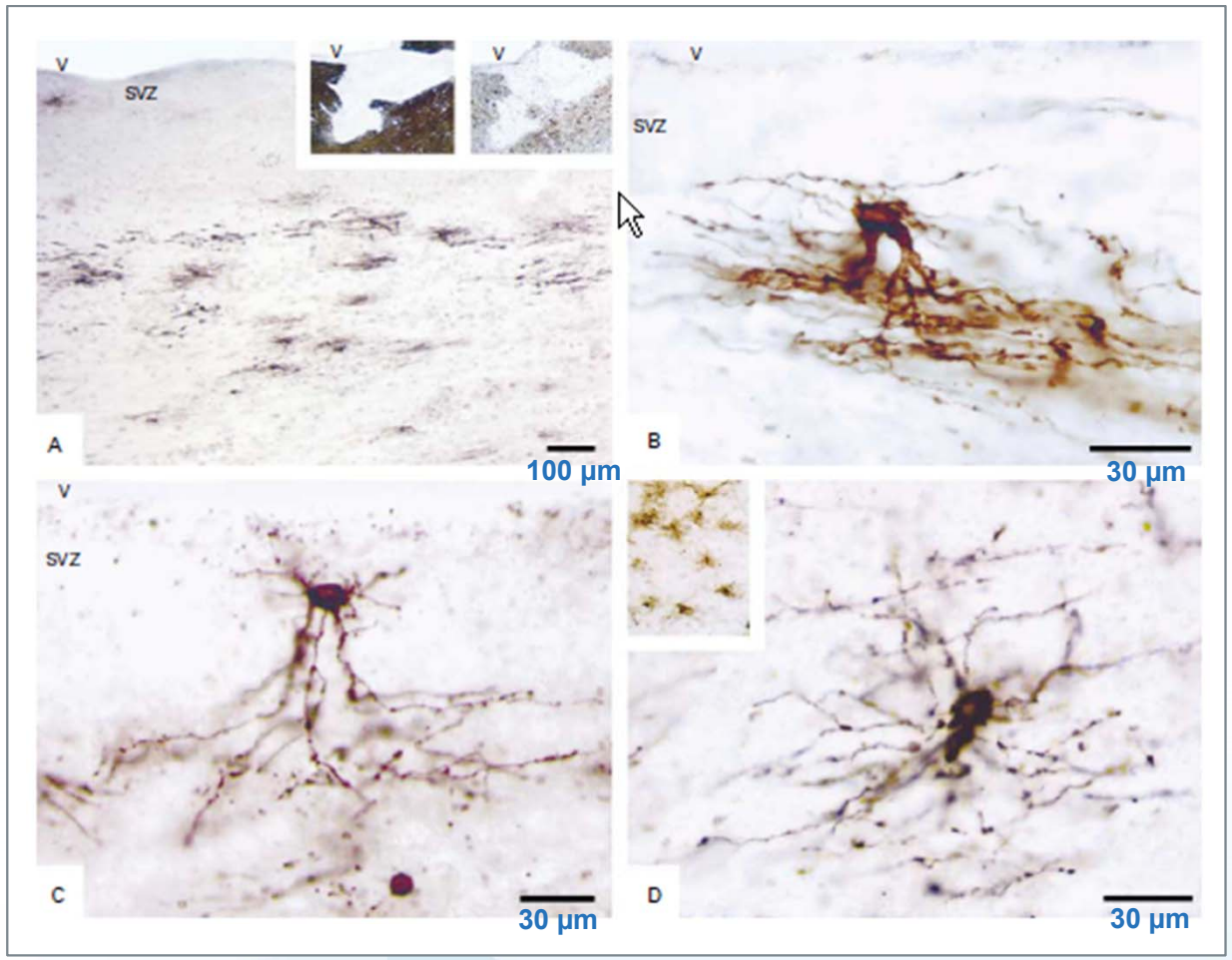
Ann Neurol 2012; 72;918-926

Myelin forming cells are found even in chronic demyelinated MS lesions

A. Demyelinated MS lesion with clusters of premyelinating oligodendrocytes

B–D. Premyelinating oligodendrocytes extending processes orientated parallel to demyelinated axons but without myelination



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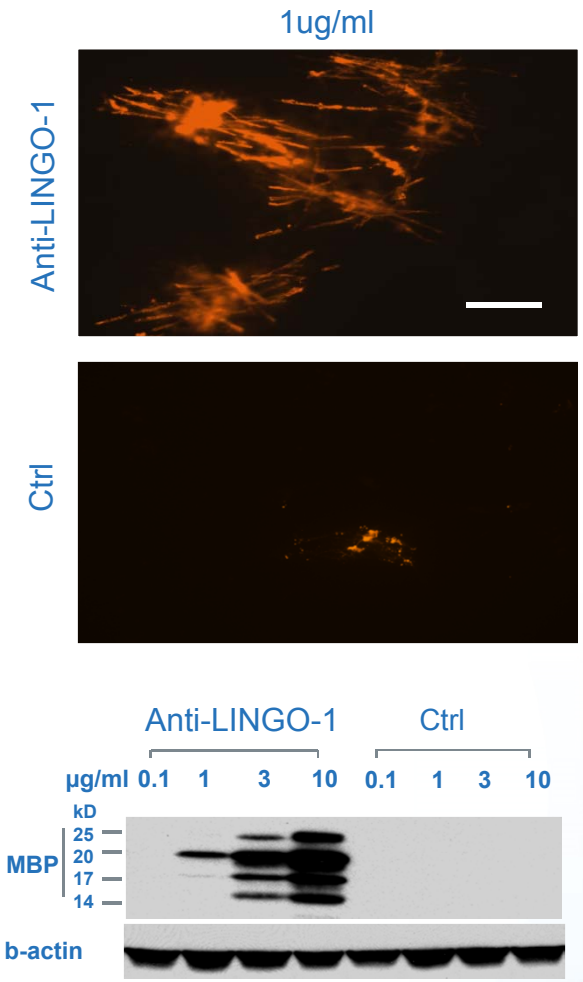
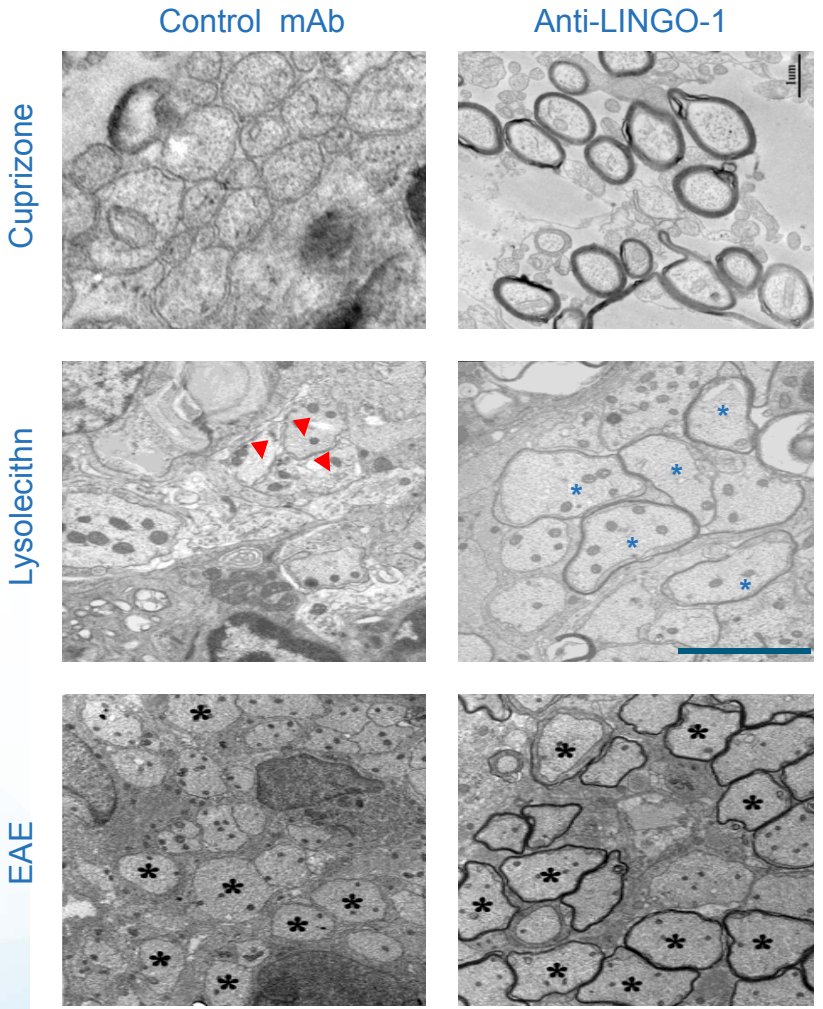
N Engl J Med. 2002 Jan 17;346(3):165-73. Premyelinating oligodendrocytes in chronic lesions of multiple sclerosis. Chang A, Tourtellotte WW, Rudick R, Trapp BD.

Anti-LINGO-1 enhances myelination *in vitro* and re-myelination *in various rodent models*





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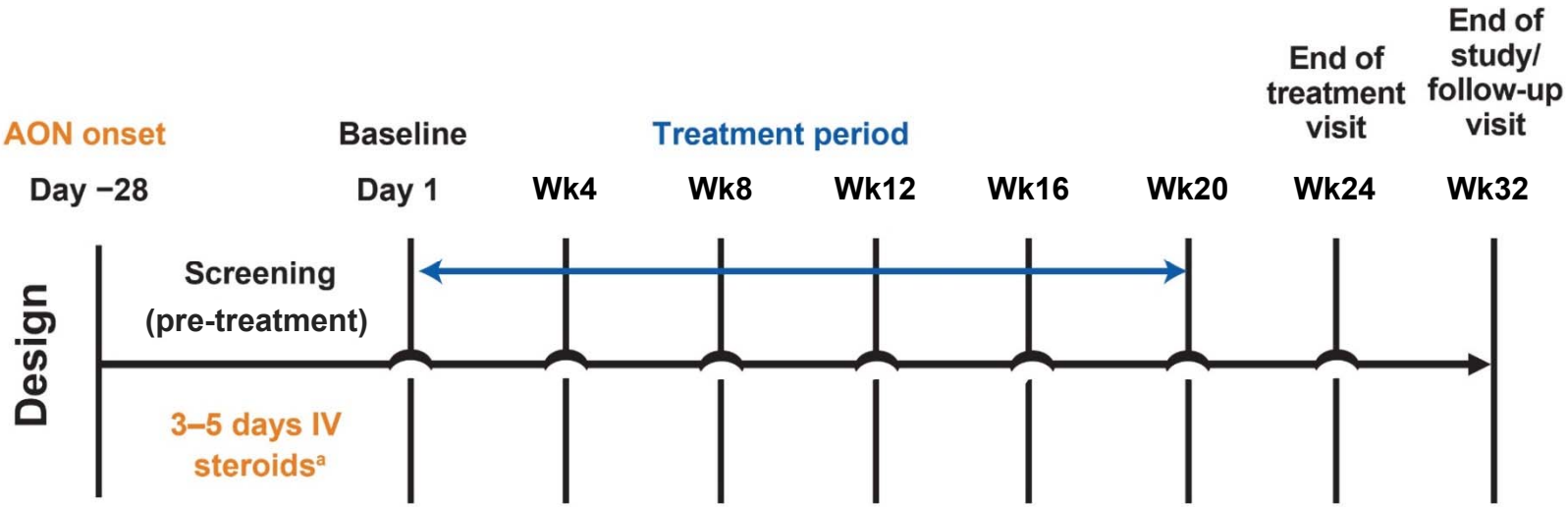
Mi S et al., Ann Neurol. 2009 Mar;65(3):304-15; Mi S et al. Presented at ECTRIMS October 13-16 2010, Gothenburg, Sweden; P731. LI-US-0078

RENEW: Phase 2 study for acute optic neuritis (AON)

Goal: Determine proof of biology and safety of anti-LINGO-1 after a first episode of AON



- Double blinded, placebo controlled study at 100 mg/kg with 82 patients
- Primary endpoint: improvement in optic nerve conduction latency by FF-VEP
- MF-VEP substudy (N=39)

IV = intravenous; FF-VEP = full-field visual evoked potential; MF-VEP = multifocal visual evoked potential.
[a]For subjects with AON who had not already been treated.

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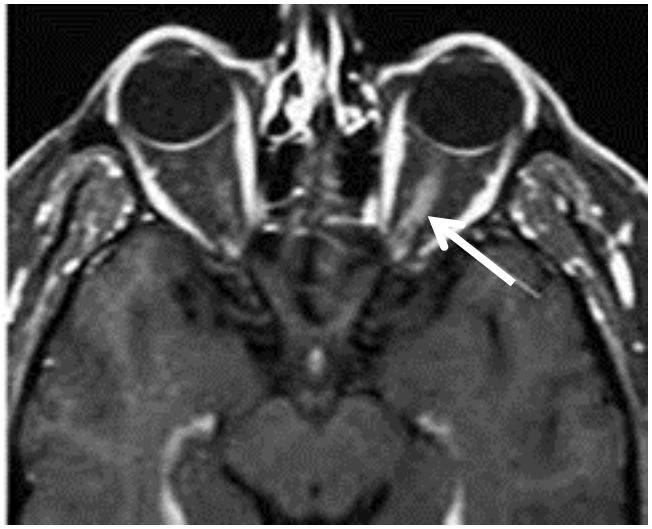
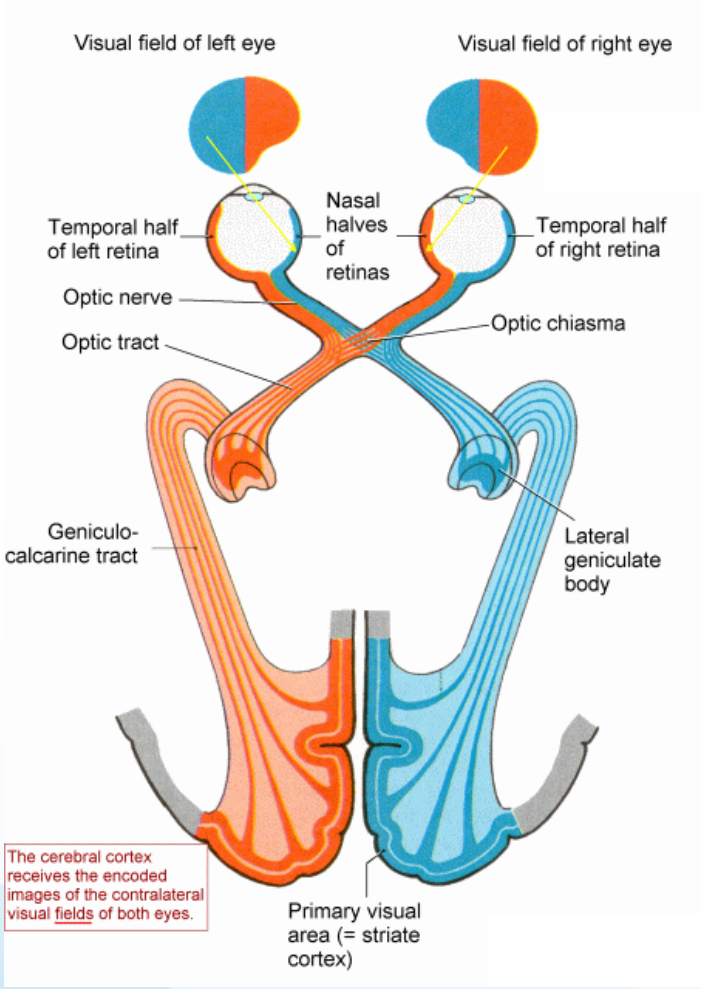
Acute optic neuritis



Human visual pathway



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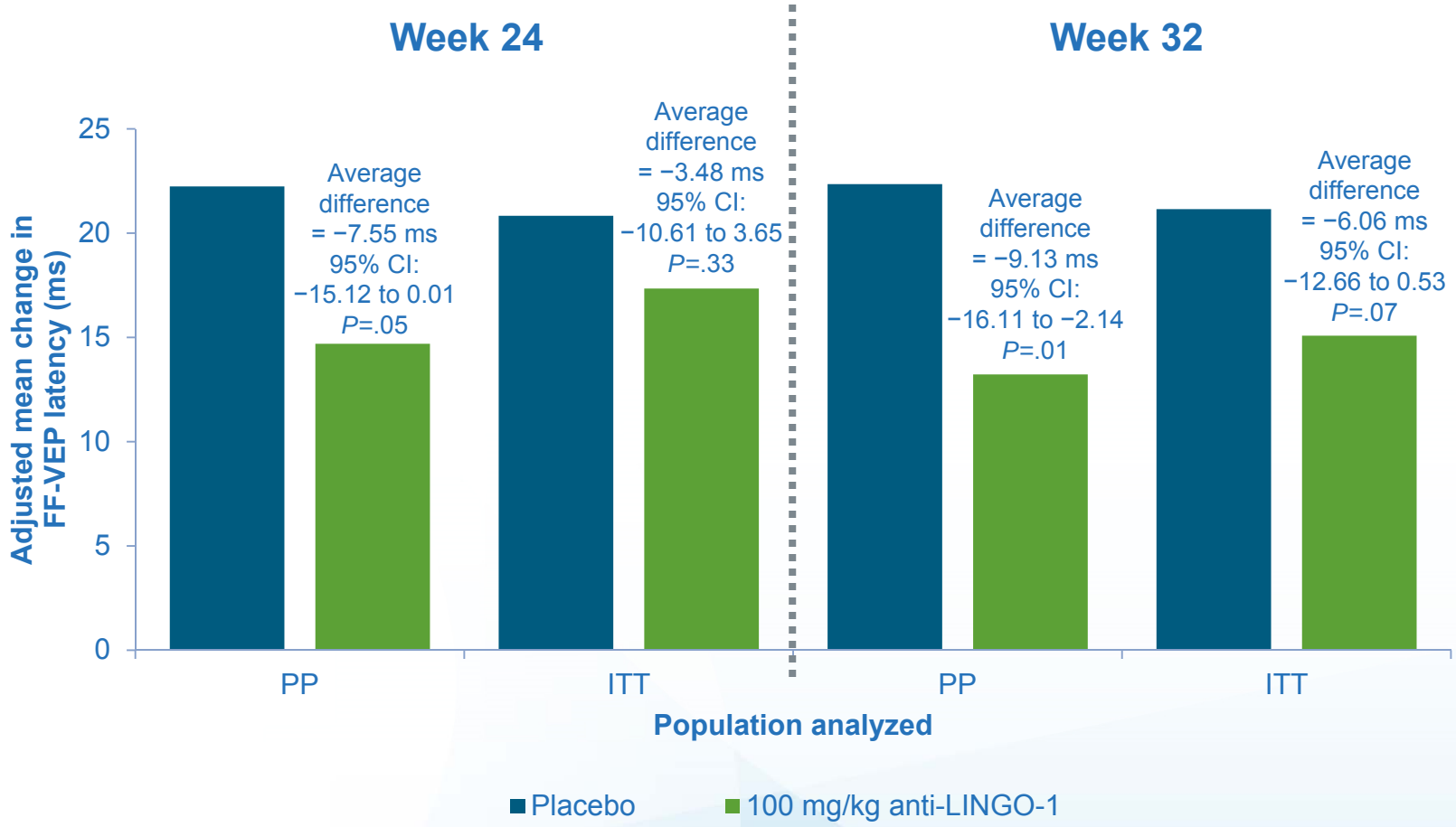
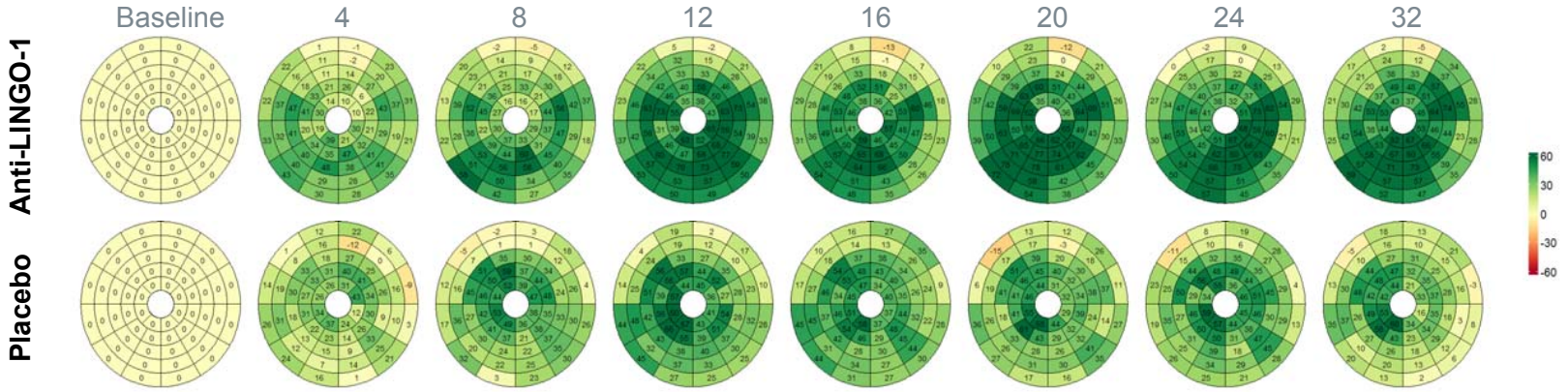
Primary endpoint:
Recovery of FF-VEP latency- indicative of remyelination



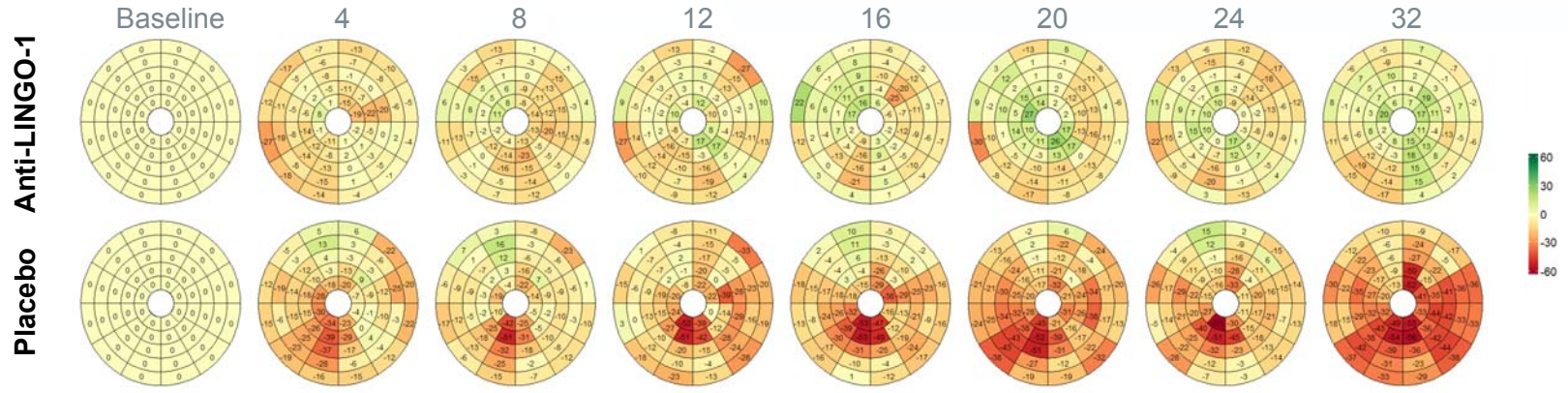
- *Adjusted mean change in optic nerve conduction latency (measured by FF-VEP) in the affected eye compared with the unaffected fellow eye at Baseline. Per protocol (PP): placebo, n=36; anti-LINGO-1, n=33. Intent to treat (ITT): n=41, both groups. Analysis by ANOVA (Week 24) and MMRM (Week 32)
- Cadavid et al., Presented at the 67th American Academy of Neurology (AAN) Annual Meeting. 23 April 2015. Washington, DC. P7.202.

Better MF-VEP amplitude preservation in anti- LINGO-1-treated group suggests neuroprotection

Affected Eye:



Fellow Eye:



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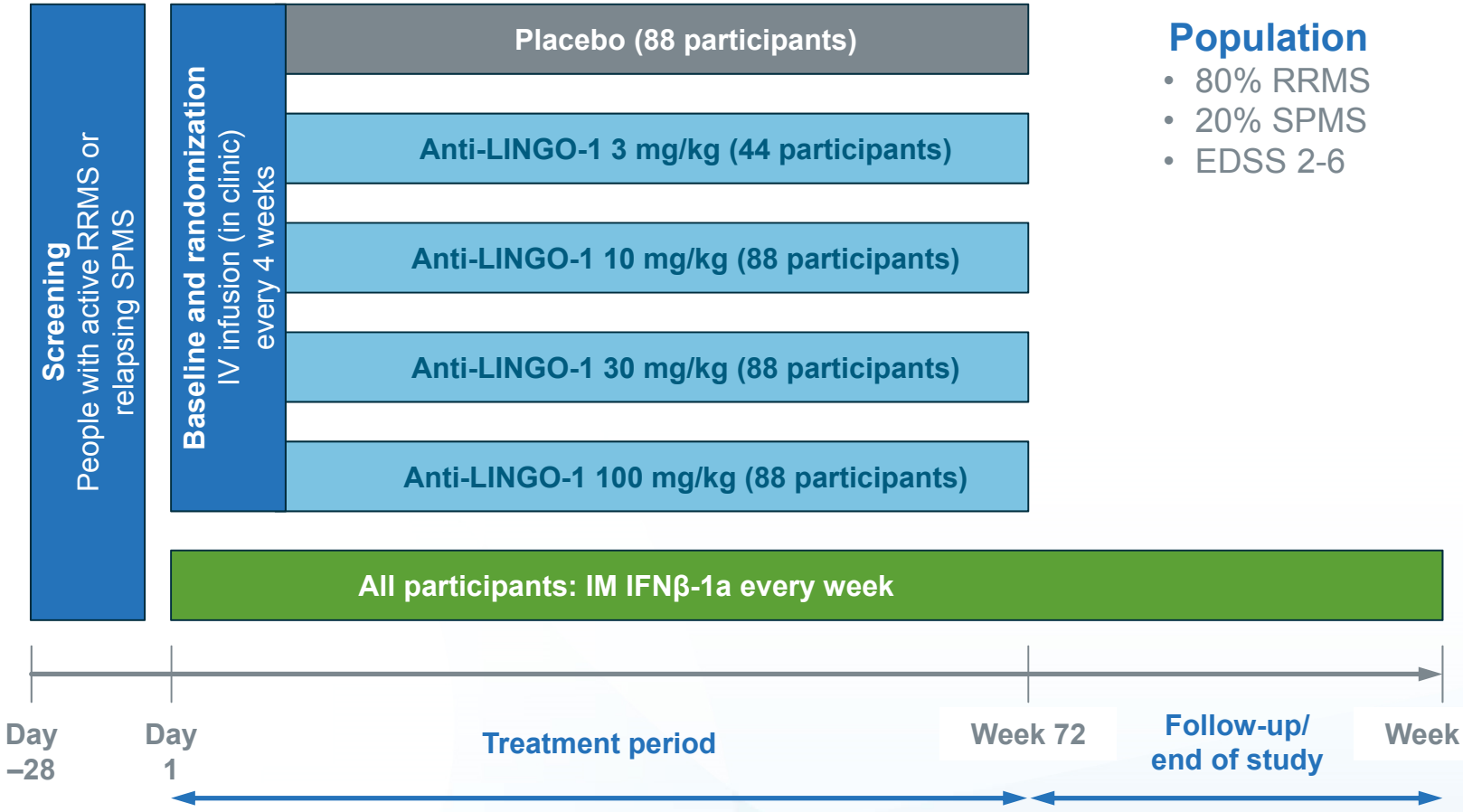
Cadavid et al., Presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), 09 October 2015, Barcelona, Spain

SYNERGY: Ongoing Phase 2 proof-of-concept study in relapsing forms of MS



Population

- 80% RRMS
- 20% SPMS
- EDSS 2-6

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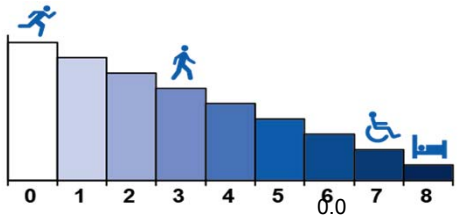
IM IFNβ-1a, intramuscular interferon beta-1a; IV, intravenous; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis. Cadavid D, et al. Poster presented at the Annual Meeting of the AAN, April 18–25, 2015. Poster P7.204; SYNERGY study protocol, Version 4.3, August 18, 2015.

Clinical and MRI endpoint in the SYNERGY Study

Disability



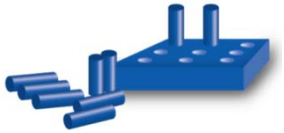
EDSS progression relapse recovery

Cognitive Function

Information processing learning and memory

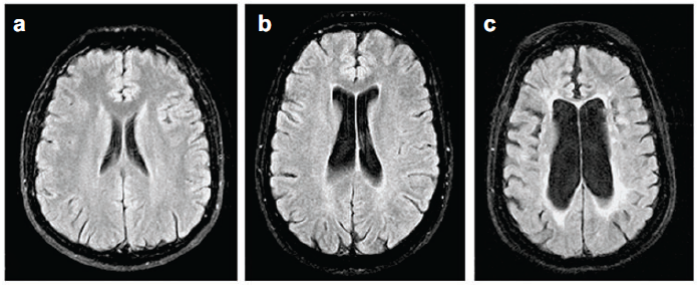
Physical Function

Timed walking



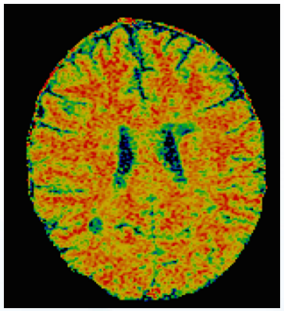
Upper limb function

Brain Atrophy



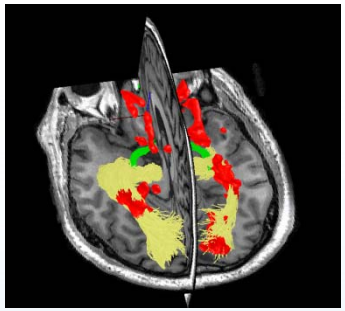
Change in brain Volumes

Magnetization Transfer Ratio



Change in magnetization transfer

Diffusion Tensor Imaging

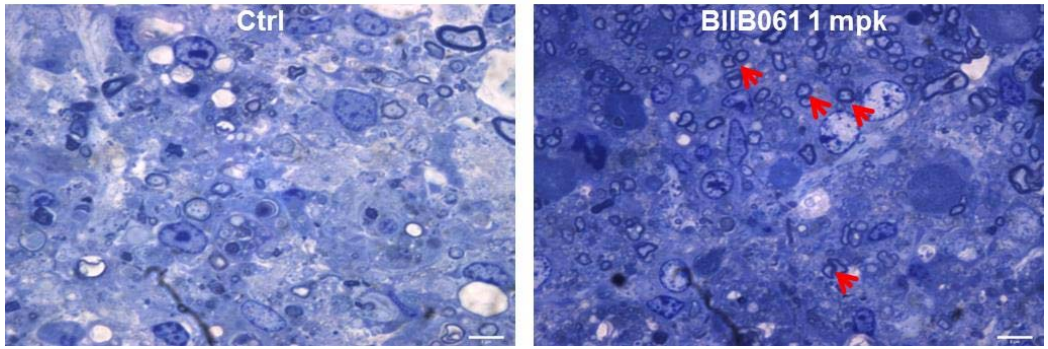


Change in lesion diffusivity

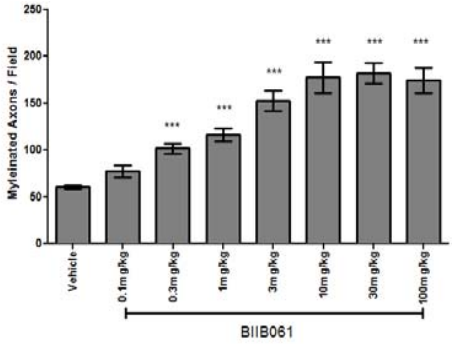
9HPT, 9-hole peg test; EDSS, Expanded Disability Status Scale; MSFC, Multiple Sclerosis Functional Composite; PASAT-3, 3-second Paced Auditory Serial Addition Test; T25FW, timed 25-foot walk. Cadavid D, et al. Poster presented at the Annual Meeting of the AAN, April 26–May 03, 2014. Poster P3.154; Hupperts RMM, et al. Poster presented at the Annual Cooperative Meeting of ENS and the EFNS, May 31–June 03, 2014. Poster EP1153.

BIIB061: Phase 2 ready potential oral remyelination therapy

- Different biological pathway from anti-LINGO-1
- Preclinical animal models demonstrate ***enhanced remyelination and axonal protection*** versus control
- Phase 1 SAD completed and MAD trial completing
  - Predictable/linear PK
  - Acceptable safety profile
- Anticipate ***Phase 2 study initiation 2016***



Data on file at Biogen



Rat LPC spinal cord model

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Summary

- High unmet need for reparative treatments in MS
- Phase 2 RENEW study provided evidence of proof of biology
- Phase 2 SYNERGY study to determine clinical effect in MS – results expected mid-2016
- An oral remyelination candidate (BIIB061) is phase 2 ready

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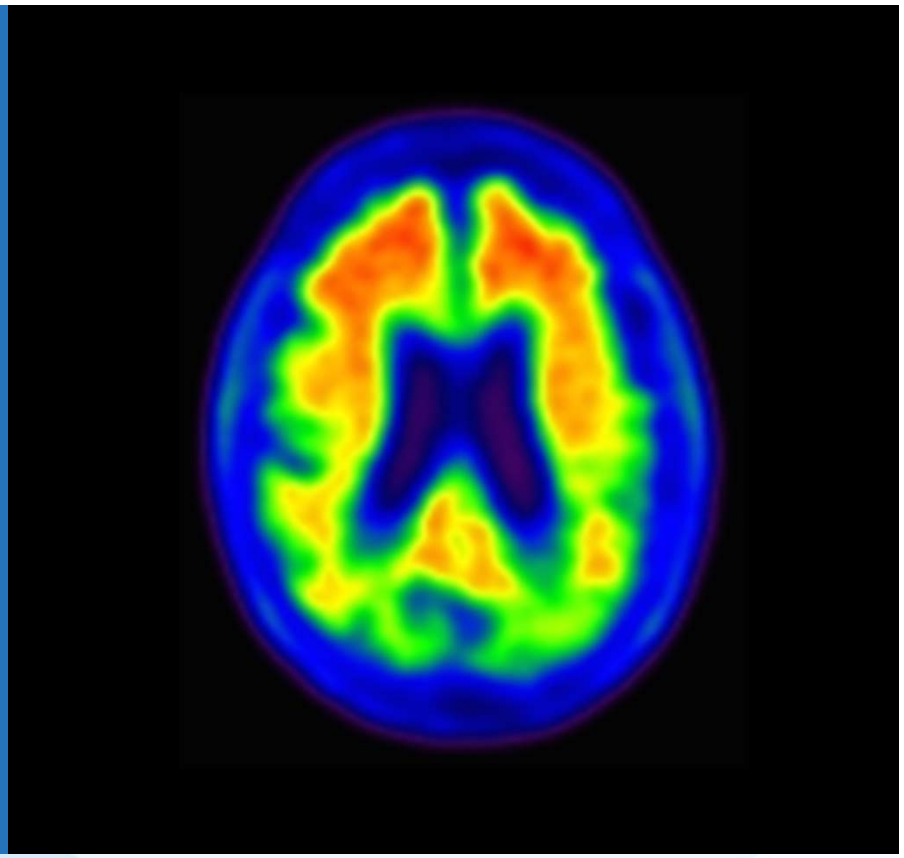
Alzheimer's disease strategy

- E2609 and BAN2401

Samantha Budd Haeberlein, PhD
VP Clinical Development



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Biogen Alzheimer's Disease strategy

Vision: A global leader, establishing aducanumab as a foundational therapy and building a portfolio of differentiated complementary therapies

Establish foundation	Advance our programs	Broaden impact
• Advance aducanumab • Enable more patients to access treatment – Prevention – Diagnosis	• Support BAN2401 and E2609 – including combinations • Implement biomarkers to enable clinical decisions	• Advance Tau programs • Investigate new MOAs

Continue to evaluate external opportunities

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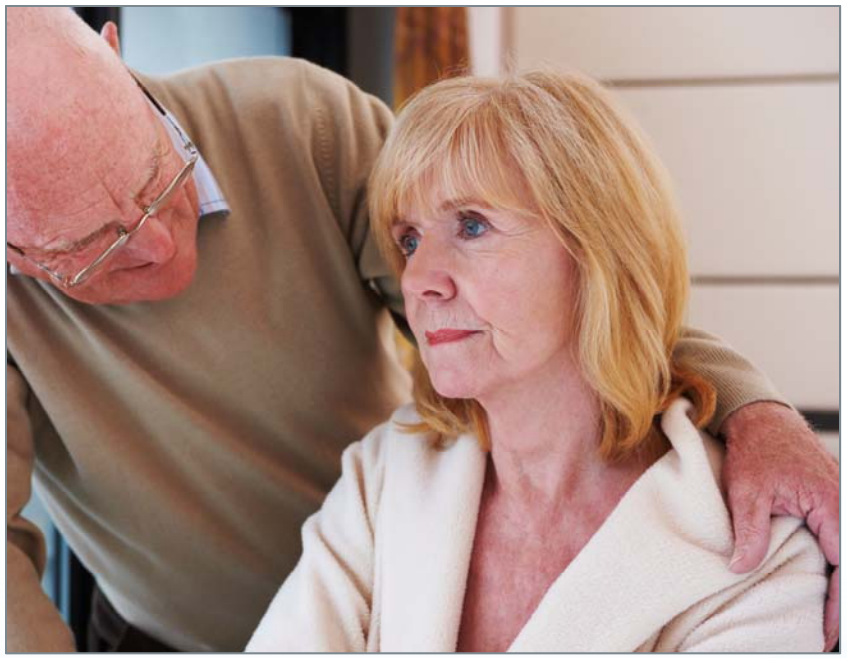
An opportunity to change the disease

- Terrible disease with modest treatment options
- ~7 year lifespan after diagnosis
- 6th leading cause of death (US)
- ~5.3M patients diagnosed (US); expected 13.8M by 2050#
- ~200k pts under age 65 (US)#
- Estimated $200B+ cost (US)#
- ~44M people affected worldwide*



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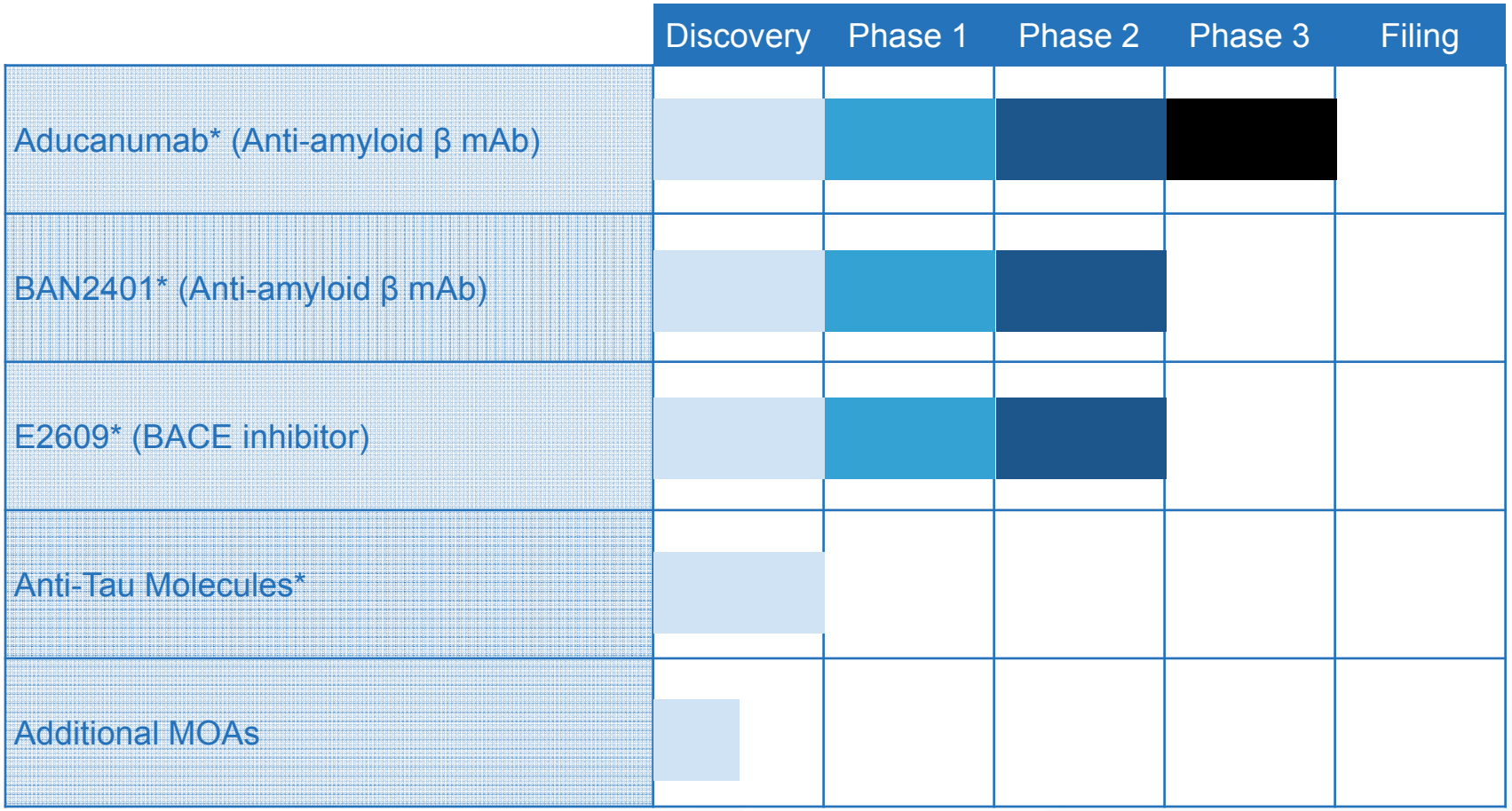
Alzheimer's Association Facts & Figures 2015, * Prince et al (2013) The Global Impact of Dementia 2013–2050.

Alzheimer's disease development efforts



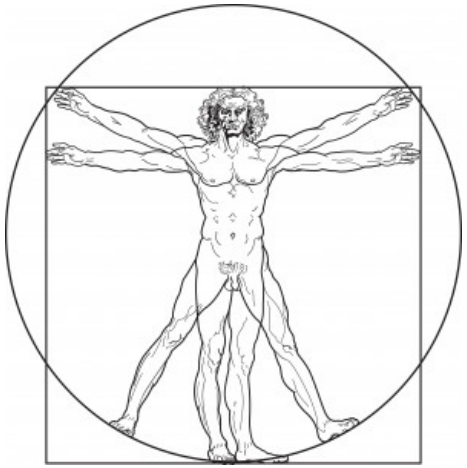
Supporting imaging and biomarker activities

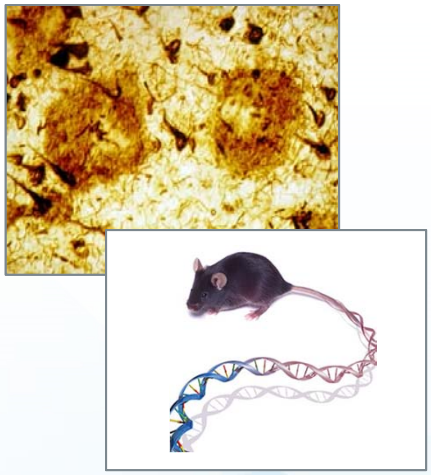
Biogen

* Collaboration program

Key evidence that β-amyloid dysregulation is central to disease

Human Genetics	Pathology	Proof of Concept
Dominantly inherited (APP, PS1, PS2) involved in processing of amyloid	Pathological hallmarks Amyloid-β (Aβ) plaques	Emerging clinical signals (aducanumab, solanezumab, crenezumab)





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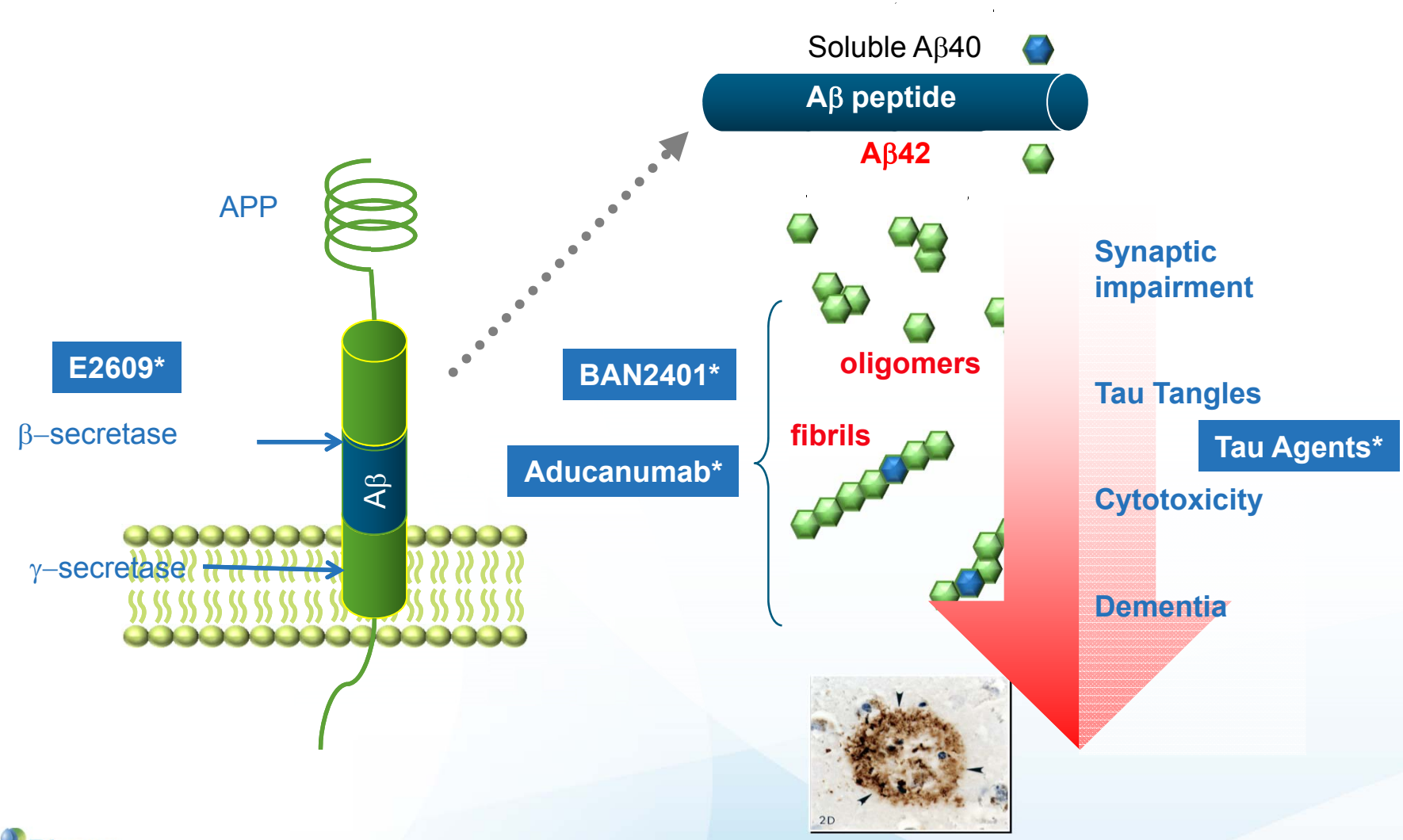
APP: amyloid precursor protein; PS1/PS2: presenilin-1/presenilin-2

Source: Goate et al Nature1991, Sherrington et al Nature 1995, Levy-Lahad et al Science 1995, Braak & Braak Neuroscience Lett 1987 & Neurobiology 1989;, Brody & Holtzman Ann Rev Neurosci. 2008,

Potential to disrupt the disease cascade



Biogen

* Collaboration program

Biogen has leveraged past learnings in advancing Alzheimer's trials

Target Engagement	• Doses limited by adverse events or tolerability reduce CNS target engagement and possibility to show efficacy
Patient Population	• Earlier AD trials did not screen patients for amyloid; approximately 25% patients enrolled without Alzheimer's • Patients enrolled in prior trials more advanced stage – potentially suboptimal population
Aducanumab & PRIME	• Binding highly selective for aggregated Aβ • Phase 1b: early Alzheimer's population (defined by cognition + amyloid PET imaging)

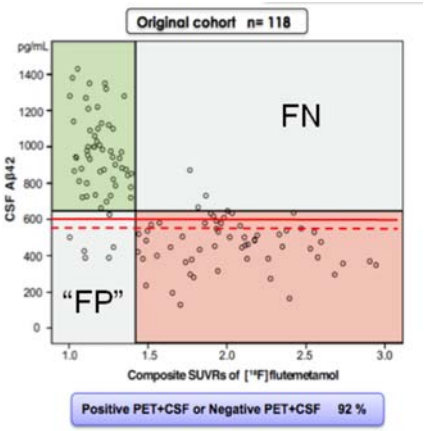
Biogen

Biomarkers – Enabling our pipeline

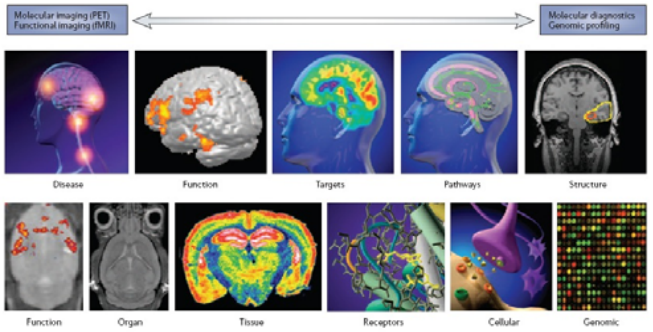
Use of biomarkers in Alzheimer's:

- In early clinical studies, to demonstrate ***target engagement***
- To select ***the right patients***
- To demonstrate ***effect on disease*** pathophysiology

Fluid-based measures



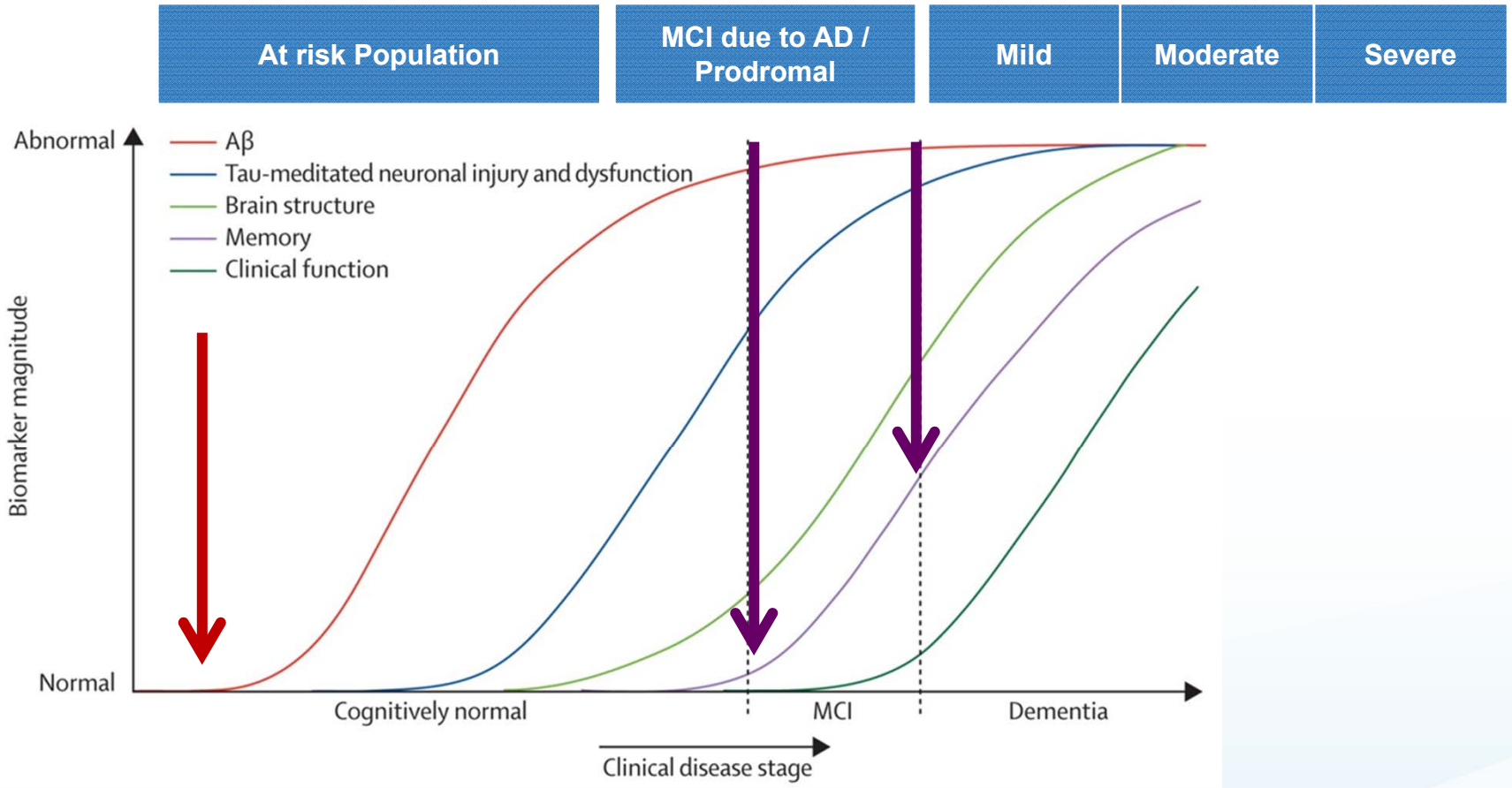
Preclinical and clinical imaging



Human physiology and devices

Biogen

Alzheimer's starts many years prior to onset of symptoms



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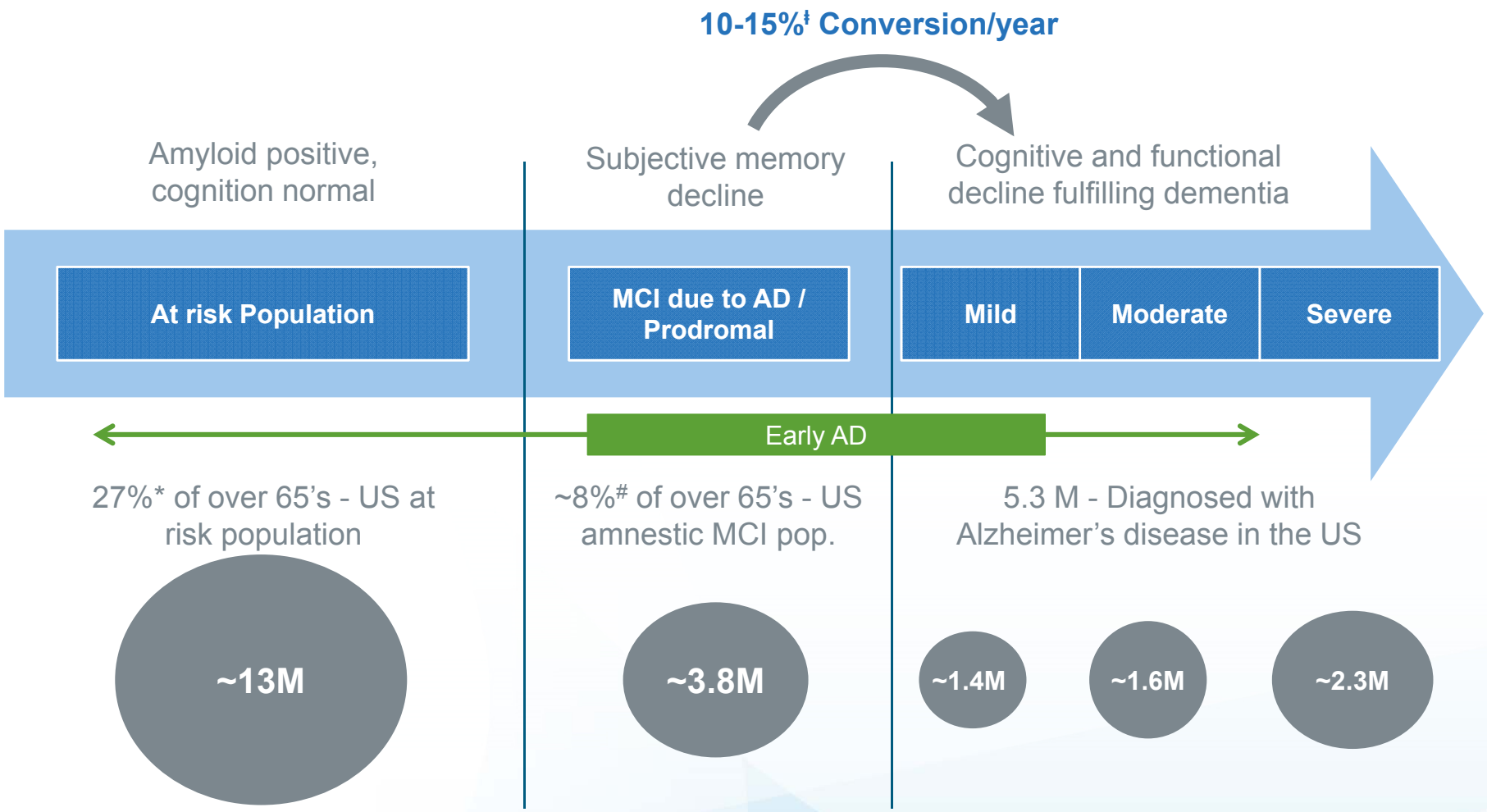
Jack, et al. Lancet Neurol (2013)

Attractive opportunity early in disease course



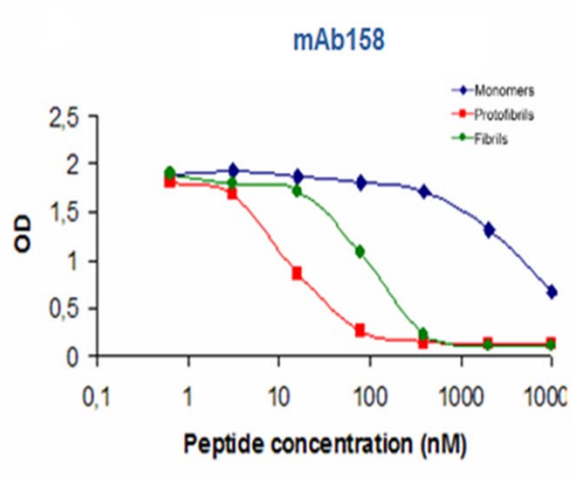
Biogen

US Census Bureau 2014, * Jansen et al JAMA 2015, ǂ Roberts et al Clin Geriatr Med 2013, Petersen et al Curr Alz Res 2009, Mitchell et al Acta Psych Scand 2009
Petersen et al Neurol 2012, Whitwell et al Arch Neurol 2012, Plassman et al Ann Int Med 2008, Manly et al Arch Neurol 2005

BAN2401 mAb to Aβ

Molecule	• BAN2401 is a humanized IgG1 monoclonal antibody that selectively recognizes Aβ protofibrils
Therapeutic Goal	• Expected to reduce the brain levels of toxic forms of Aβ
Reason to Believe	• High affinity and selectivity for Aβ protofibrils, resulting in slowing the clinical progression of AD
Clinical Status	• Evaluated in a SAD and MAD study in subjects with mild to moderate AD. • Ongoing global Ph2 study in subjects with early AD • Ph2 study topline results anticipated in 2016

Murine mAb Model



- High affinity and selectivity for Aβ protofibrils

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Eisai presentation at AD/PD in March 2011 (Barcelona, Spain)

BAN2401 Ph2 study

Population

- MCI due to AD and mild AD (Early AD)
- MMSE ≥22-30
- Stable concomitant medications
- Positive amyloid PET/CSF

Dose design

- Placebo
- 2.5 mg/kg: bi-weekly
- 5 mg/kg: bi-weekly
- 10 mg/kg: bi-weekly
- 5 mg/kg: once every 4 weeks
- 10 mg/kg: once every 4 weeks

Endpoints

Primary

- Change from baseline in the ADCOMS at 12 months
- Safety and tolerability

Secondary

- Change from baseline in the ADCOMS at 18 months
- Change from baseline in total hippocampal volume at 6, 12, and 18 Months
- Change from baseline at 12 and 18 months in brain amyloid levels as measured by amyloid PET

- Maximum planned sample size 800 subjects
- Bayesian design
- Frequent interim analyses to update randomization allocation

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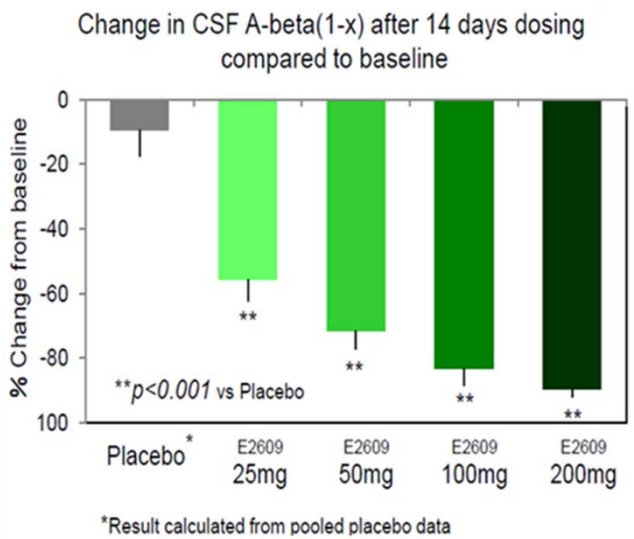
E2609 β-secretase inhibitor

Molecule	• E2609 is a highly potent beta-site amyloid precursor protein (APP)-cleaving enzyme-1 (BACE1) inhibitor
Therapeutic Goal	• Stops the production of β-amyloid, aimed at slowing the disease progression
Reason to Believe	• In Ph1 demonstrated target engagement (inhibition of BACE activity), and lowering of CSF Aβ by >90%
Clinical Status	• Safe & well tolerated in Ph1 SAD and MAD studies • Ongoing Ph2 safety study in subjects with AD • Interim Ph2 safety results expected in 2016

CSF in Healthy volunteers; after 14d

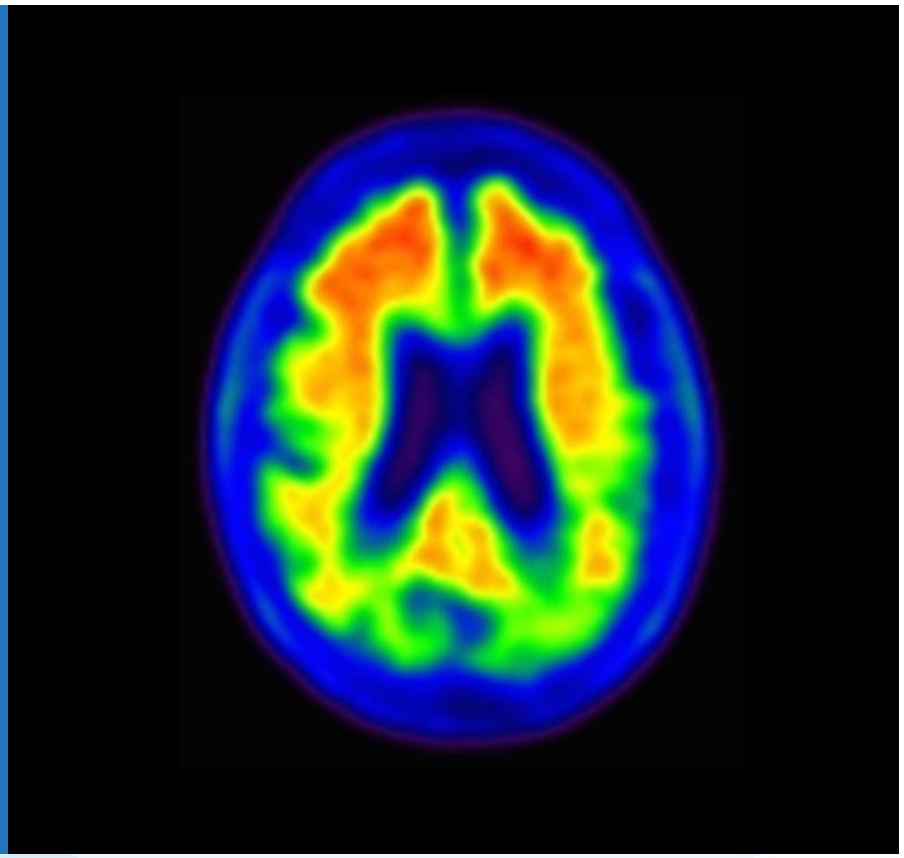


- Dose-dependent reduction of CSF Aβ compared to baseline
- 55% reduction at 25mg & 89% at 200mg

Biogen. Eisai Presentation at AAIC in July 2012 (Vancouver, Canada)

Aducanumab for early Alzheimer's disease

Jeff Sevigny, MD
Senior Medical Director



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Program highlights

- Phase 1b study (PRIME) demonstrated proof of biology and concept
- Two pivotal Phase 3 studies (ENGAGE & EMERGE) have begun enrolling subjects with early AD under SPA agreement
- Aducanumab has the potential to fundamentally change treatment paradigm of AD by slowing the course of the disease

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Phase 1b (PRIME) study design

Population

- Prodromal or mild AD
- MMSE ≥20
- Stable concomitant medications
- Positive amyloid PET scan

Dose Escalation Design

1 & 3 mg/kg: placebo (Arms 1-3)

10 mg/kg: placebo (Arms 4-5)

6 mg/kg: placebo (Arms 6-7)

Titration: placebo (Arms 8-9)

- Planned sample size: 188 subjects
- Randomization 3:1, active vs placebo
- Planned enrollment: 30 subjects per active arm
- Stratified by ApoE ε4 status
- Dose escalation based on independent DMC review of safety, tolerability, and PK data

Endpoints

Primary

- Safety and tolerability

Secondary

- Serum PK
- Anti-aducanumab antibodies
- Amyloid PET, change from baseline to Week 26

Exploratory

- CDR-SB, MMSE
- Amyloid PET, change from baseline to Week 54

Exploratory – Ongoing

- NTB, FCSRT, NPI-Q
- Fluid biomarkers
- Volumetric MRI
- FDG-PET
- tf-fMRI
- ASL-MRI

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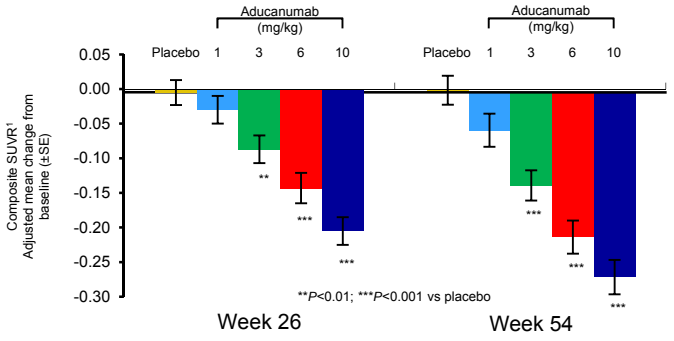
Prodromal AD: MMSE 24-30; spontaneous memory complaint; total free recall score ≤27 on FCSRT; CDR Global Score 0.5; absence of significant levels of impairment in other cognitive domains; essentially preserved activities of daily living and absence of dementia
Mild AD: MMSE 20-26; CDR Global Score 0.5 or 1.0; meeting NIA-AA core clinical criteria for probable AD

Phase 1b interim results: Biological and clinical effects with acceptable safety

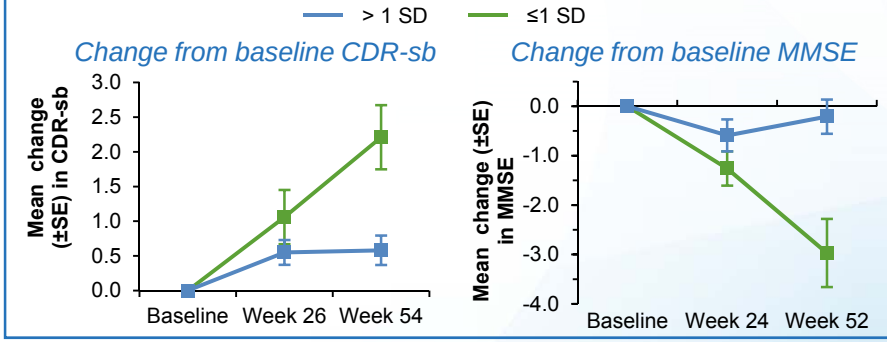
Amyloid plaque reduction with aducanumab (secondary endpoint)



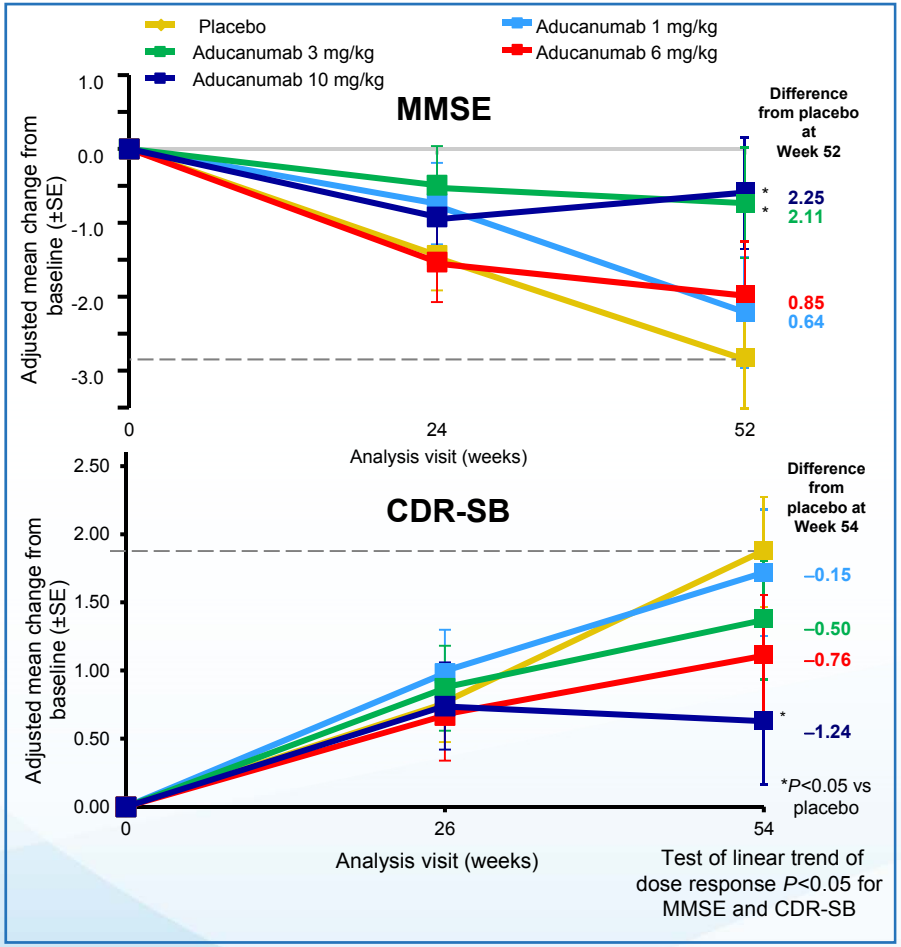
Correlation between changes in PET SUVR and CDR-sb and MMSE in aducanumab-treated patients

Change in SUVR vs Change in	Spearman correlation	P-value
CDR-sb	0.27	<0.05
MMSE	-0.38	<0.001

PET Reduction Relative to SD of Week 54 Placebo Change



Clinical effect of aducanumab (exploratory endpoints)



Phase 1b interim safety: ARIA is the main finding

- Imaging abnormality
- Dose and ApoE ε4 carriage dependent
- Majority of events are asymptomatic. Symptoms, when present
  - Mostly rated as mild to moderate
  - Generally transient and self-resolving
  - Include headache, confusion, visual disturbances
- Monitorable and Manageable
  - 56% of subjects who develop ARIA-E able to resume dosing without ARIA-E recurrence

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ARIA: Amyloid–related imaging abnormality

Phase 1b on-going activities

- Titration cohort (Arms 8 and 9; ApoE ε4 carriers only)
  - Test effect of titration in reducing risk of ARIA
  - Report 1-year placebo period results 2H2016
- Long term extension (3 years)
  - Understand long term safety and tolerability of aducanumab
  - Test effect of titration in reducing risk of ARIA
  - Evaluate amyloid plaque reduction

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Phase 3 study design

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Phase 3 study in early AD trial design

Studies	Two identical randomized, double-blind, placebo-controlled studies • ENGAGE (NCT02477800) • EMERGE (NCT02484547)
Population	Early AD: MCI due to AD + mild AD all with positive amyloid PET • CDR Global Score of 0.5 • MMSE score 24–30 • RBANS score ≤85
Doses	Two active doses vs. placebo Differential dosing based on ApoE ε4 status • ApoE ε4 carrier: titration to 3 or 6 mg/kg • ApoE ε4 non-carrier: titration to 6 or 10 mg/kg
Duration	18 months + 24 month long-term extension
Primary endpoint	CDR-SB (change from baseline at week 78)
Other key endpoints	Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI Tertiary: amyloid PET (subset)
Sample size	~1350 per study (450/dose level; 1:1:1) across ~150 sites globally

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CDR, Clinical dementia Rating Scale; MMSE, Mini Mental Status Examination; ADAS-Cog 13, Alzheimer's Disease Assessment Scale-Cognitive Subscale (13-item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); MCI, mild cognitive impairment; vMRI, volumetric MRI

Key areas of focus for aducanumab

- Expediting recruitment and retention
- Mitigating ARIA risk
- Exploring additional patient populations
- Developing screening tools and diagnostics for AD

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SMA and nusinersen (SMN_{Rx}) program update

Wildon R. Farwell, MD, MPH
Senior Medical Director

Biogen

Nusinersen program overview

- Patients with SMA have urgent, high unmet medical needs
- Two ongoing Phase 3 trials in collaboration with Isis Pharmaceuticals, data expected by early 2017
- Increasingly encouraging data from the Phase 2 open-label studies
- Ongoing regulatory discussions with health authorities across the EU and US

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SMA overview

- SMA is the #1 genetic cause of death for infants
- Rare, genetic, progressive disorder that causes muscle degeneration and weakness, often leading to death
- Incidence is estimated at 1 in 6,000-10,000 live births
- Decreased SMN protein production secondary to an *SMN1* gene mutation and subsequent dependence on the *SMN2* gene(s)
  - SMN protein is required by spinal cord motor neurons
- Primarily diagnosed and managed by Pediatric Neurologists
- No treatments currently available

Lunn M, et al. (2008)
Pictures provided by CureSMA

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SMA types characterized by different disease severity

	Type I	Type II	Type III
SMN2 Copy Number	Primarily 2 copies	Primarily 3 copies	Primarily 3 or 4 copies
Age of Symptom Onset	<6 mos	7-18 mos	>18 mos
Age at Diagnosis	4-5 mos	17-19 mos	4.5-7 yrs
Life Expectancy	<2 yrs	~70% live to early adulthood	Normal
Milestones Achieved	***Never sits*** without support	Sits independently, ***never walks independently***	Walks independently but ***may lose ability over time***

Crawford TO, et al. (2012)
Lunn M, et al. (2008)
Lin CW, et al. (2015)

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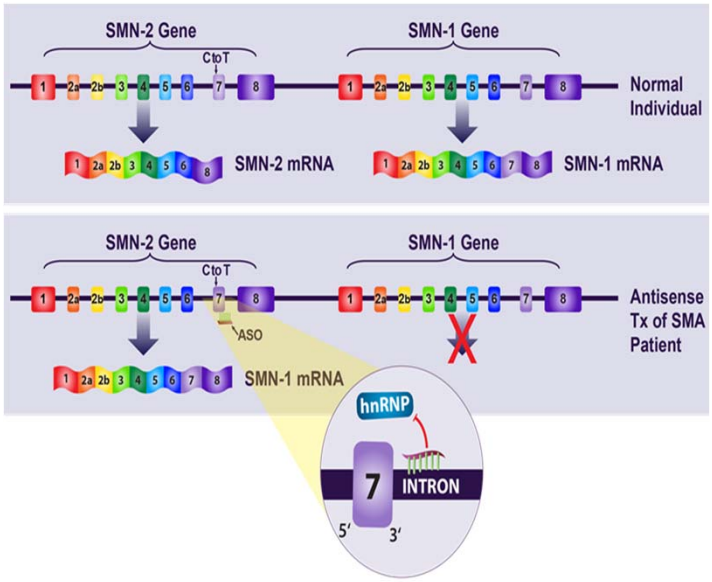
Nusinersen designed to increase SMN protein in spinal cord motor neurons

Mechanism of Action

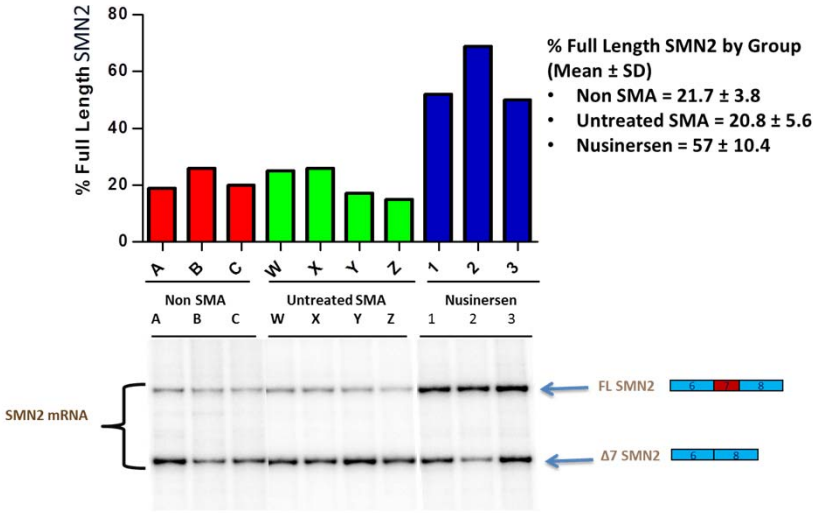
Nusinersen modulates splicing of the SMN2 pre-mRNA to increase full length SMN2 mRNA expression



Proof of Biology

Greater amount of full length SMN2 mRNA observed in infants treated in CS3A compared to untreated SMA infants

Semi-Quantitative RT-PCR Analysis of Thoracic Spinal Cord Segment Obtained from Autopsy



Chiriboga CA., et al. (2015)

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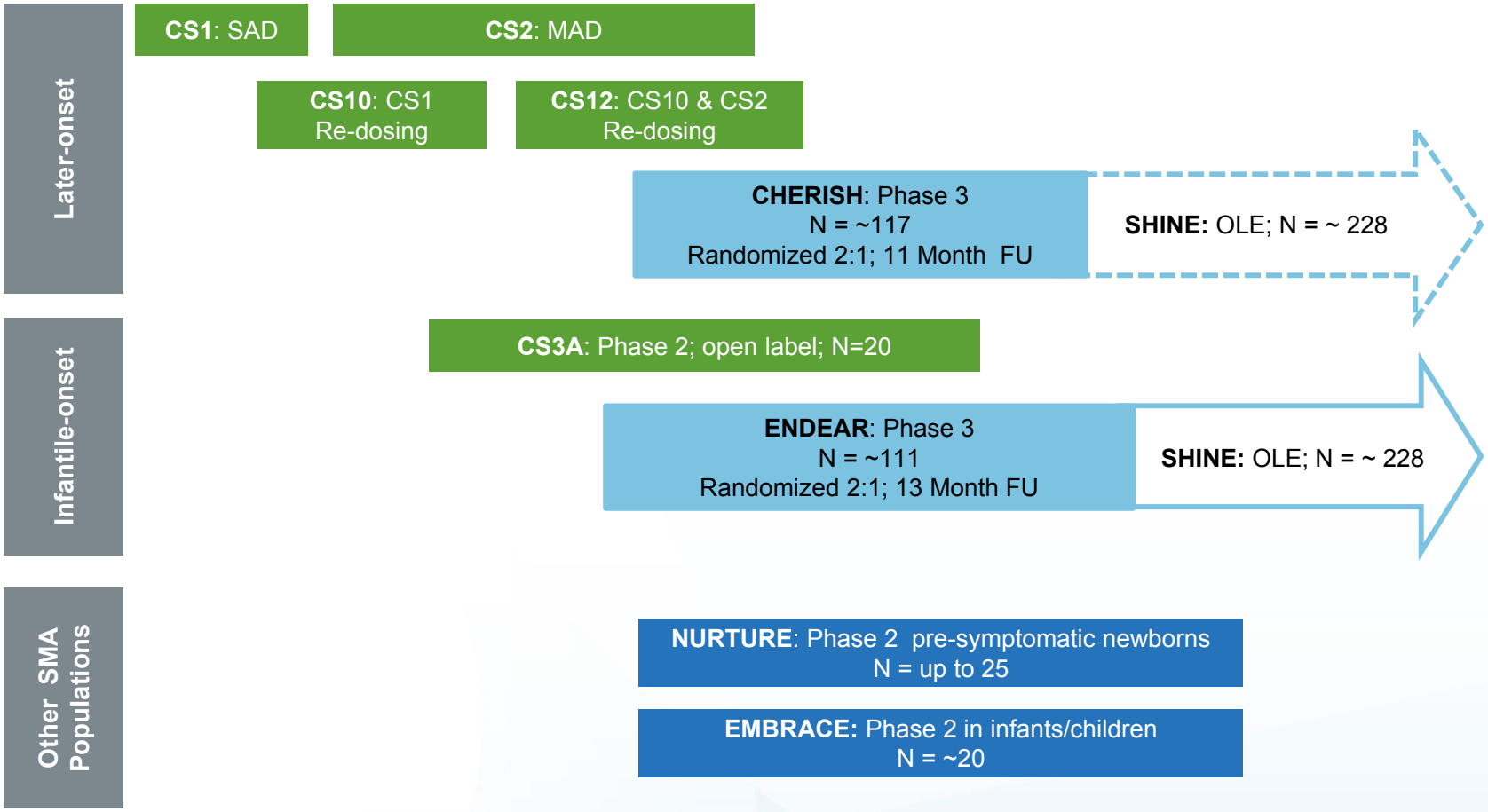
ISIS PHARMACEUTICALS

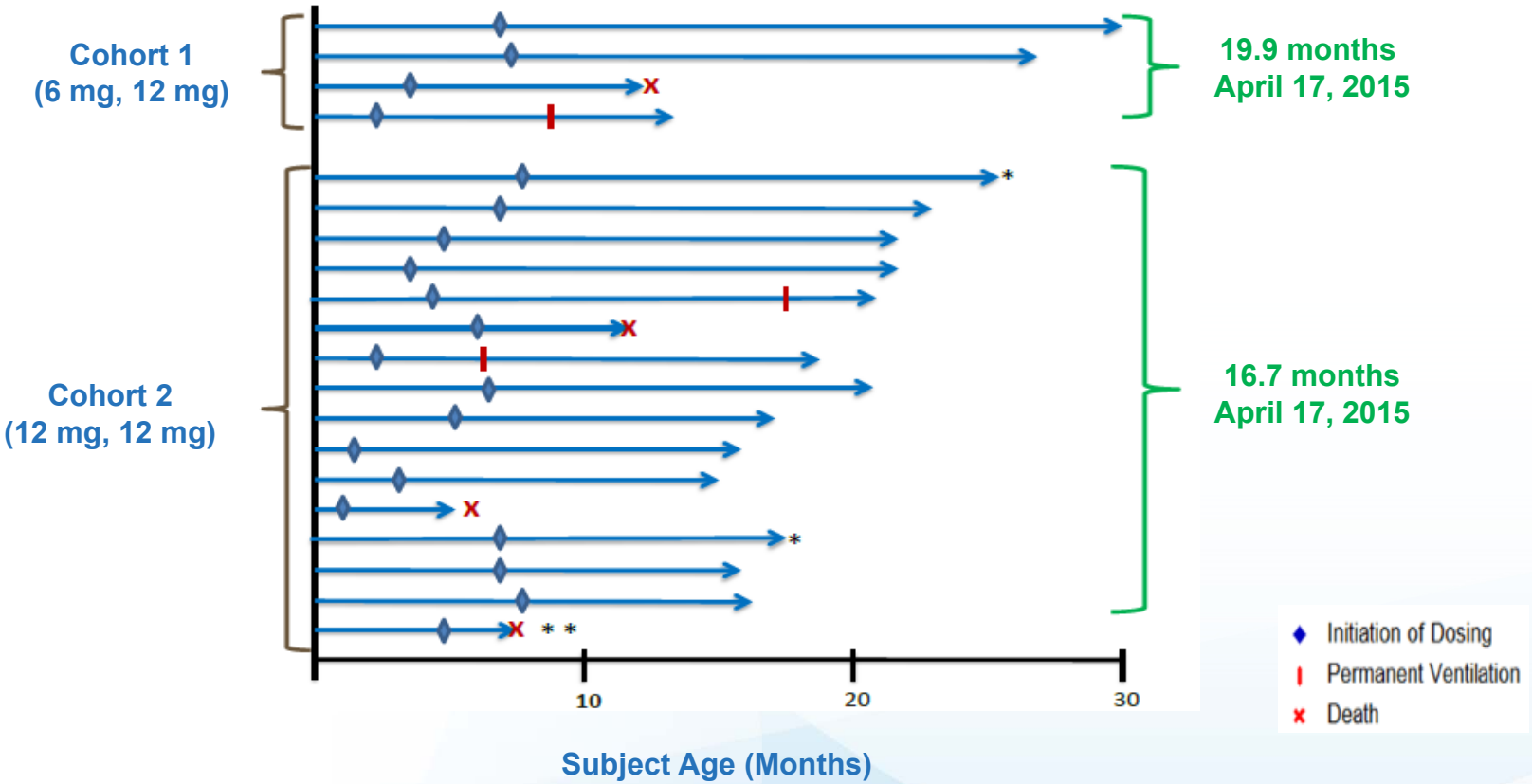
Two Phase 3 studies are ongoing



SAD = single ascending dose; MAD = multiple ascending dose; OLE = open-label extension.

Median event-free ages continues to be encouraging in open-label Phase 2 study

CS3A, Infantile-onset SMA



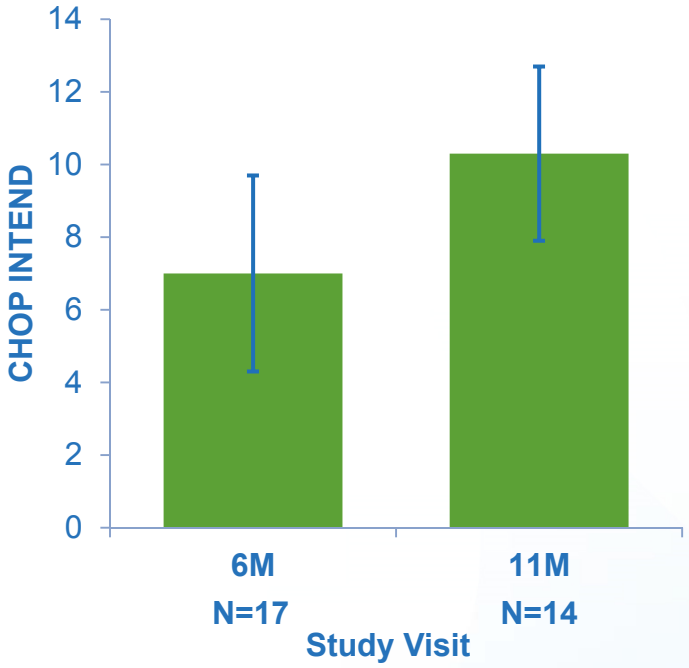
*SMN2 copy number of 3; **SMN2 copy number not known; all other infants have SMN2 copy number of 2

Muscle strength and motor function continue to improve in open-label Phase 2 study, as of April 17, 2015

CS3A, Infantile-onset SMA

Strength

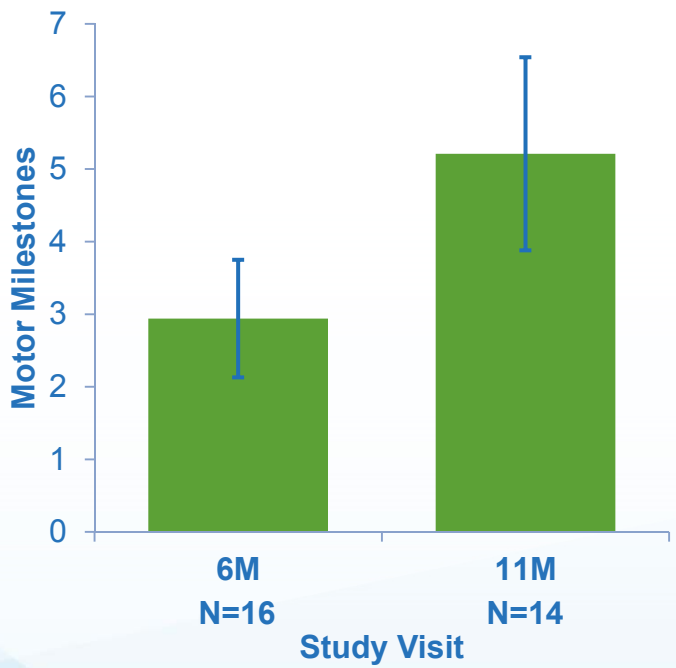
Mean change (± SEM) from baseline in CHOP INTEND



Patients typically decline 1.27 pts/yr of follow-up (Finkel R, et al, 2014)

Motor Function

Mean change (± SEM) from baseline in Motor Milestones



Patients typically do not gain multiple new motor milestones after symptom onset

Biogen

ISIS PHARMACEUTICALS

We are moving quickly

- Patients with SMA have urgent, high unmet medical needs
- Our top priority is to focus on the controlled Phase 3 trials to demonstrate Nusinersen is safe and effective
- We continue to engage in regular and productive discussions with health authorities in the US and across the EU to understand the most expeditious path forward for Nusinersen

Pictures provided by CureSMA

Biogen

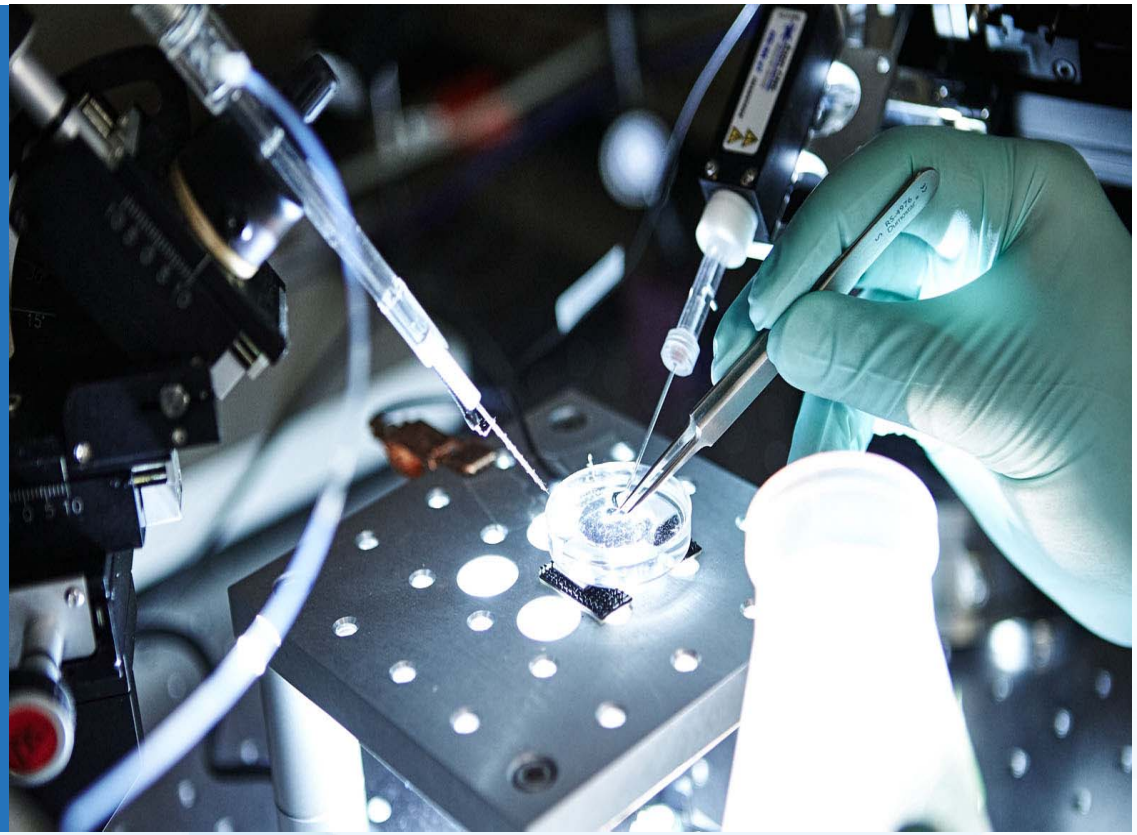
References

1. Lunn M, et al. (2008) “Spinal muscular atrophy.” Lancet **371**: 2120-2133.
2. Crawford TO, et al. (2012) “Evaluation of SMN Protein, Transcript, and Copy Number in the Biomarkers for Spinal Muscular Atrophy (BforSMA) Clinical Study.” PLoS ONE **7**(4): e33572. doi:10.1371/journal.pone.0033572
3. Lin CW, et al. (2015) “Delay in diagnosis of spinal muscular atrophy: a systemic literature review.” Pediatr Neurol **53**(4): 293-300.
4. Chiriboga CA., et al. (2015) Neurology, In Press.
5. Finkel, R., et al. (2014). “Observational study of spinal muscular atrophy type I and implications for clinical trials.” Neurology **83**:1-8.
6. Pictures provided by CureSMA

Biogen

MT-1303 for autoimmune diseases

Jeff Bornstein, MD
Senior Medical Director



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MT-1303: Biogen – MTPC agreement overview

- MT-1303 is a phase 3 ready sphingosine 1-phosphate 1 (S1P1)-specific functional antagonist
- Agreement to license worldwide rights (excluding Asia) to MT-1303
- Differentiated asset for indications in ulcerative colitis (UC), Crohn's Disease (CD), and possibly multiple sclerosis (MS)
  - Low first dose HR effect without need for titration
- Transaction with Mitsubishi Tanabe closed on October 30, 2015

Biogen

Large unmet need in inflammatory bowel disease (IBD)

- UC and CD are serious conditions associated with substantial health burden
  - Abdominal pain, diarrhea, rectal bleeding, weight loss, need for hospitalization
- Current treatments include anti-inflammatories (5-ASA, corticosteroids), immunosuppressants and biologics

Unmet need

- Option for patients who are intolerant to or refractory to anti-TNF therapy
  - Onset of IBD is in teens and 20s
  - Anti-TNF remission rates after 1 year of therapy ~20%
  - Vedolizumab (SC) addresses a small % of anti-TNF inadequate responders
- Safe, oral therapy for long term maintenance of remission
  - Injectable biologic therapies (anti-TNFs, anti-integrins) and emerging oral agent (Tofa) associated with opportunistic infection and malignancy concerns

Opportunity

- Moderate-to-severe segment estimated to be:
  - UC: ~300K US/ 230K EU[1]
  - CD: ~370K US/ 240K EU[1]

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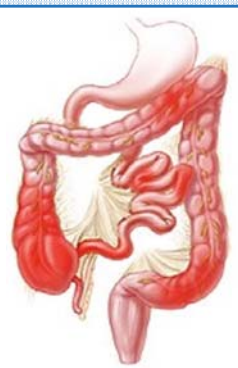
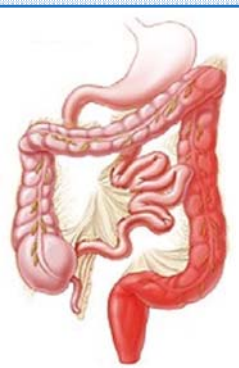
[1] Decision Resources, 2015 and Biogen market research

Inflammatory Bowel Disease (IBD)

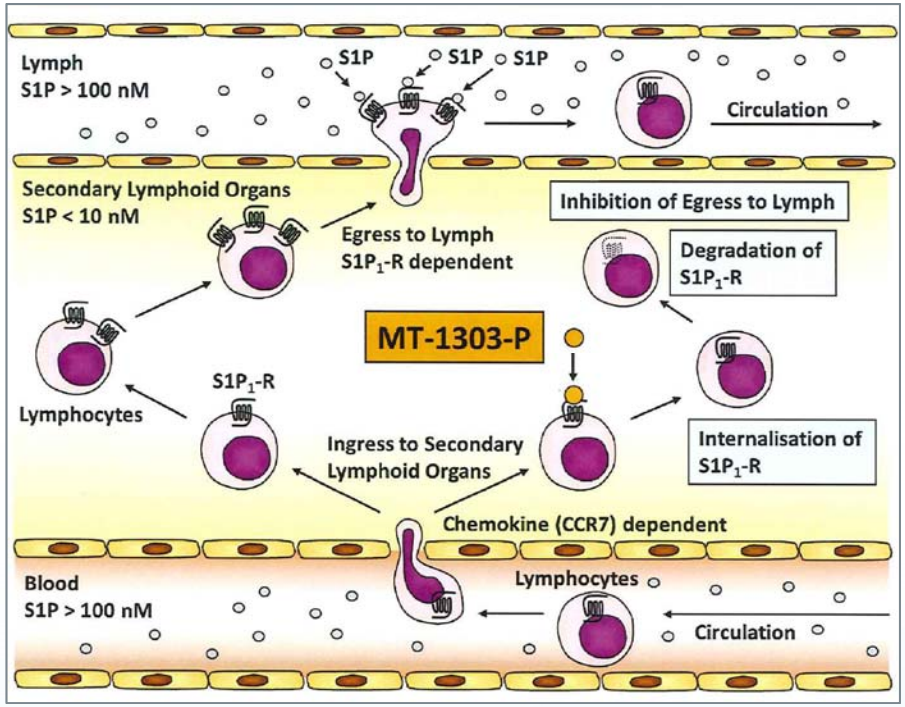




Crohn's Disease	Ulcerative Colitis
Inflammation of the GI Tract	Inflammation of the colon
Transmural inflammation	Inflammation limited to mucosa
Patchy distribution	Continuous distribution
Can occur anywhere from mouth to anus	Limited to colon and rectum
Typically spares the rectum	Rectum always involved
Complications include strictures, fistulae and abscesses	Significantly increases the risk of colon cancer

MT-1303: A functional antagonist of the S1P1 receptor

- Activated T lymphocytes drive inflammation in IBD. Egress of lymphocytes from lymphoid organs is mediated by sphingosine phosphate binding to S1P1 receptors.
- MT-1303-p binds the S1P1-R leading to
  - Receptor internalization
  - Reduced lymphocyte egress from secondary lymphoid organs
  - Attenuated lymphocyte-mediated inflammation
- Therapeutic potential in IBD supported by observations with
  - Ozanimod (S1P1-R)
  - Vedolizumab ($\alpha 4\beta 7$)
  - Natalizumab ($\alpha 4\beta 1/7$)



Chalfant. J Cell Sci 2005;118:4605
Chiba. AIMS Mol Sci 2014;1(4):162
Chiba. Folia Pharmacol. Jpn 2013 139;265
Rosen, Ann Rev Biochem 2013 82;23.1

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Potential best in class molecule

- No CV effects in pre-clinical safety studies
- Improved specificity: no effect on S1P3 receptor
- Less potent activator of GiRK channels
- Lower concentrations in cardiac tissue
- Slower conversion to active metabolite

	Fingolimod-p*	Ozanimod*	MT-1303-p*
Pre-clinical Safety Findings	HR ↓(monkey, rat) BP ↑ (dog)	Pre-clinical HR and BP effects not reported	No CV changes observed in any species
Receptor Specificity	S1P1,3,4,5	S1P1,5	S1P1,4,5
S1P1 EC50 (nM)	0.09	0.16	0.08
S1P2 EC50 (nM)	>1000	>10,000	> 10,000
S1P3 EC50 (nM)	5.1	>10,000	>10,000
GiRK Channel EC50 (nM)	8.5	Multiple active metabolites	41.6
Tmax (human)	8 hrs (0.5 mg)		12 hrs (0.5 mg)
Heart:plasma ratio @ Cmax (rats)	↑ (Relative to MT-1303)		↓ (Relative to fingolimod)

* Not comparative head-to-head studies.

MTPC ECTRIMS, 2015

Recepetos, DDW 2012

Fingolimod Clin. Pharm. and Biopharm.Review, FDA

Biogen

MT-1303 has demonstrated Phase 2 efficacy and lymphocyte reduction in relapsing MS comparable to ozanimod Phase 2 and Gilenya Phase 3

MTPC "MOMENTUM" study

- Randomized, double-blind, placebo-controlled study
- PBO, MT-1303 0.1 mg, 0.2 mg, 0.4 mg N= ~100/arm
- 1° endpoint: Gd+ lesions on MRI 8-24 weeks

Assessment	MT-1303*			Ozanimod*		Gilenya*
	0.1 mg	0.2 mg	0.4 mg	0.5 mg	1 mg	0.5 mg
Reduction in cumulative Gd+ T1 lesions	47%	61%	77%	86%	86%	81%
Lymphocyte count reduction	40%	59%	68%	~50%	~60%	73%
Reduction in ARR	17%[1,2]	1%[1,2]	82%[1]	31%[2]	53%[2]	54%

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* Not comparative head-to-head studies.
[1] Individual relapse rate (total relapses/days of follow-up)
[2] Not significant

Kappos et al., ECTRIMS 2015
Kappos et al., NEJM 2010
Receptos ECTRIMS 2014

Phase 2 results demonstrate acceptable safety profile

No dose- dependent trends observed in incidence of TEAEs

System Organ Class (SOC)	Placebo N=103 n (%)	MT-1303 0.1 mg N=105 n (%)	MT-1303 0.2 mg N=103 n (%)	MT-1303 0.4 mg N=104 n (%)	Overall N=415 n (%)
Subjects with ≥1 TEAEs	66 (64.1)	59 (56.2)	69 (67.0)	58 (55.8)	252 (60.7)
Total Number of TEAEs	194	223	204	229	850
TEAE with Incidence of > 5%					
Infections and Infestations	**26 (25.2)**	**28 (26.7)**	**33 (32.0)**	**28 (26.9)**	**115 (27.7)**
Nervous System Disorders	22 (21.4)	23 (21.9)	17 (16.5)	20 (19.2)	82 (19.8)
Investigations	10 (9.7)	8 (7.6)	14 (13.6)	15 (14.4)	47 (11.3)
Gastrointestinal Disorders	12 (11.7)	14 (13.3)	5 (4.9)	12 (11.5)	43 (10.4)
Musculoskeletal and Connective Tissue Disorders	11 (10.7)	8 (7.6)	9 (8.7)	9 (8.7)	37 (8.9)
General Disorders and Administration Site Conditions	4 (3.9)	13 (12.4)	14 (13.6)	6 (5.8)	37 (8.9)
Cardiac Disorders	4 (3.9)	8 (7.6)	6 (5.8)	5 (4.8)	23 (5.5)
Skin and Subcutaneous Tissue Disorders	3 (2.9)	6 (5.7)	7 (6.8)	7 (6.7)	23 (5.5)
Psychiatric Disorders	4 (3.9)	5 (4.8)	10 (9.7)	2 (1.9)	21 (5.1)

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Treatment Emergent Adverse Events (TEAEs) are coded using the MedDRA coding dictionary, Version 17.0.

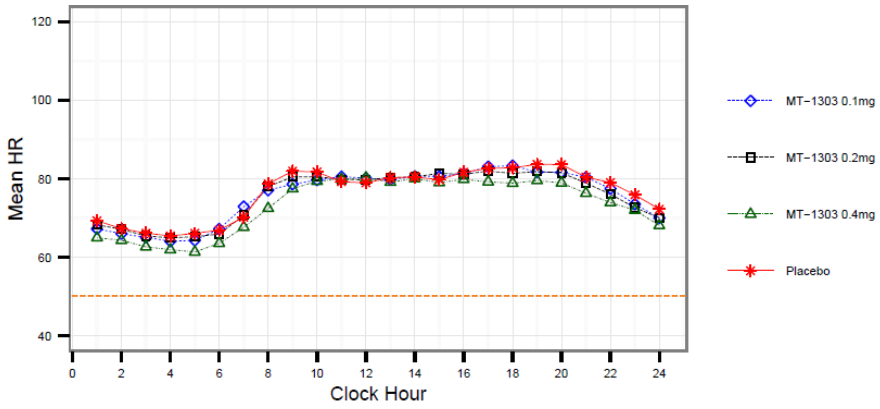
Kappos, et al, ECTRIMS, 2015

MT-1303 E04 phase 2 Study in RRMS: Heart rate findings and monitoring outcomes

Without titration, MT-1303 showed

- No heart rate effect on 12-lead ECG post first dose
- Outcomes of monitoring with MT-1303 no different from PBO
- Differentiated from dose-related findings reported with fingolimod

Day 1



Treatment	Subjects Discharged from Clinic at 6 hours			
MT-1303 (MOMENTUM)	Placebo N=103	MT-1303 0.1 mg N=105	MT-1303 0.2 mg N=103	MT-1303 0.4 mg N=104
	92 (89.3%)	93 (88.6%)	92 (89.3%)	94 (90.4%)
Fingolimod (Phase 3)	Placebo N=773	IFN N=431	Fingolimod 0.5 mg N=1212	Fingolimod 1.25 mg N=1219
	703 (90.9%)	422 (97.9%)	1006 (83.0%)	944 (77.4%)

Biogen

MT-1304 MOMENTUM Study data provided by MTPC, Kappos, et al, ECTRIMS, 2015, DiMarco JP. Mult Scler Relat Disord. 2014; 3: 629

Next steps in ulcerative colitis and Crohn's disease

- Anticipate two Phase 3 studies for each indication:
  - Placebo-controlled 10 week induction study, 1° endpoint = proportion with clinical response
  - Placebo-controlled maintenance study, 1° endpoint = proportion with clinical remission at 52 weeks
- Patients with moderate-severe disease with inadequate response to conventional therapy (including anti-TNFs, immunomodulators and corticosteroids)
- FPI anticipated in H2 2016

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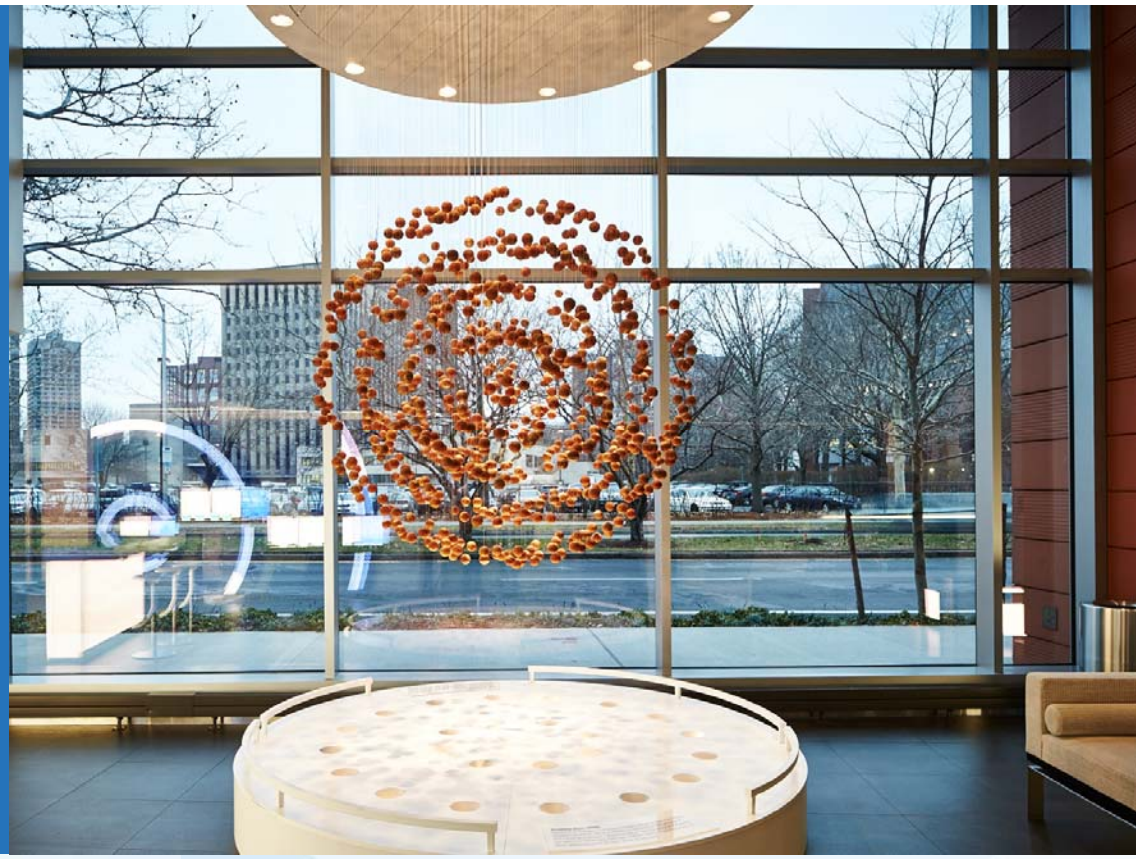
Biogen 2015 R&D Day

Q&A



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Track 1

BIIB054 for Parkinson's disease

Amyotrophic lateral sclerosis development

Gene therapy & gene editing

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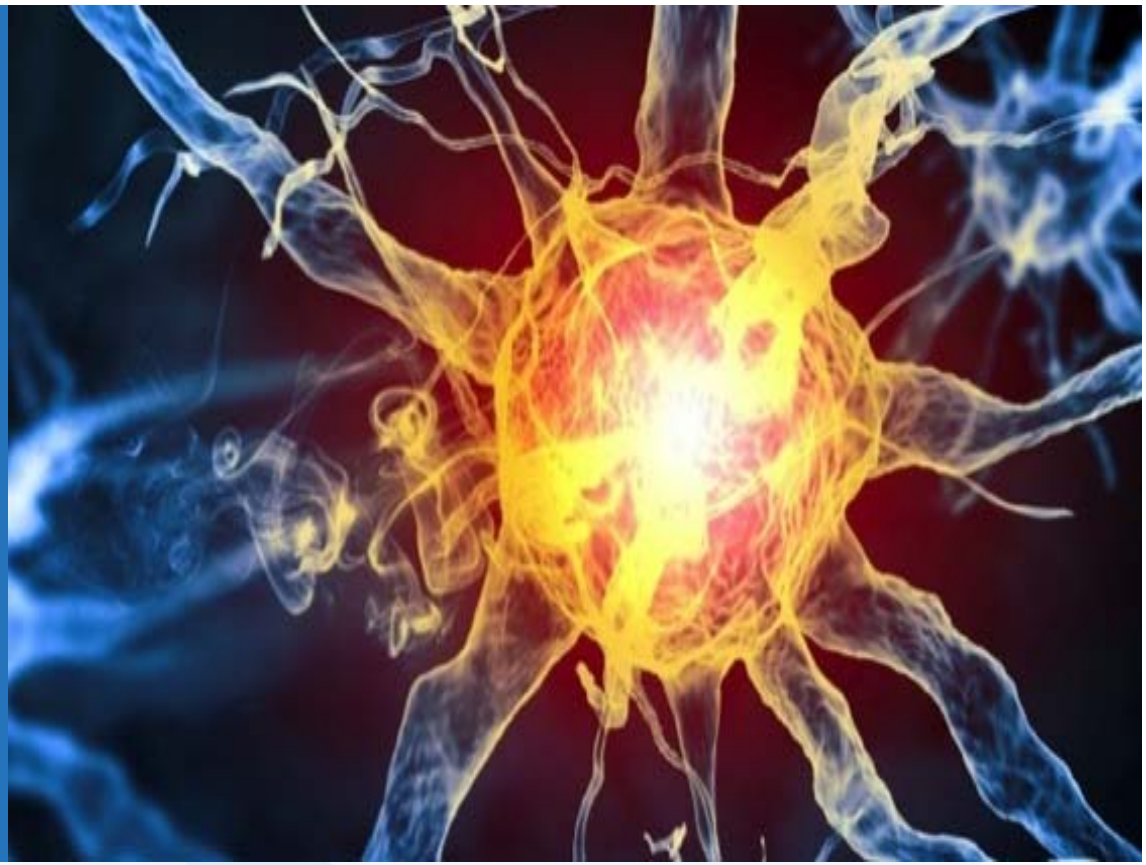
BIIB054 for Parkinson's disease (PD)

Jesse Cedarbaum, MD
VP Clinical Development



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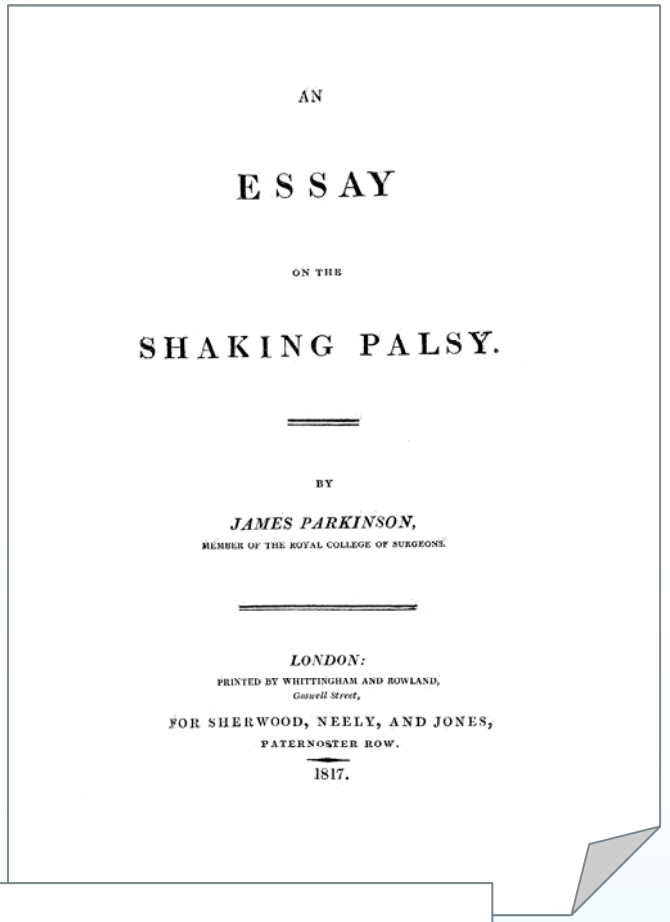
Parkinson's disease is the second most common neurodegenerative disease

- Cardinal Symptoms: ***resting tremor, muscular rigidity, bradykinesia, and postural instability***
- Motor symptoms are due to loss of dopamine neurons in the brain
- Non-motor manifestations (low blood pressure, constipation, incontinence), sensory problems, sleep disorders and neuropsychiatric problems and dementia. Largely non-dopaminergic in origin.
- Significant caregiver burden
- Average age at onset is in the late 50s to early 60s
- ~1 Million patients in US, perhaps 7 million worldwide



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

"Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured."

Biogen

Sources: Lees A, Neurology in Practice 2010, 240-246; Wirdefeldt K et al, Eur J Epidemiol 2011, S1-S58; Decision Resources 2013

Progressive clinical evolution in PD: motor, cognitive and behavioral impairment

Hoehn & Yahr Stage

1	2	3	4	5
Pre-Motor	**Early PD**	**Moderate-Advanced PD**		

- ***May begin 10-15 years prior to diagnosis***
- ***Symptoms non-specific and do not resemble classical PD symptoms***
- Hyposmia
- REM Sleep Disturbance
- Autonomic Dysfunction
  - Constipation/GI Sx
  - Urinary symptoms
  - Loss of R-wave variability
- ***Motor signs subtle or absent***

Unilateral involvement, mask-like face

Resting tremor

Difficulty with simple manual tasks

- Symptoms inconvenient but not disabling
- Often tolerable without treatment or respond well to early lines of treatment (one medicine)
- ***Levodopa naïve; Treatment Begins***

Bilateral involvement, slow shuffling gait

Pronounced gait and posture disturbance, falls

- Ranging from minimal disability to generalized, moderately severe dysfunction
- Significant slowing of movement
- Impairment of equilibrium develops
- Levodopa is initiated
- ***Motor related (levodopa related) complications develop with prolonged use of levodopa***

Limited ambulation with assistance disturbance, falls

Bed or chair confinement

- Profound motor symptoms
- Severe dyskinesia, significant off-time
- ***Significant cognitive decline and psychosis***

60 — 65 — 70 — 75

Age

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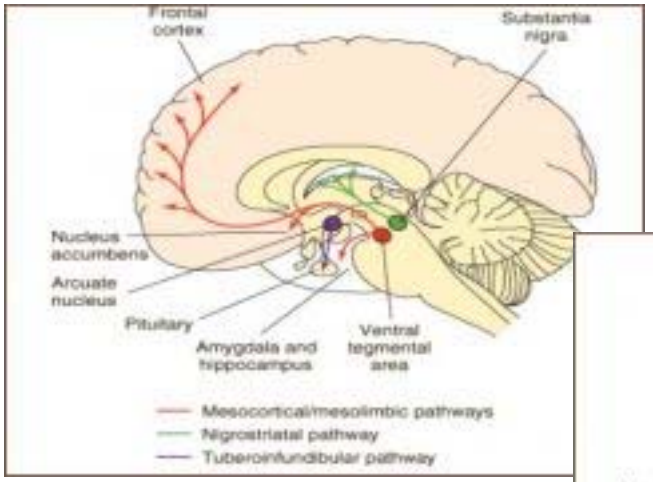
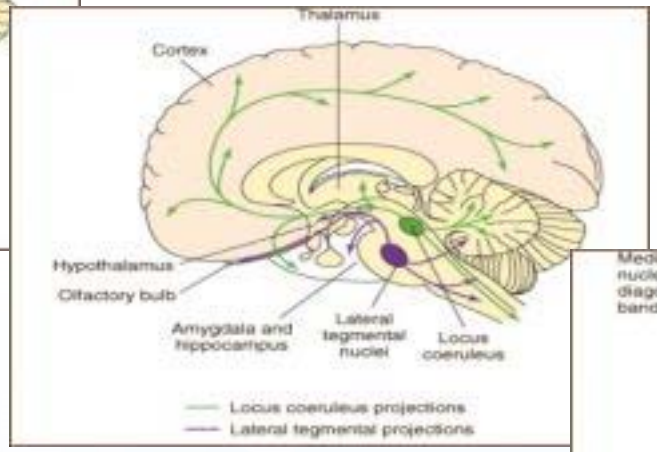
Parkinson's disease attacks multiple neuronal systems in the brain

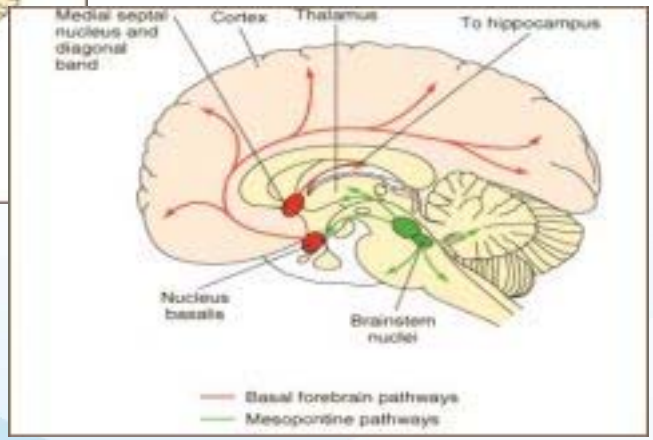
Dopamine



Norepinephrine



Acetylcholine



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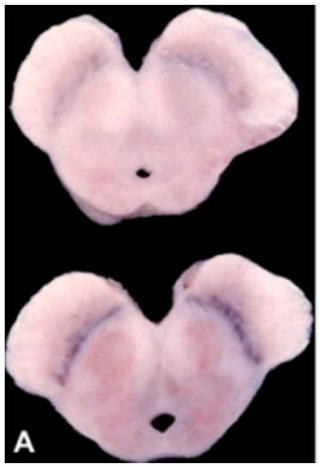
α-Synuclein as a therapeutic target

Motor symptoms due to degeneration of dopamine-containing neurons in the Substantia Nigra

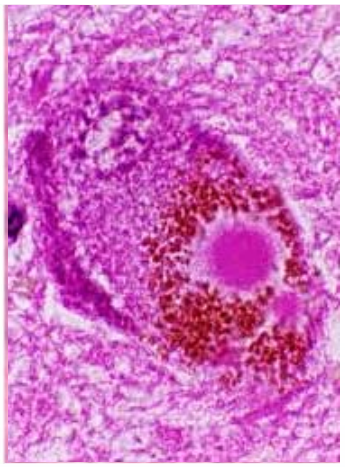
- Degenerating dopamine neurons contain Lewy body inclusions

α-Synuclein (α-syn) is major component of Lewy bodies and Lewy neurites

- Role in synaptic function in the brain
- Mutations associated with familial forms of PD
- Gene duplication / triplication sufficient to cause PD
- Overexpression in cell culture and mice mimics important aspects of pathology
- Injection of α-syn aggregates into animal brains causes pathological changes resembling PD



Loss of dopamine-containing neurons in Substantia Nigra



Lewy Body in Substantia Nigra of a PD patient

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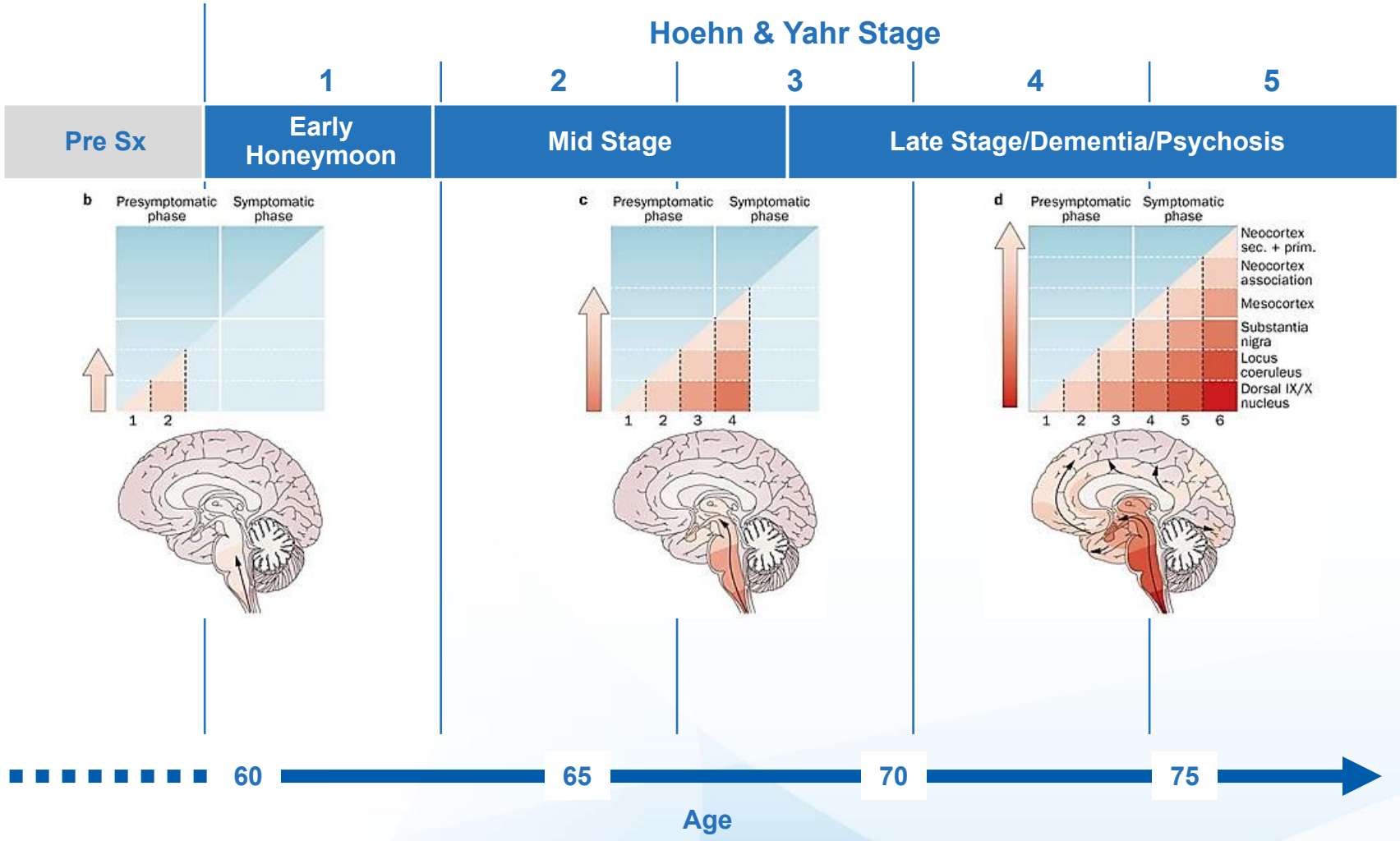
Braak staging of the spread of synuclein pathology in the PD CNS



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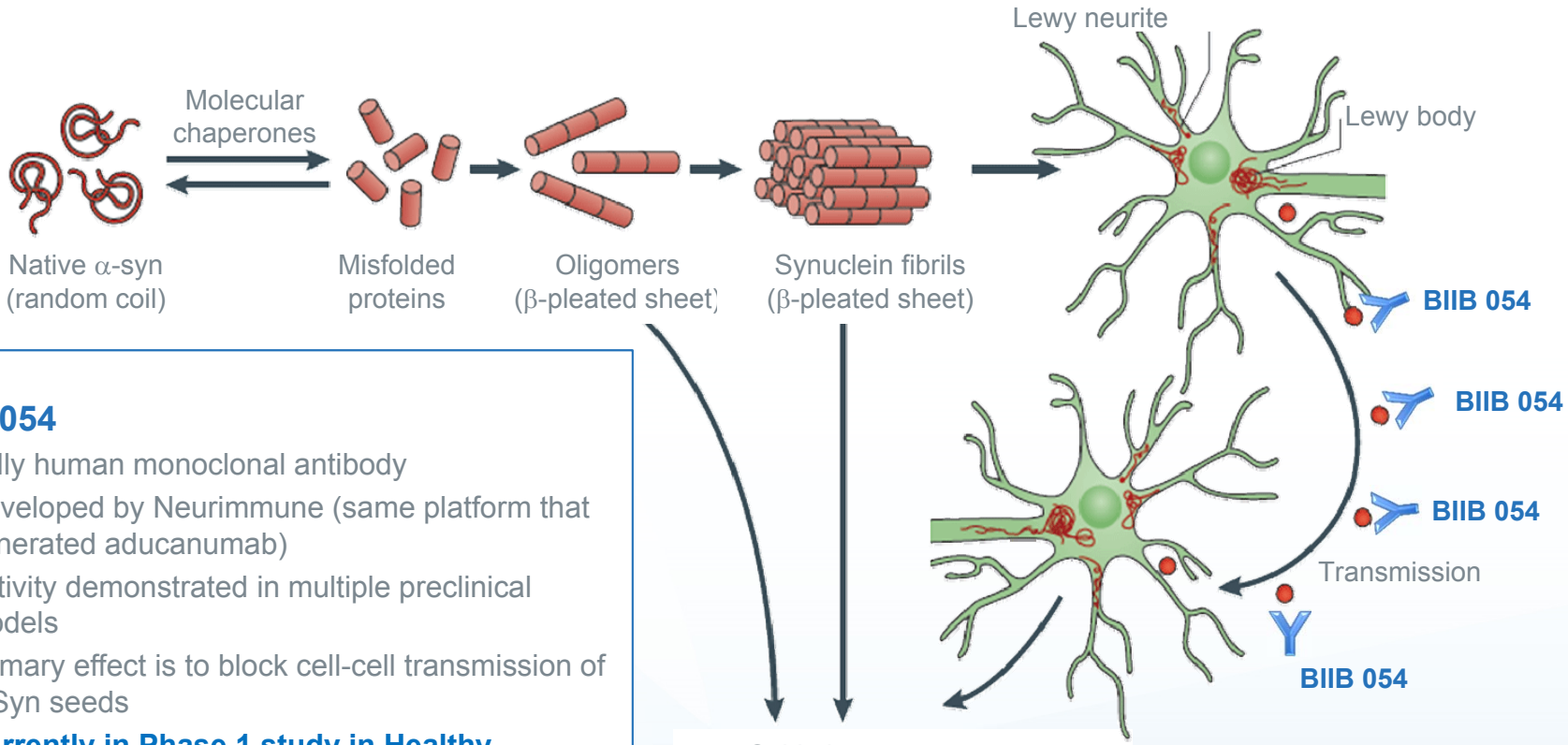
Modified after Goedert M, et al. Nat Rev Neuro. 2013

BIIB 054: Targeting α-synuclein pathology in PD

Goal: Target and seek to reduce the build up of α-synuclein and prevent its spread in the brain



BIIB054

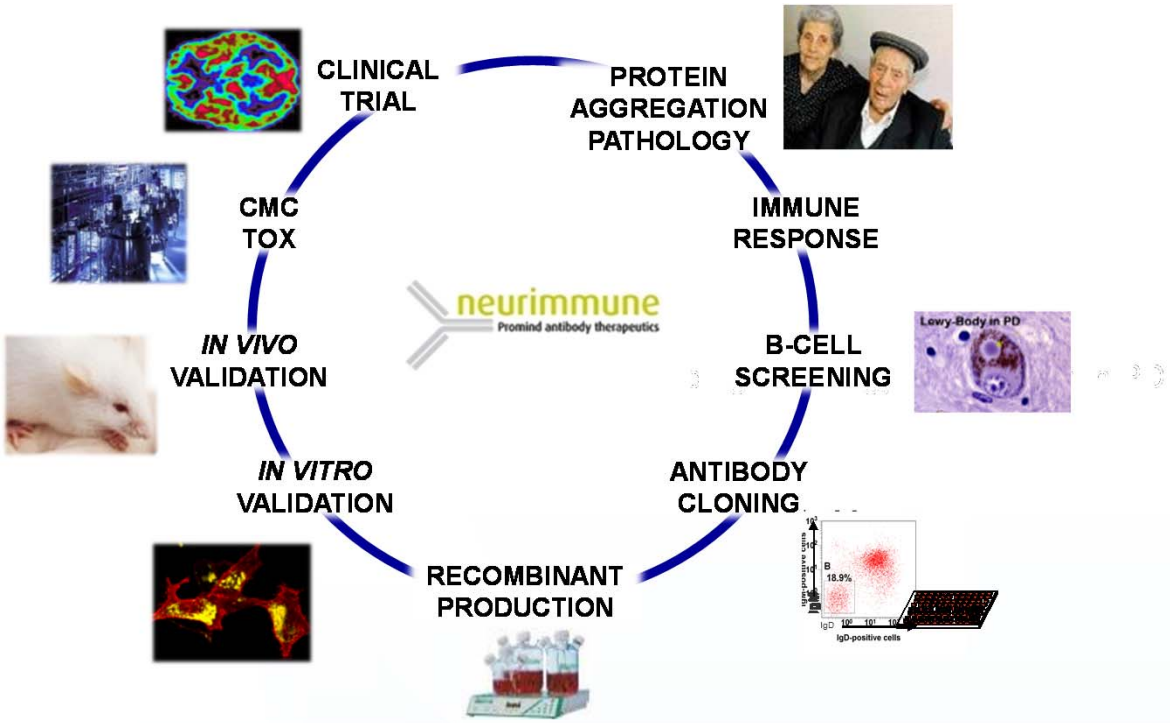
- Fully human monoclonal antibody
- Developed by Neurimmune (same platform that generated aducanumab)
- Activity demonstrated in multiple preclinical models
- Primary effect is to block cell-cell transmission of α-Syn seeds
- **Currently in Phase 1 study in Healthy Volunteer Subjects**

- Oxidative stress
- Protein sequestration
- Disruption of axonal transport
- Synaptic dysfunction
- Inhibition of UPS
- Mitochondrial dysfunction

Biogen

Modified after Irwin DJ, et al. Nat Rev Neuro. 2013

BIIB054 is a fully human antibody derived from Neurimmune's Reverse Translational Medicine (RTM) technology platform



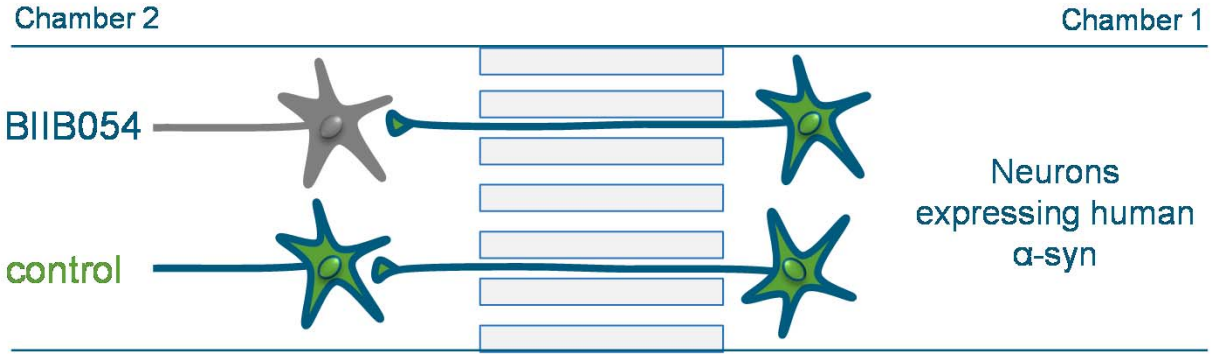
Neurimmune Antibodies in BIIB pipeline

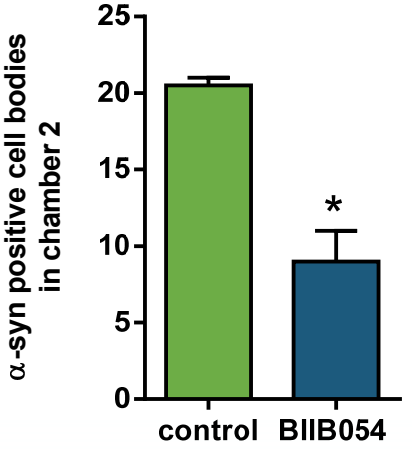
Aducanumab (Aβ)	Phase III in 2015
BIIB054	Phase I in 2015
Tau	Research

Biogen

Anti-synuclein antibody attenuates spread of α-synuclein pathology *in vitro* neurons and mouse models

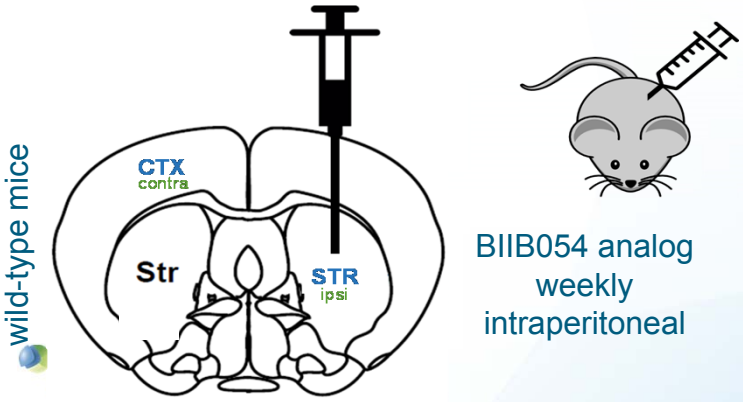
BIIB054 reduces spreading of α-synuclein in cultured neurons (microfluidic system)



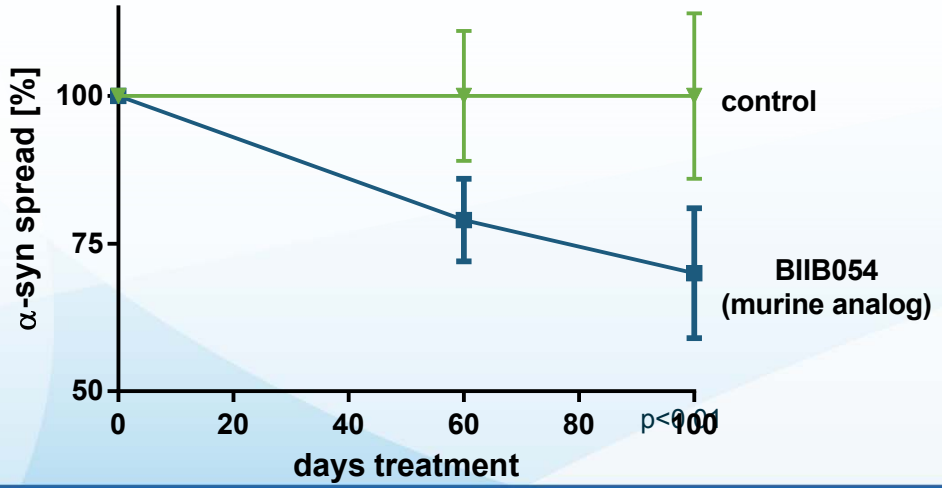


BIIB054 reduces spreading of α-synuclein in preformed fibril inoculation mouse model

Preformed α-synuclein fibrils



BIIB054 analog
weekly
intraperitoneal



Biogen data on file

AD and PD: Similarities and differences

	AD	PD
Pathological		
Aggregating Proteins	Ab, Tau >> Synuclein	Synuclein>> Abeta & Tau
Brain Pathology	Cortical > Subcortical	Subcortical > Cortical
Clinical		
Symptomatic Rx	Modest	Effective early => complications, loss of effectiveness
Prodromal Syndrome	Well-characterized; early manifestations similar to later disease	Poorly characterized; non-specific symptoms
Imaging Biomarkers	Amyloid & Tau PET	No αSyn PET yet; rely on indirect measures

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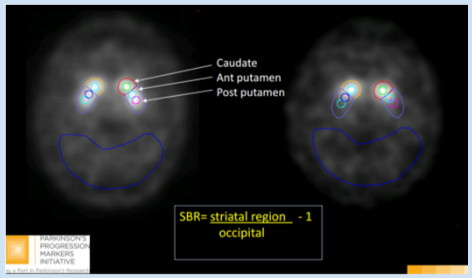
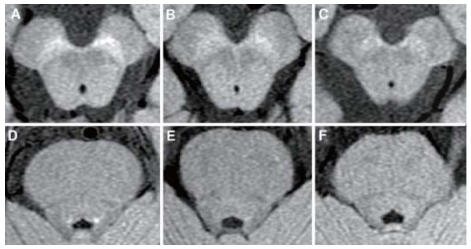
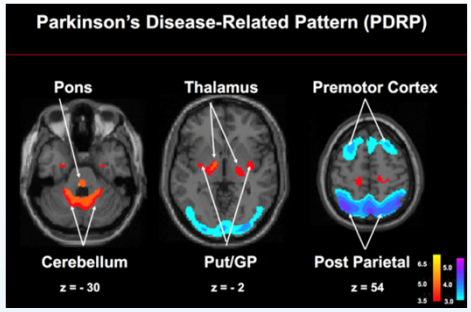
PD brain imaging: Potential biomarkers for trials

Modality	Visualizes	Example
Dopamine Transporter SPECT (DatScan)	**Nerve terminals of dopamine neurons in basal ganglia**	
Neuromelanin MRI imaging	Brain volumes occupied by cell bodies of dopaminergic and noradrenergic neurons that degenerate in PD	
PD-related Brain Metabolic Patterns using FDG	Pattern of brain metabolism related to loss of function and cognition in PD	

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Neuromelanin Imaging: Nakamura et al., Neural Regeneration Research 2014
PDRP: Huang et al, Brain 2007

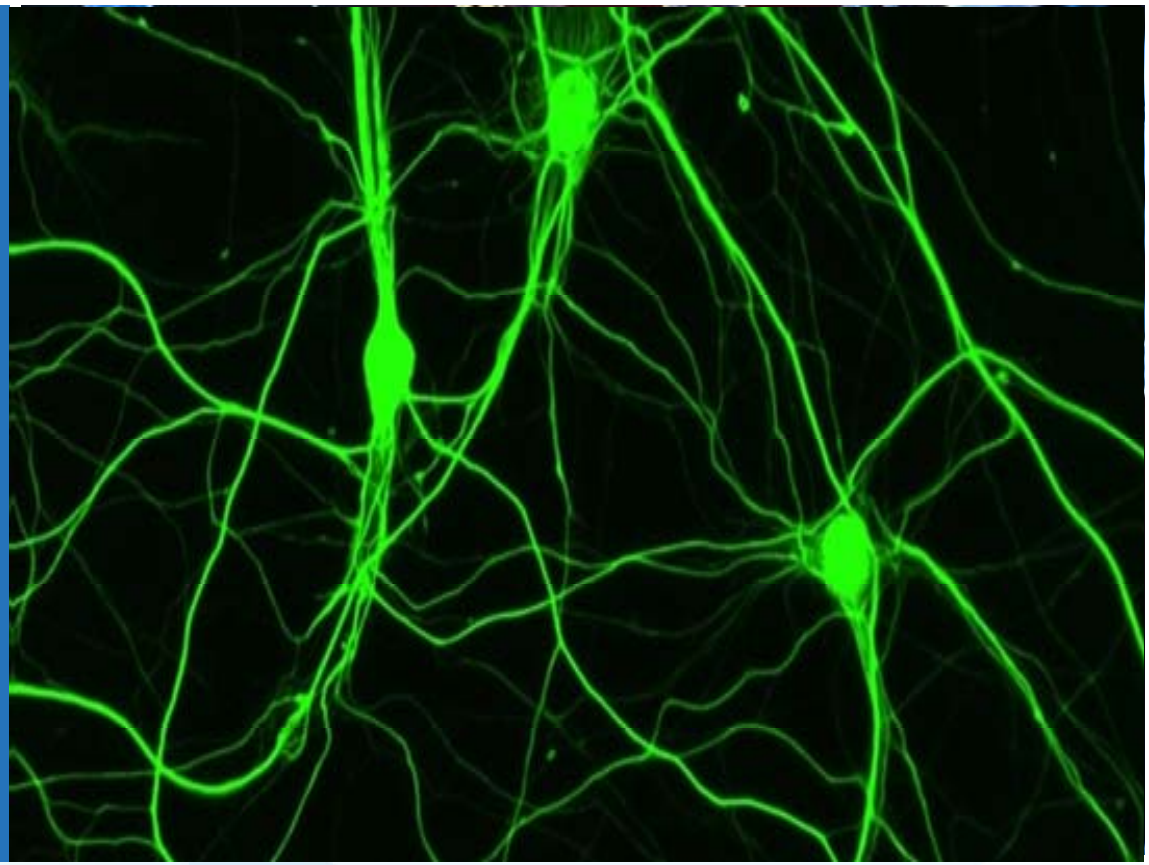
Summary and next steps

- PD constitutes an exciting new therapeutic area for Biogen
- BIIB 054 (Anti-Synuclein Antibody) in Phase 1 trials
  - SAD in healthy volunteers underway
  - Next study in patients projected for 2016
- Disease biology is increasingly understood – active discovery research ongoing

Biogen

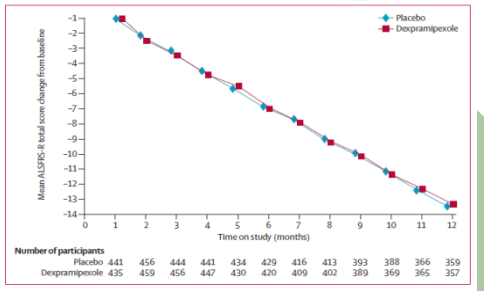
Amyotrophic lateral sclerosis (ALS) development

Donald R. Johns, MD
VP Clinical Development



Biogen

Biogen is uniquely positioned to discover and develop treatments for ALS



Cudkowicz et al., 2013

- EMPOWER study
- Develop novel end-points

Clinical know-how

Motivation

Emerging science

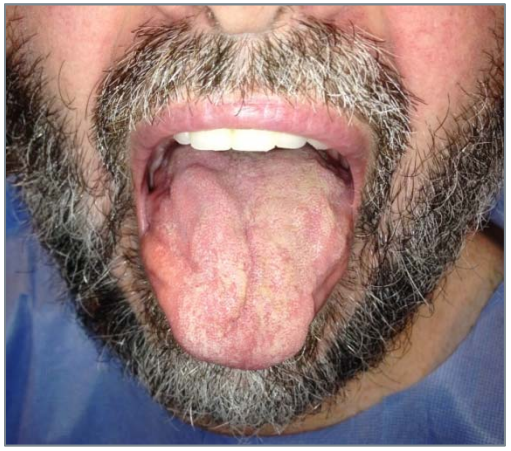
- Profound unmet medical need

- Human genetic advances
- Rich supply of targets
- Multiple ALS models

Biogen

ALS: Profound unmet medical need

- ***Fatal:*** death typically within 2-5 years
  - Similar to deadly forms of cancer (ovarian, lung)
- ***Progressive muscle weakness***: leads to respiratory failure & death
- ***Orphan disease:*** 12k-30k U.S. patients (~350K worldwide)
  - 1/400 people will be diagnosed with ALS over course of a lifetime
  - Incidence ~40% of Multiple Sclerosis
- ***One FDA-approved medicine:*** (Riluzole®)
  - Only extends life by 2-3 months
- ***>50 failed ALS randomized controlled clinical trials[1]***



Courtesy S. Han

Biogen

1(Mitsumoto H, et al, Lancet Neurology 2014)

Biogen is advancing ALS drug development

Reasons for prior study failures

- Target unknown or not validated
- Heterogeneous patient population
- Lack of mechanistic biomarkers
- Underpowered Phase 2 studies
- Insensitive measures (ALS-Functional Rating Scale & death)

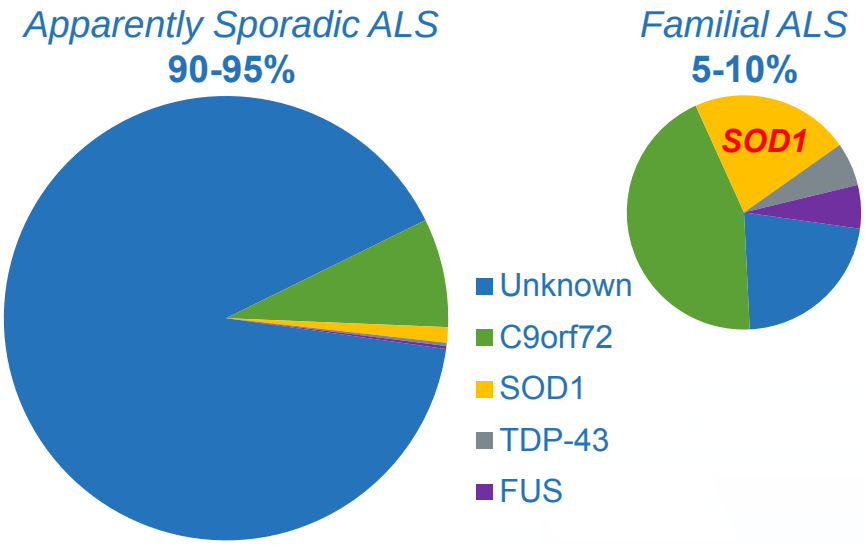
Biogen's approach

- Pursuing validated, genetically identified targets
- Data mining dexpramipexole Phase III Study (n=943) to identify improved endpoints
- Biogen methodology study to validate novel endpoints

Biogen

ALS genetics guides target selection and clinical study populations

Genetics of ALS[1]



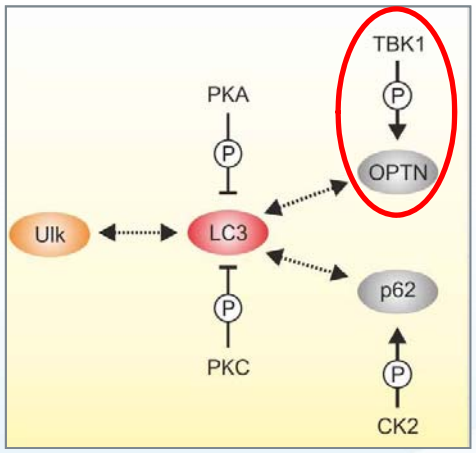
- ALS genetics is rapidly advancing
- Superoxide dismutase (SOD1) and C9orf72 = most common causes of familial ALS

New ALS Gene[2]

Whole exome sequencing (Biogen ALS Sequencing Consortium) identifies new ALS gene:

TBK1 (TANK binding kinase 1)

Autophagy[3]



[1] Turner et al., 2013.
[2] Cirulli et al. Science 2015.
[3] Stork et al., 2012.

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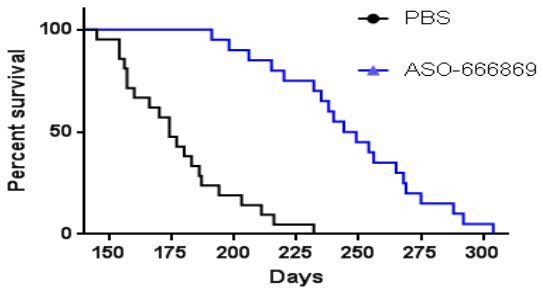
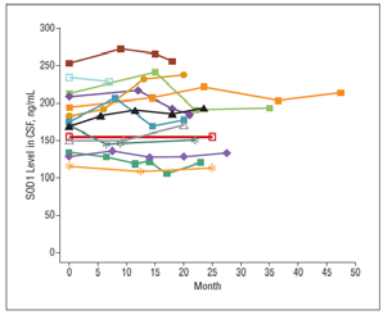
SOD1: Rational first therapeutic target for ALS

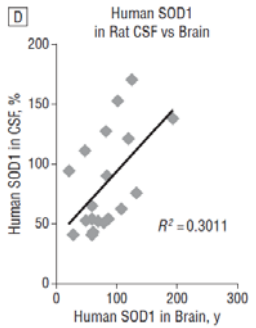
- ***Validated Target:*** SOD1 = 1st identified human genetic cause of ALS[1]
- ***Robust preclinical data*** with SOD1 Antisense Oligonucleotides[2]
  - ASOs target SOD1 protein by binding and destroying SOD1 mRNA[3]
- ***Homogeneous population:*** all with genetically confirmed SOD1 ALS
- ***Mechanistic Biomarker:*** ↓ SOD1 levels in cerebrospinal fluid allow rapid determination of Proof-of-Biology
- ***Phase 1 expected to start in 2016***

Survival in SOD1-G93A[4]



CSF SOD1 levels vary little over time in man





Tissue SOD1 levels correlate with CSF levels

Winer et al., 2013

[1] Rosen et al., 1993.
[2] ASOs.
[3] Smith et al., 2006.
[4] BIIB data

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ISIS PHARMACEUTICALS

Need better endpoints for ALS clinical trials

- Sensitive & specific to track disease progression
  - Detect changes in shorter time period (< 6-12 months)
  - Require fewer patients (n = < 100/arm)
  - Clinically meaningful
  - Predictive of FDA accepted endpoints (ALSFRS, survival)
- Robust operational characteristics
  - Objective, standardized, feasible
  - Reliable & reproducible

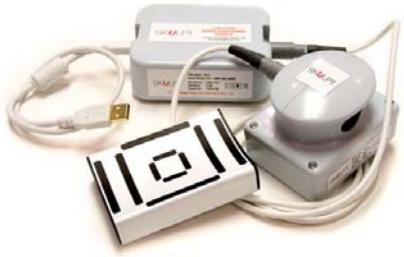
Biogen

Biogen methodology study: identify sensitive measures of disease progression

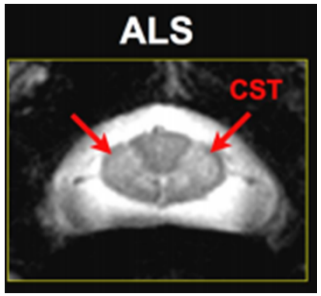
Longitudinal head-to-head comparison of measures for future proof-of-concept (POC) studies:

- Strength (Hand Held Dynamometry)
- Electrophysiology (EIM)
- Spinal cord imaging (MRI, DTI)

HHD



EIM



Cohen-Adad et al., 2012

MRI = Magnetic Resonance Imaging, DTI = Diffusion Tensor Imaging, CST = Corticospinal Tract
HHD= Hand Held Dynamometry
EIM= Electrical Impedenace Myography

Biogen

ALS Clinical Trials, Then and Now

Assumption(s)	Previous Clinical Trials	Improved PoC
Population	Sporadic ALS Patients	Familial & Sporadic ALS Patients (select subpopulations)
Sample Size	*Fully powered N=440 (n=220/arm)	n=160 (n=80/arm)
Outcome measure	ALSFRS-R Survival	Novel measure
Treatment Period	12 months	6 months
Biomarker	Rarely done	Target engagement required for dose selection
Cost	5X	1X
Note	*Phase II Trials ~always underpowered (required size/cost) More than 50 failed trials (RCTs)#	Positive Proof-of-Biology Required to trigger Phase III

Biogen

#Clinical trials in amyotrophic lateral sclerosis: why so many negative trials and how can trials be improved? Mitsumoto H[1], Brooks BR[2], Silani V[3]. Lancet Neurology 2014

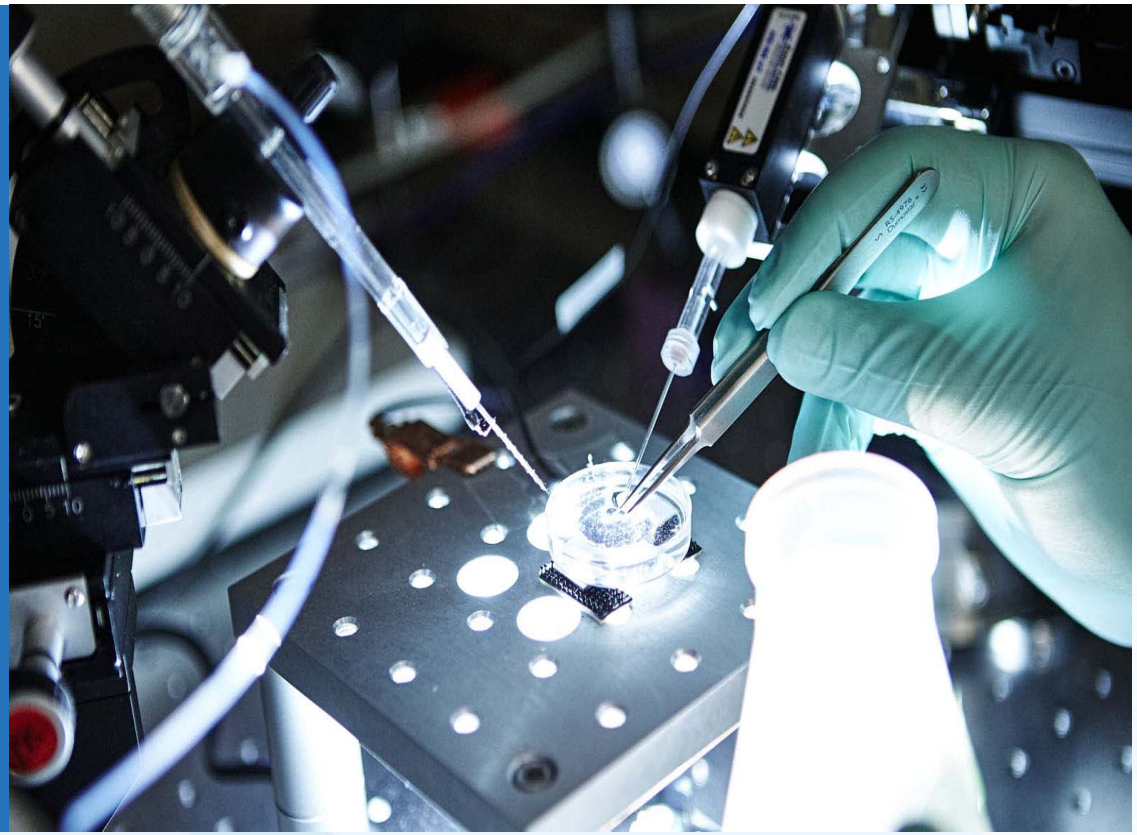
Biogen's integrated approach to ALS

- Aided by genetics, redefine ALS in ***actionable molecular pathophysiologic terms***
  - Validated targets, in causal biological pathways
  - New therapeutic approaches to accelerate path: gene → drug (e.g. ASO)
- Integrated research-development efforts focus on efficient early phase ALS trials: Gateway to Phase III
  - Validated targets and target engagement biomarkers
  - Defined ALS sub-population
  - Study population stratified by key parameters
  - Data mining of EMPOWER Phase III study
  - Robust, sensitive measures of disease progression:
    sensitivity > specificity
- SOD-1 ALS ASO Phase 1 clinical study to commence Q1 2016

Biogen

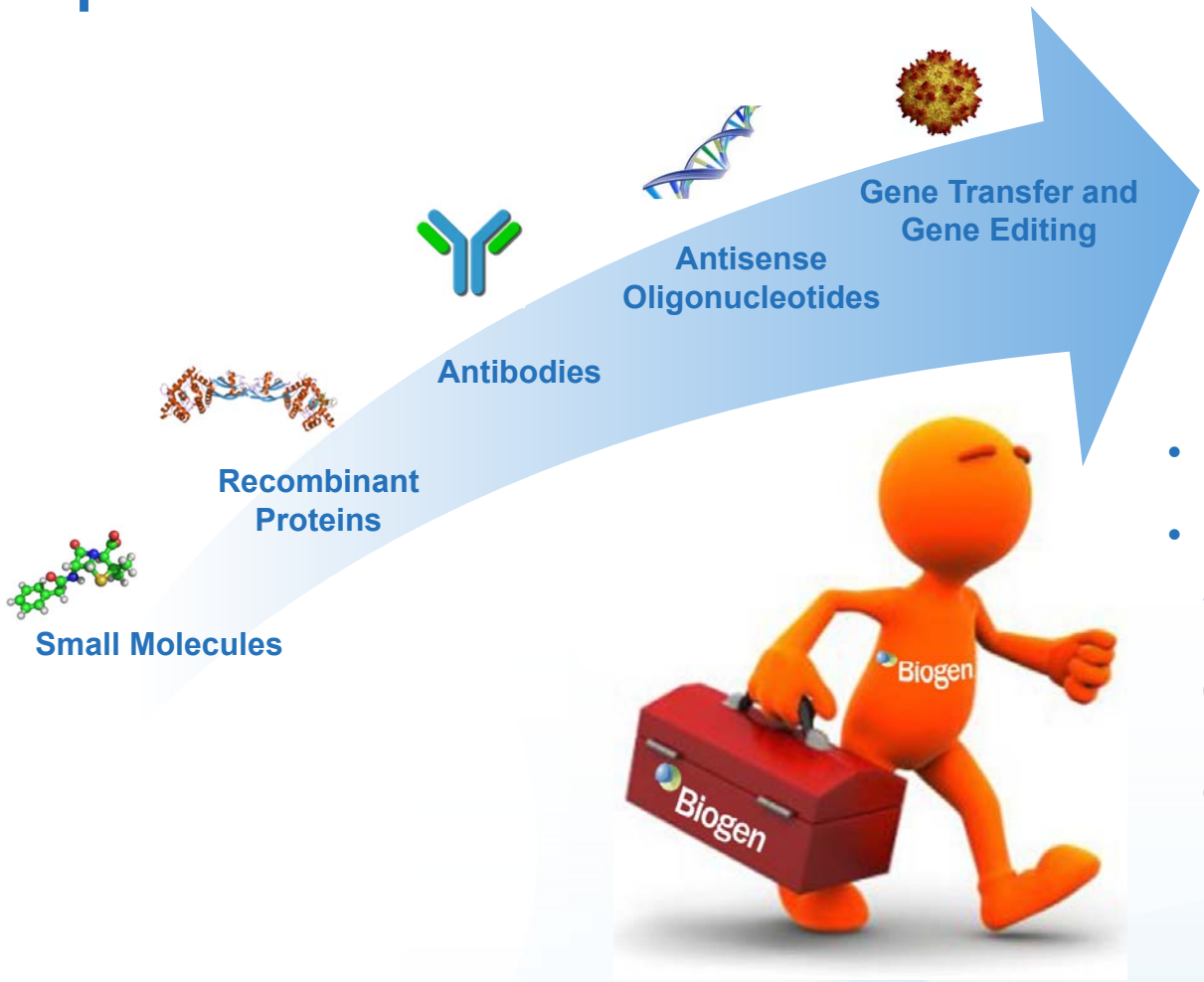
Gene therapy & gene editing

Olivier Danos, PhD
SVP Cell & Gene Therapy



Biogen

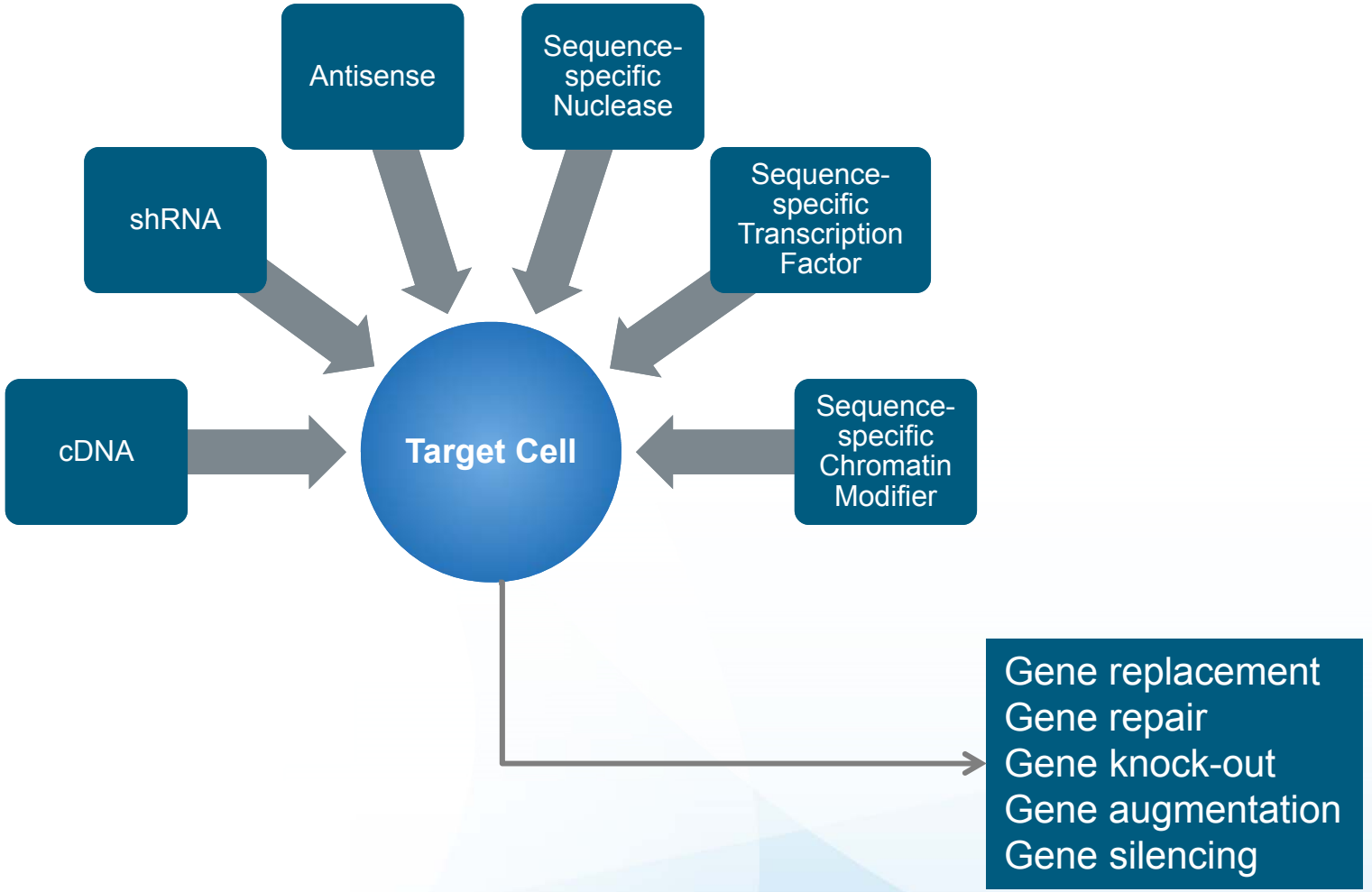
Gene transfer and gene editing expand Biogen's capabilities



- ***Novel therapeutic modality***
- ***Gene therapy is about reprogramming cells.*** It provides unique opportunities of curing or modifying the course of diseases in patients with high unmet needs.

Biogen

Therapeutic reprogramming



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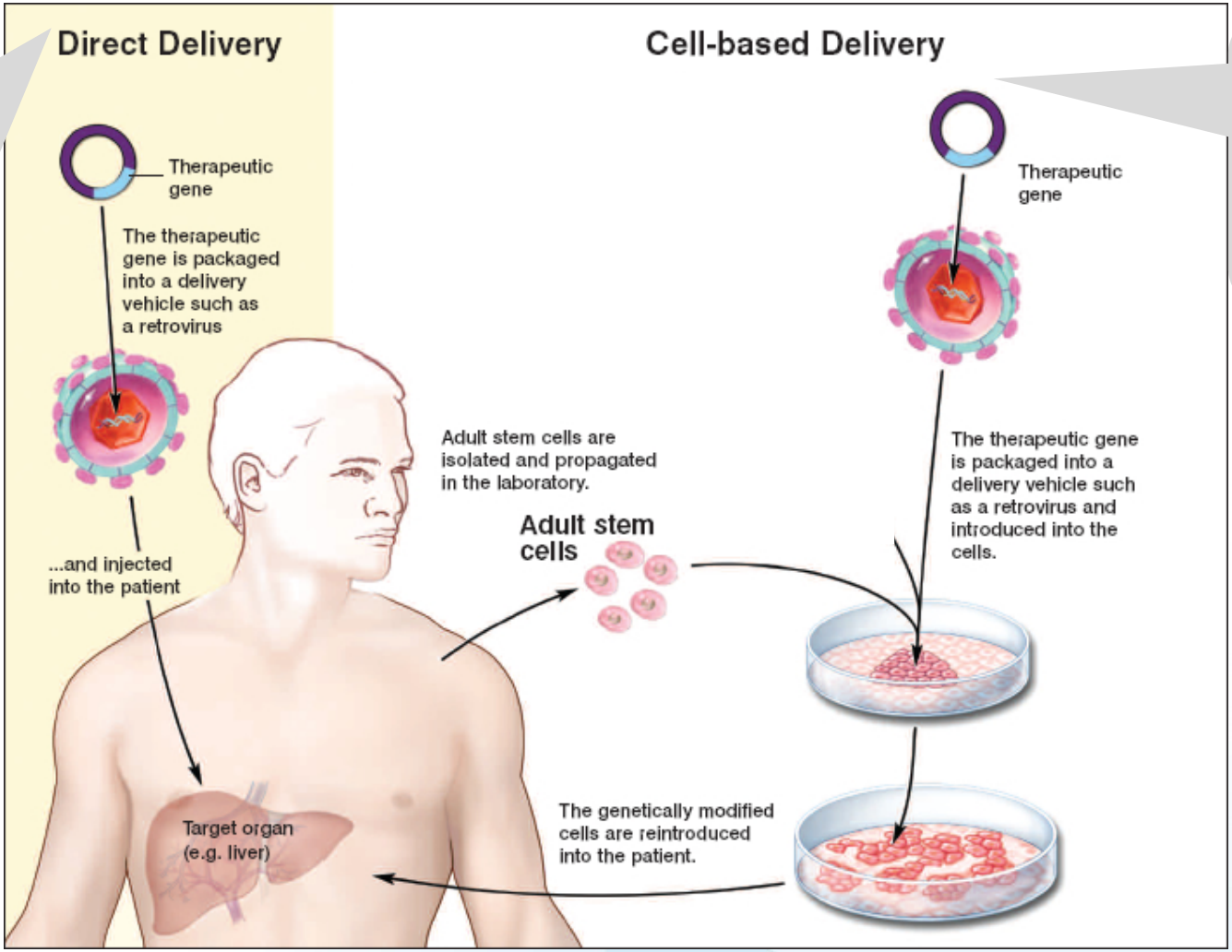
Biogen utilizing both *in vivo* and *ex vivo* approaches

agtc

Ocular diseases (XLRS / XLRP)

TELETHON INSTITUTE FOR GENE THERAPY tiget

Hemophilia A & B



SANGAMO

Beta-thalassemia Sickle cell disease

Biogen

http://stemcells.nih.gov

Biogen is well positioned to address the key challenges in gene therapy

Gene transfer and gene editing technology improvements:

- Specificity and off targets effects
- Immune responses
- Control of therapeutic sequences activity levels

State of the art research and technology platforms

Product development:

- Clinical gene therapy is still an unchartered territory
- Poorly defined pharmacology
- Commercial scale manufacturing
- Commercialization of one-off transformative treatments

Culture of breakthrough clinical research and product development using new therapeutic modalities

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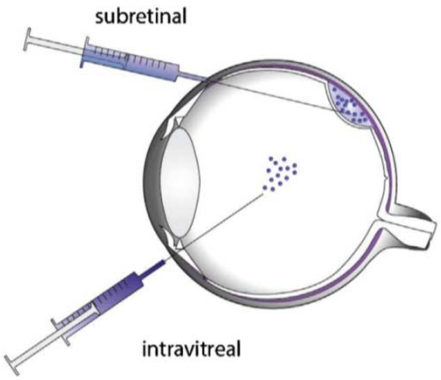
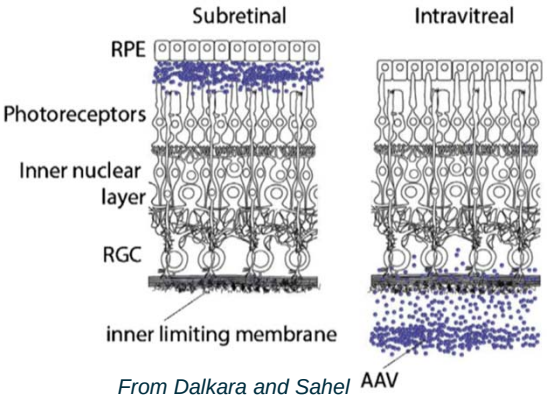
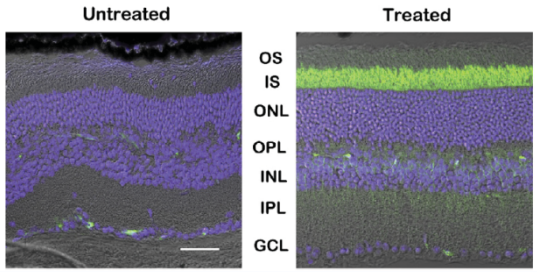
Gene Therapy for Inherited Retinal Degenerations: X-linked retinoschisis and X-linked retinitis pigmentosa

Indication	Description	Symptoms	Gene Therapy approach	Development stage
XLRS	Deficiency in RS1, a protein that connects the retinal cell layers 19,000 US patients	Bilateral reduction in visual acuity and peripheral vision. Non-progressive	Intravitreal injection of AVV	Phase I/II FPI June 2015
XLRP	Deficiency in RPGR, a protein essential to photoreceptor function 12,000 US patients	Night blindness, constriction of peripheral visual fields, and loss of central vision. Progressive	Subretinal injection of AAV	Pre-IND





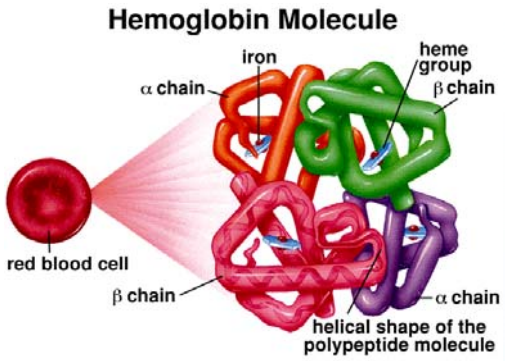
From Dalkara and Sahel

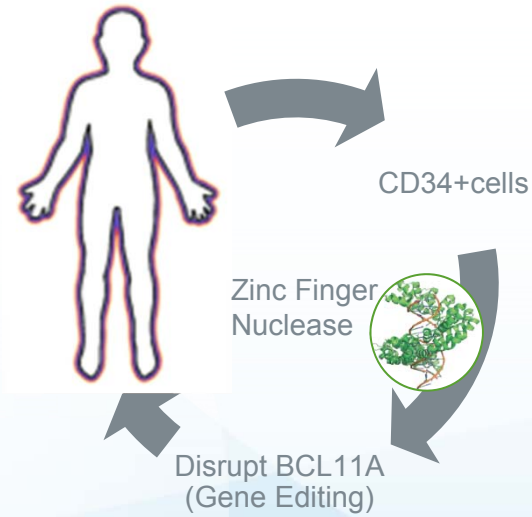


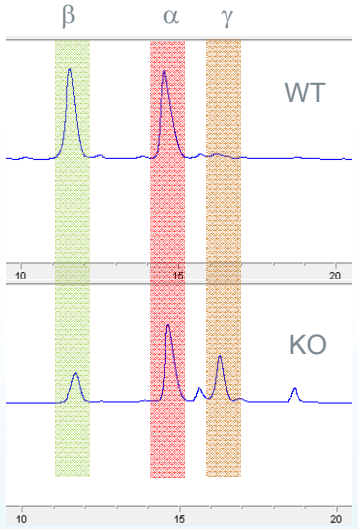
Gene therapy in RS1 KO Mouse

Gene therapy for hemoglobinopathies

Indication	Description	Symptoms	Gene Therapy approach	Development stage
Beta - Thalassemia	Inactivating mutations in the beta-globin gene. Dysfunctional hemoglobin. 1,300 US patients (190,000 WW)	Severe anemia managed by life-long transfusions. Iron overload	Reactivation of fetal hemoglobin (BCL11A editing)	IND target 2016
Sickle Cell Disease	Sickling mutation in the beta-globin gene. Abnormal hemoglobin forms hemolytic polymers. (90,000 US patients)	Hemolytic anemia, vascular occlusion, sickling crisis.	Reactivation of fetal hemoglobin (BCL11A editing)	IND target 2H:2016







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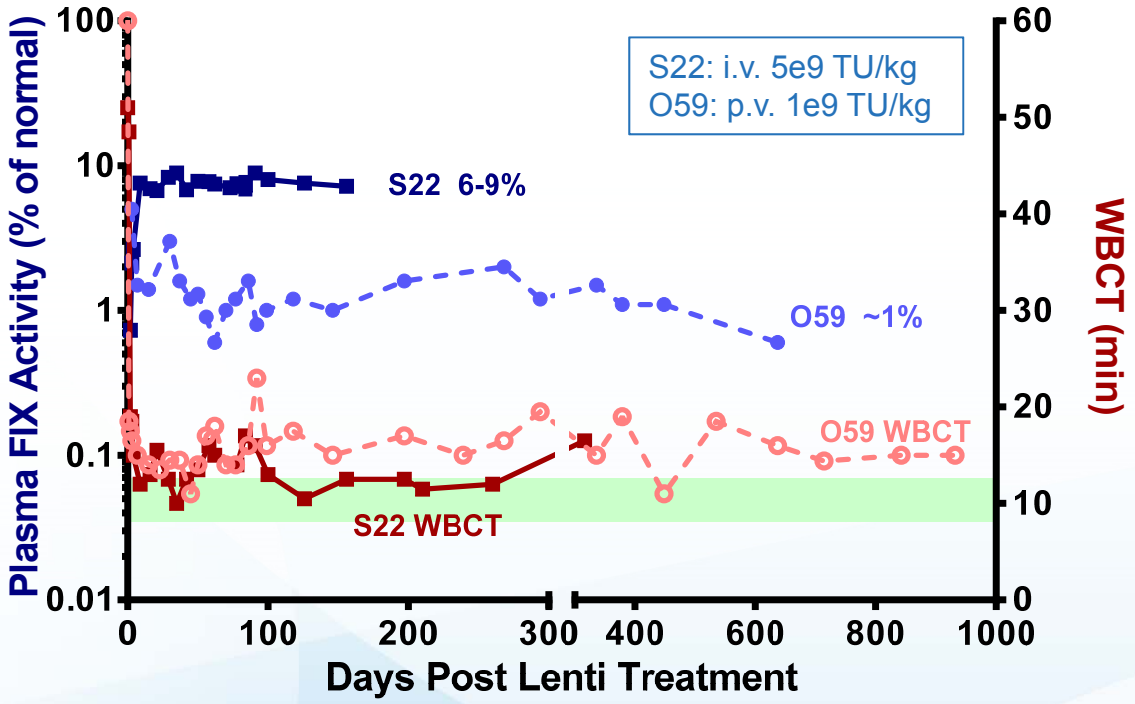
Gene therapy for hemophilia A&B

Indication	Description	Symptoms	Gene Therapy approach	Development stage
Hemophilia A and B	Bleeding disorders resulting from deficiencies in coagulation Factor VIII or IX. 16,000/4,000 US patients	Recurrent bleeding episodes.	Lentivirus-mediated production of coagulation factors in the liver.	Research / pre IND

Lentiviral vectors for the treatment of Hemophilia

- No preexisting immunity to the vector
- Integrating virus - no loss of treated cells in pediatric patients
- Favorable genotoxicity profile



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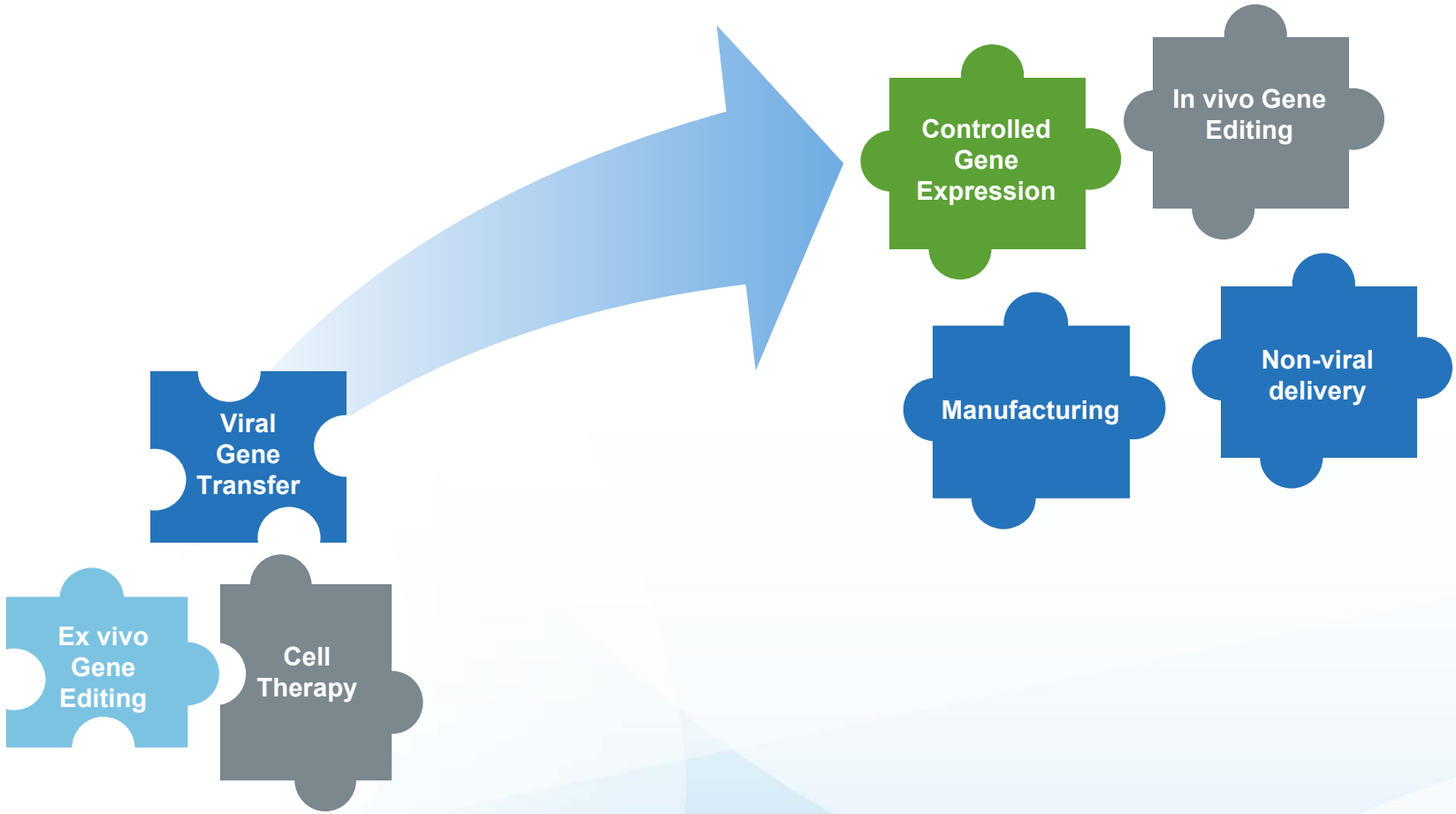
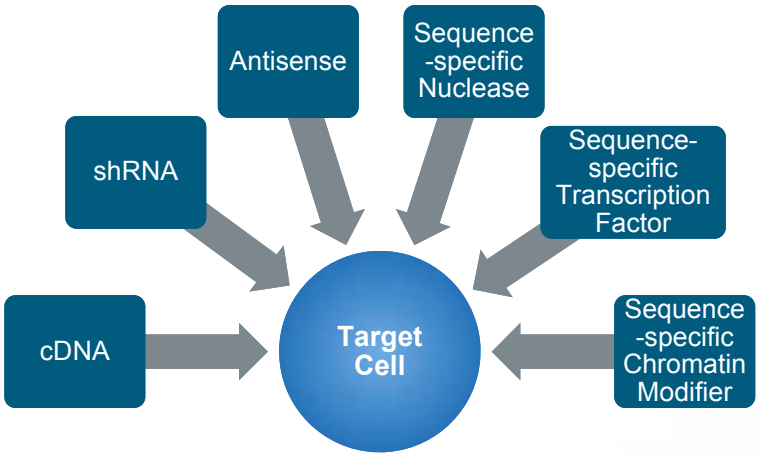
Note: WBCT: whole blood clotting time

Solving technology challenges to develop commercial products and broaden the scope of applications



Biogen

Multiple future applications in neurology



Disease	Rx Gene	Target Tissue
Spinal Muscular Atrophy	*SMN2*	Motor neurons, Skeletal muscle
Adrenomyelo-neuropathy	*ABCD1*	Motor neurons
Duchenne Muscular Dystrophy	*DMD*	Skeletal& cardiac muscles
Friedreich Ataxia	*FXN*	Dorsal Root Ganglia, Cardiac muscle
Amyotrophic Lateral Sclerosis	*SOD1*	Motor neurons
Progressive Multiple Sclerosis	*LINGO*	All CNS
Parkinson Disease	*GBA, MAPT, SNCA*	Substantia Nigra / Striatum

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Summary

- Biogen develops gene transfer and gene editing as new therapeutic modalities for patients with high unmet medical needs.
- We currently focus on developing products for selected applications that are tractable with the current technology.
- A strong emphasis is placed on improving technologies.
- With improved tools and acquired expertise in clinical development we will be uniquely positioned to extend the use of gene transfer and gene editing to diseases that affect large populations.

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Track 2

The future of SMARTER drug development with biomarkers

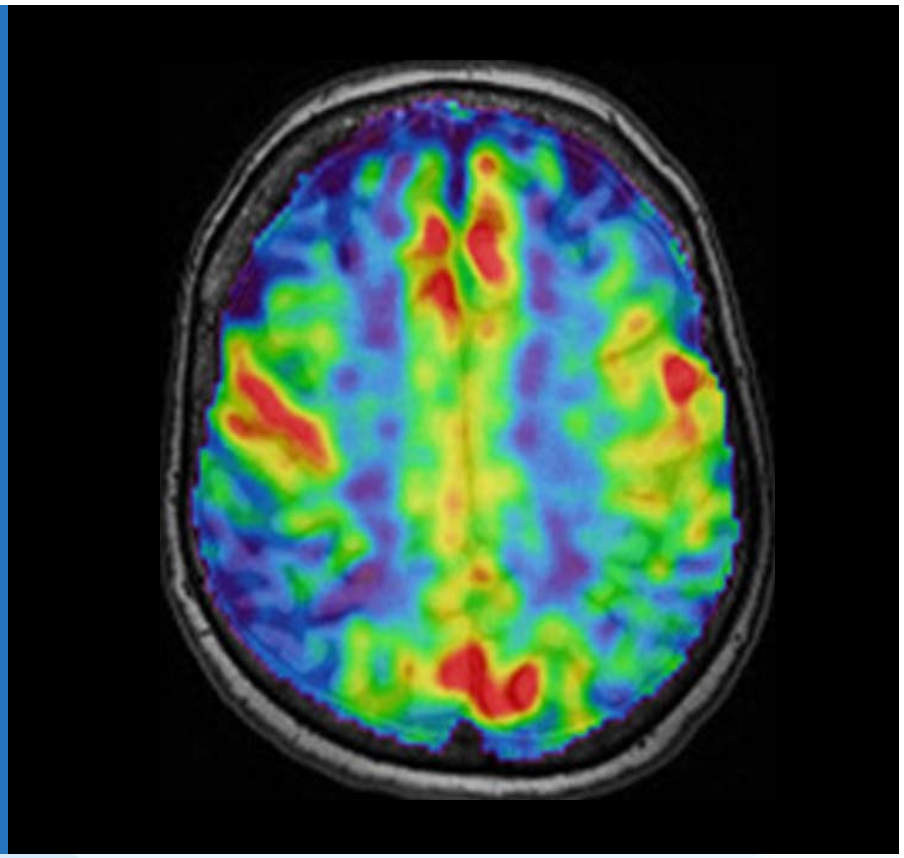
Value based medicine

Biogen

The future of SMARTER drug development with biomarkers

Richard Hargreaves, PhD
VP Neuropharmacology and Biomarkers

Ajay Verma, MD, PhD
VP Experimental Medicine



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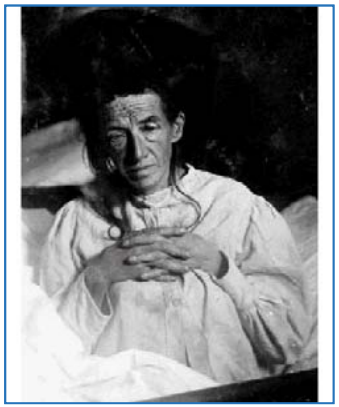
Todays healthcare needs are challenging

Aging disorders and neurodegenerative disease



- Epidemics in chronic neurological illnesses
- Need to evaluate novel disease modifying mechanisms
- Outcome studies are long and expensive
- Need to identify “winners and losers” early to focus research investments
- Rigorous use of biomarkers for early decision making reduces risk and the penalty for innovation

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Biogen is investing in novel biomarkers

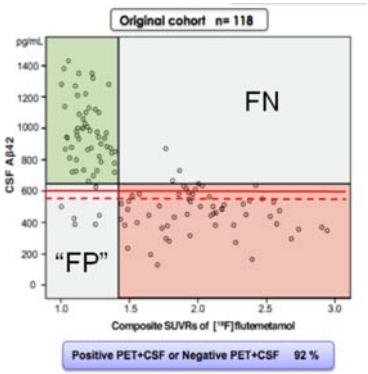
- Innovation is inversely proportional to validation
- Novel targets rarely have qualified biomarkers
- Need to invest off critical development path
  - Have to be ready for initial clinical trials to make impact
  - Develop biomarkers in advance of drug candidates
  - Requires early investment in novel tools and technologies

Biogen

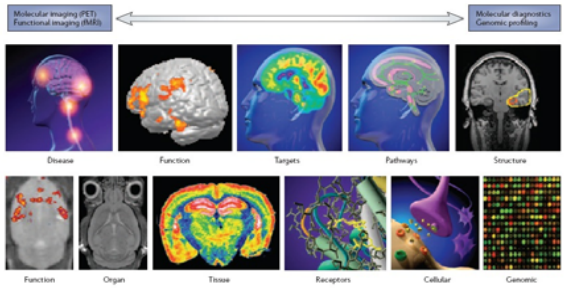
Working “smarter” at Biogen

- Paradigm shift: obligatory use of biomarkers:
  - Pathway: proof of biology
  - Disease: patient selection and disease progression
  - Safety

Fluid Based Measures



Preclinical and clinical imaging



Human physiology and devices

Goal: Test mechanisms not molecules

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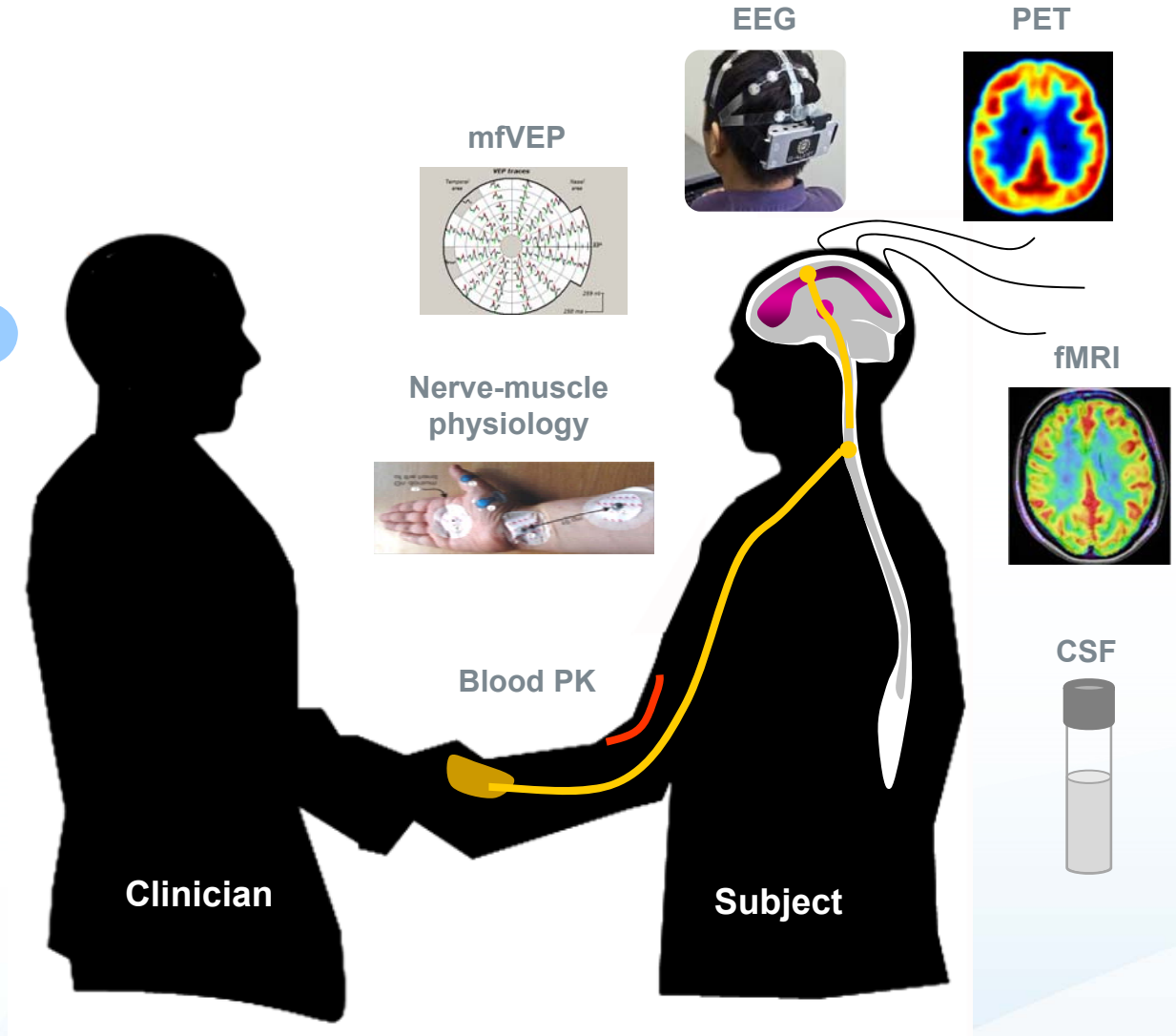
Palmqvist et al. JAMA Neurol, 2014 *Borsook et al: Nature Rev Drug Discovery 5: 2006*

Biomarkers enable early proof of biology

Did the drug engage the target?

Have we selected the right dose?

Did the drug Impact biology?



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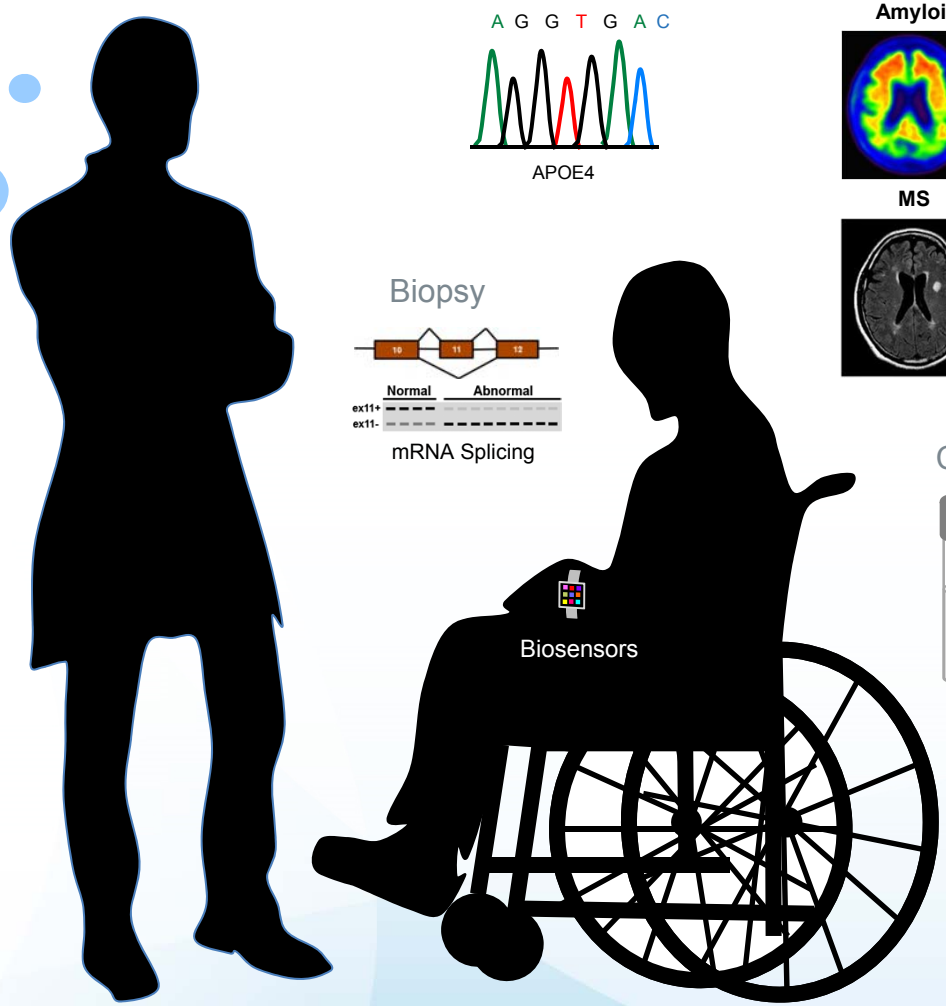
Biomarkers support drug development

Is the drug being tested in the right subset of patients?

Are measured biomarkers reflective of disease mechanism?

Can biomarkers provide support for efficacy?



Genotype

A G G T G A C

APOE4

Lesion Imaging

Amyloid

Tau

MS

Stroke

Biopsy

Normal Abnormal

ex11+

ex11-

mRNA Splicing

Biosensors

CSF

- Aβ
- Tau
- A-Syn
- SOD1

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Imaging is central to neurodegenerative drug development in Biogen

- Multiple advantages of imaging:
  - Bridge post-mortem histopathology to living patients
  - Select patients for trials
  - Enrich for appropriate pathology
  - Assess drug effects – pharmacodynamics
  - Track disease progression
  - Evaluate impact of therapeutic on brain function

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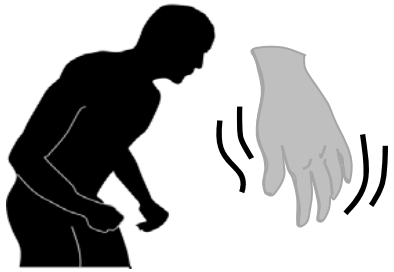
A biomarker driven view of neurodegenerative diseases is emerging

Diagnosis driven by constellation of clinical signs and symptoms

Dementia

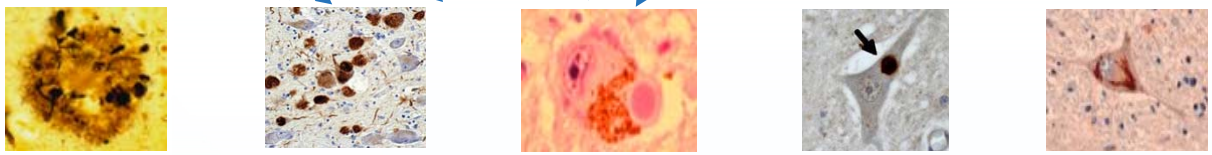
Movement Disorder



Weakness and Atrophy

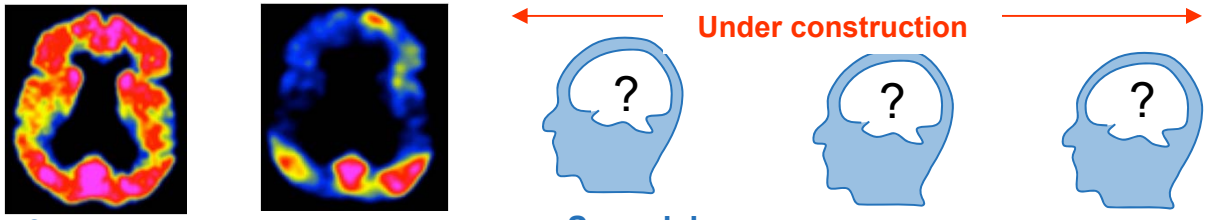
Molecular pathology and CSF analytes classify neurodegenerative diseases

AD PD-dementia PSP PD MSA DLB FTLD ALS



β-amyloid tau α-Synuclein TDP-43 SOD1

Molecular imaging can visualize molecular pathology



β-amyloid tau α-Synuclein TDP-43 SOD1

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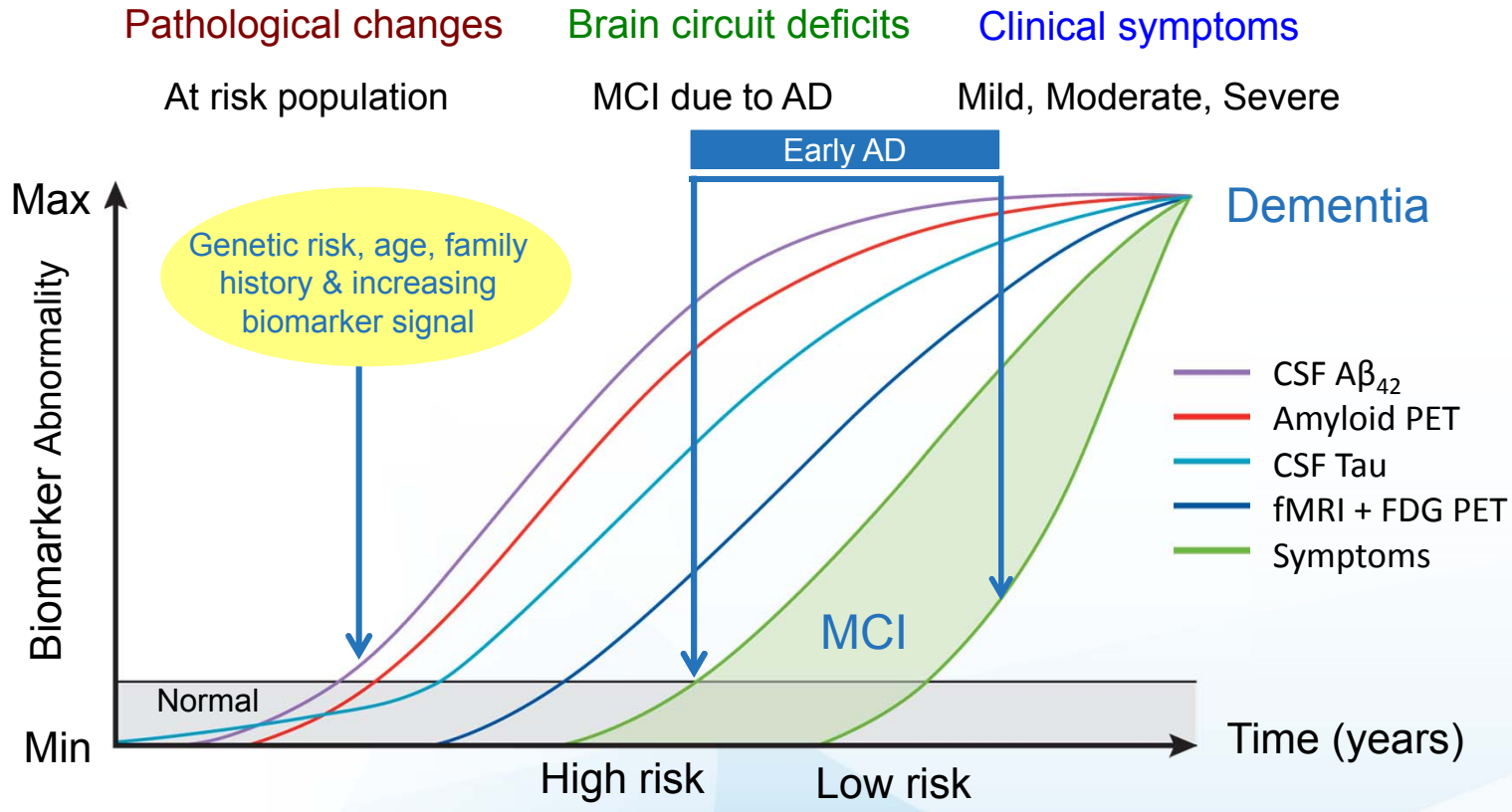
Neurodegeneration is staged using biomarkers

- Alzheimer's disease example
  - Aβ amyloid accumulation may precede clinical disease by 10 years
  - Tau-mediated neuronal injury is more proximal to clinical symptoms



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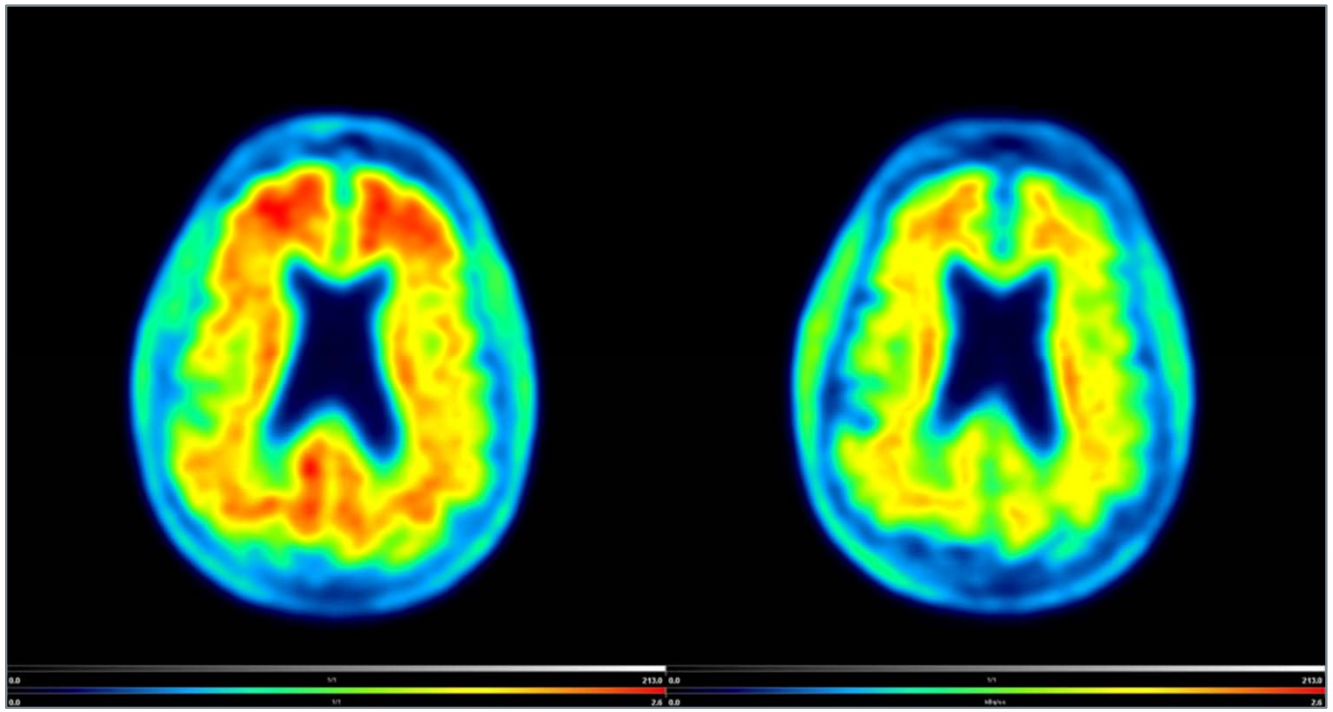
Adapted from Jack CR, et al. Lancet Neurol (2013) 12; 207.

Aducanumab – Clinical proof of concept



[^{18}F] Florbetapir (Amyvid^{TM}) positron emission tomography (PET) scans at baseline (left) and week 54 (right) showing reduction in amyloid plaques in a patient with mild AD

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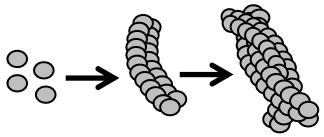
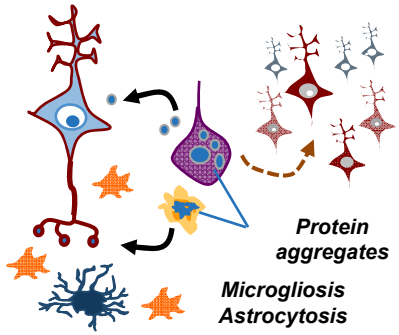
Novel imaging of tau in Alzheimer's disease

Hypothesized pathophysiology

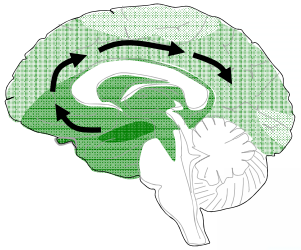
Protein aggregate lesion



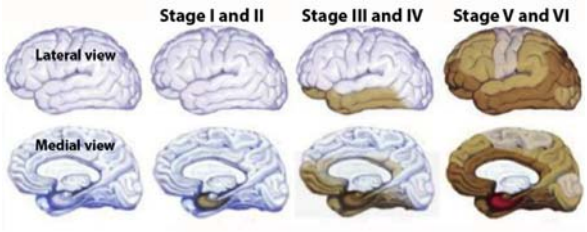
Spreading Pathology



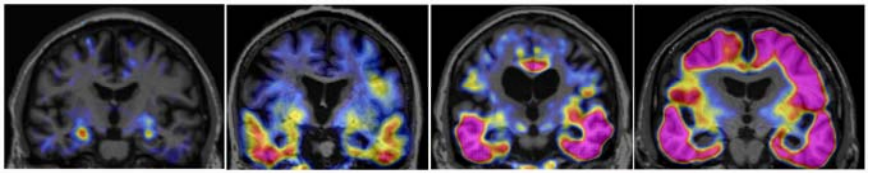
Altered brain circuit function



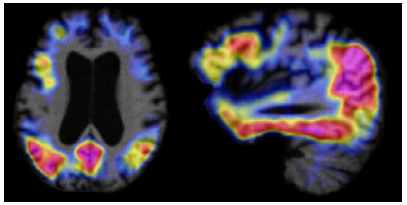
Autopsy based Braak staging of AD Tau pathology



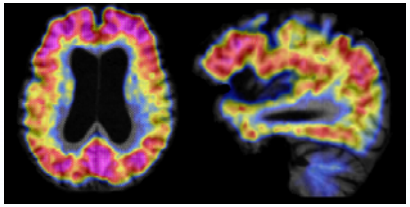
Towards in vivo staging of tau pathology with ^{18}F-T807 PET



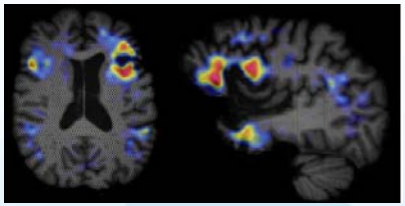
AD patient Tau ^{18}F-T807 PET



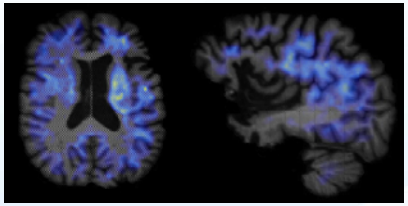
AD patient Amyloid ^{11}C-PIB PET



FTD patient Tau ^{18}F-T807 PET



FTD patient Amyloid ^{11}C-PIB PET



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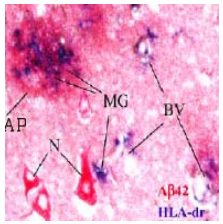
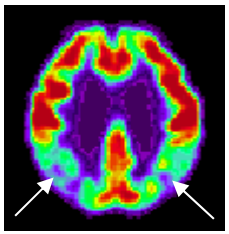
Collaboration with Keith Johnson, MGH

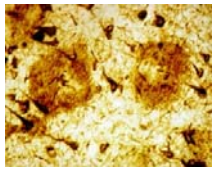
Alzheimer's disease imaging roadmap

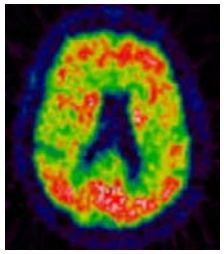
Symptoms



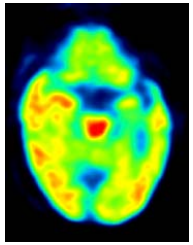


[18F]FDG PET
Diagnosis

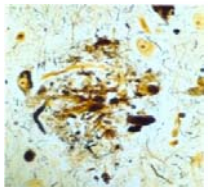


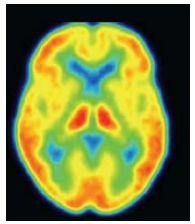


Amyloid



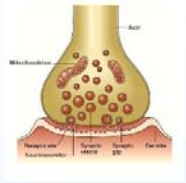
Tau

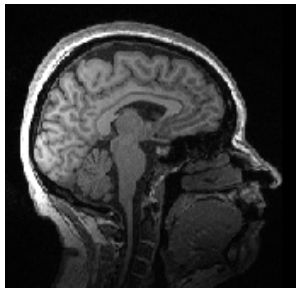




Neuro-
Inflammation
TSPO

Synaptic
markers
vGlut1, sv2A





Structure

Disease
Modification

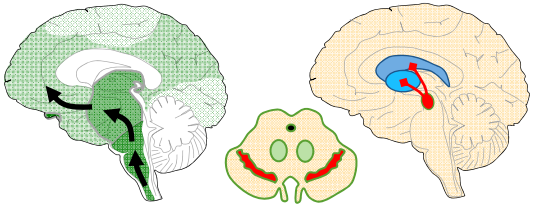
Cross validation of neuroimaging with fluid biomarkers

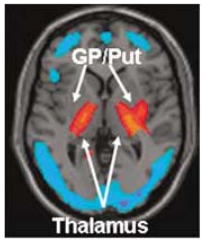
Biogen

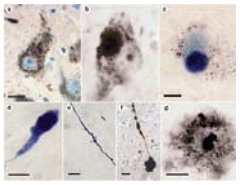
Adapted from Clinical Pharmacology and Therapeutics; 2008 83:349

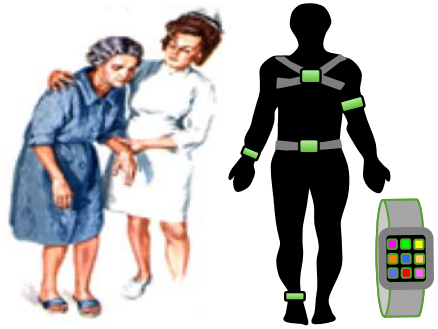
Parkinson's disease imaging roadmap

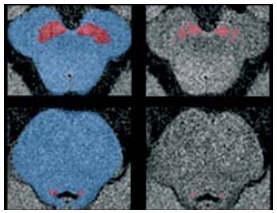
Symptoms

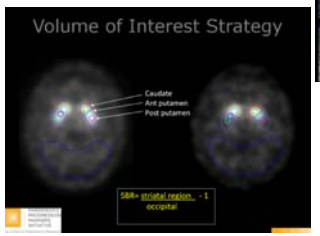












DAT SPECT
Diagnosis

MRI T1W
Neuro-melanin

^{18}F-FDG
PDRP
Function

Alpha-synuclein PET/SPECT pathology

α-synuclein load & spread

Objective measures of symptoms

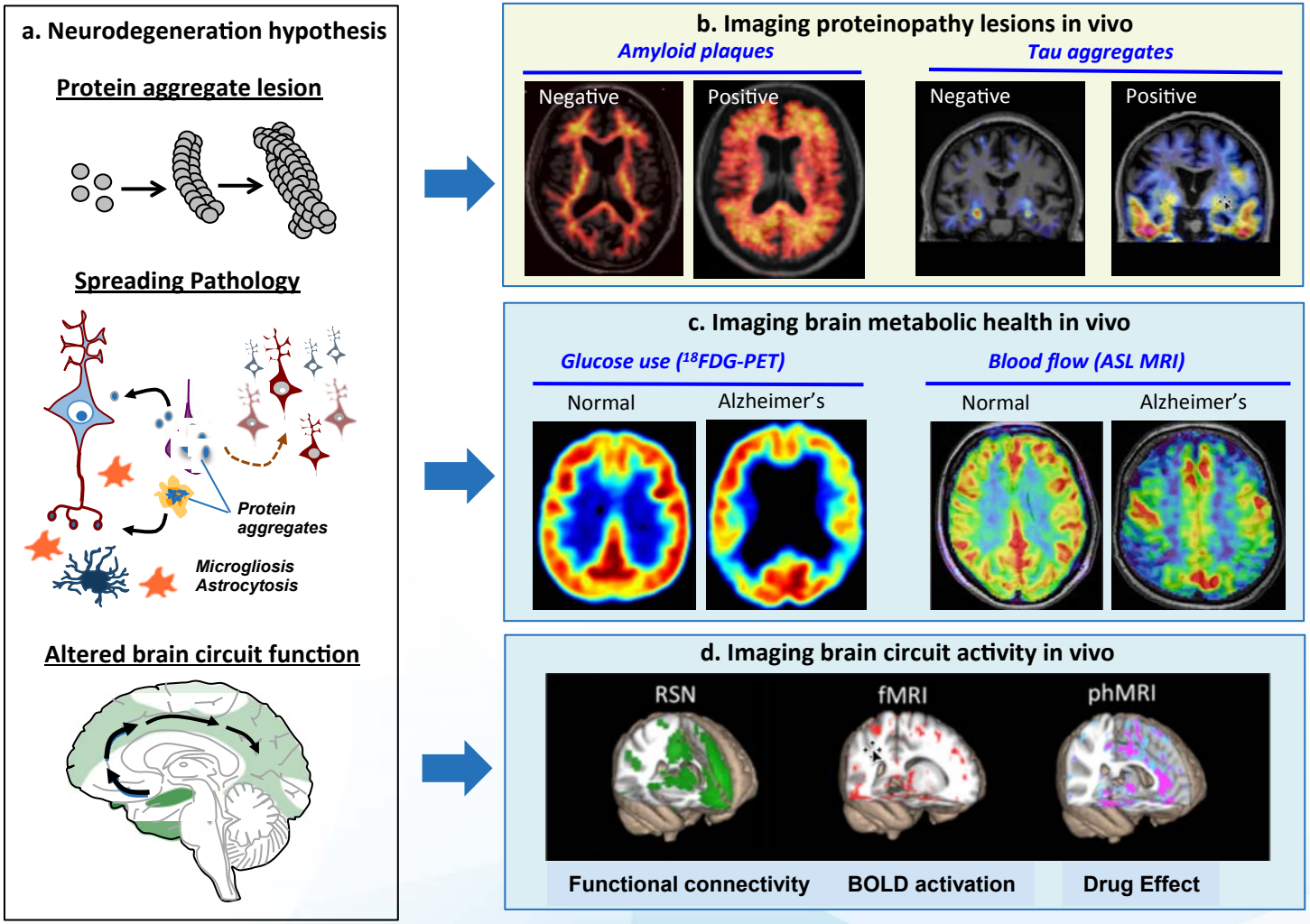
Efficacy

Cross validation of neuroimaging with fluid biomarkers

Biogen

Brain. 2007 130:1834 Mov, Disord. 2015; 30:945

Biogen is de-constructing neurodegeneration using molecular and functional neuroimaging



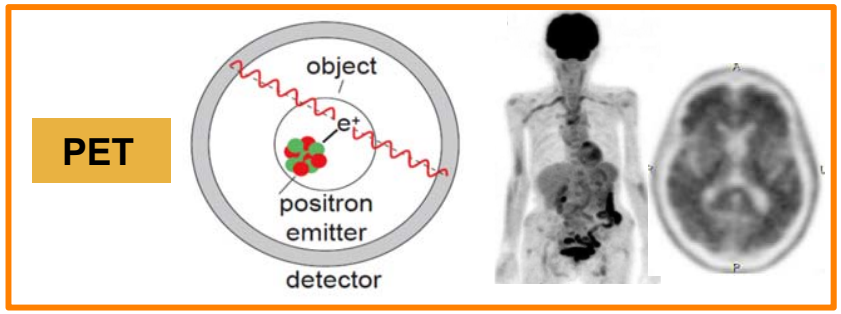
Biogen

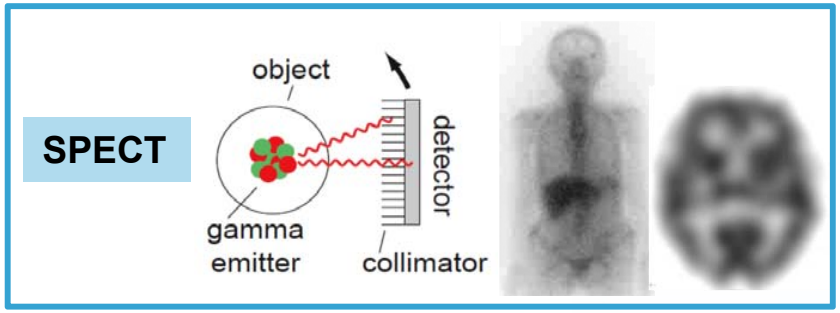
Biomarker technology innovation

- Increasing access to imaging biomarkers
- Improving early diagnostic accuracy
- Reducing cost

Biogen

Molecular imaging technologies: PET vs. SPECT





Feature	PET	SPECT
Clinical Resolution	~4mm (~50µL)	~8mm (~500µL)
Sensitivity	nM-pM	µM-nM
Scanner Install Base (Global)	~7,500	~35,000
FDA Approved Radiopharmaceuticals	<10	> 50
Radio-pharmacy Requirements	Cyclotron and Synthetic Chemistry	Compounding or Centralized
General Radioisotope Characteristics	Shorter Half-Lives	Longer Half-Lives
Typical # Repeat Scans in a Trial	2-3	2-5

Map of US Nuclear Pharmacies

69 PET Alone
333 SPECT Alone

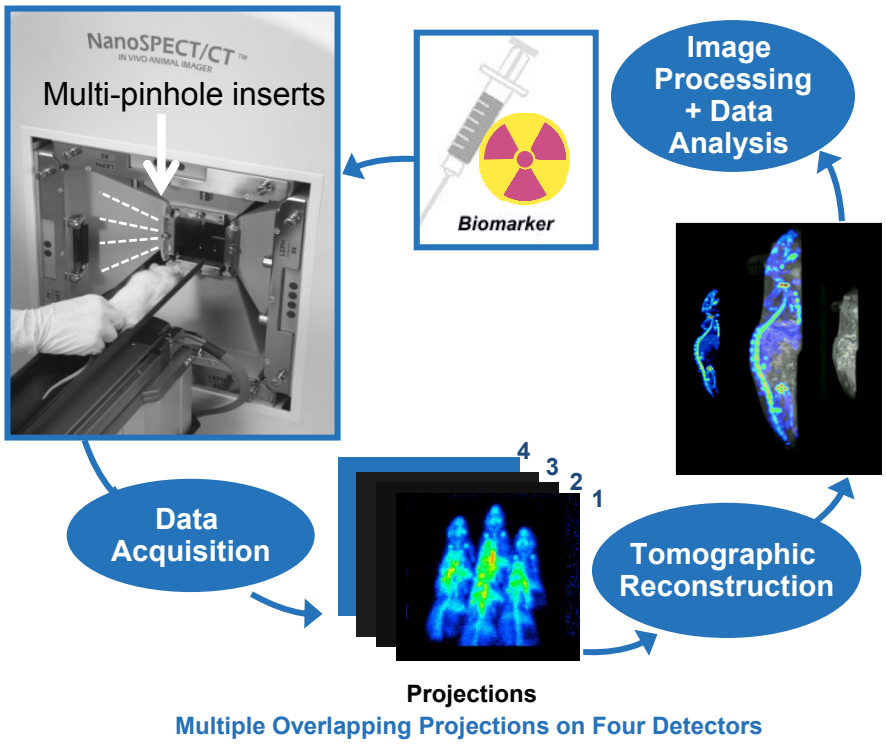
42 Both PET & SPECT

Biogen

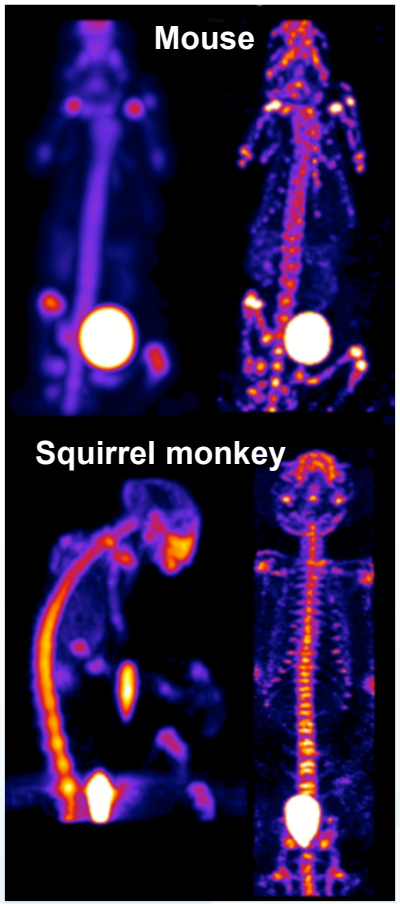
Advances in SPECT imaging resolution and sensitivity

Multi-pinhole inserts

Multi-pinhole based high-resolution SPECT/CT functional and anatomical imaging system



Previous Generation Multi-pinhole



Biogen

Hi-Res SPECT scanner project: “BioSPECT”

- Clinical SPECT scanner collaboration between Biogen, Mediso and InviCRO
- World’s highest resolution and sensitivity commercial SPECT-CT system
  - Absolute quantification of radioactivity concentrations
  - Exchangeable imaging aperture systems
  - Specific configurations for dedicated brain regions (cortex, striatum)

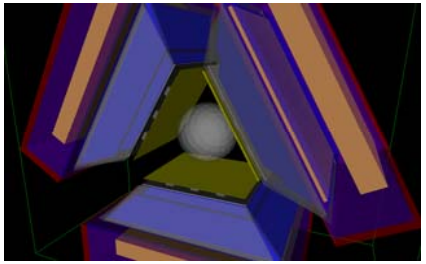
Biogen

New imaging capabilities for drug development

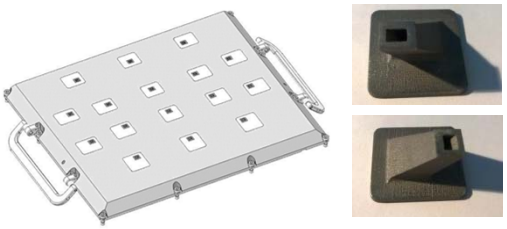
Novel scanner features for brain specific imaging applications

BioSPECT scanner

Triple head model



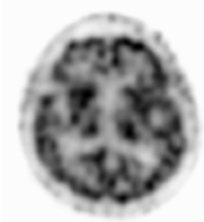
Brain sub-region specific collimators

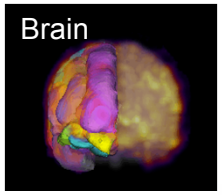


Body and head apertures

Bone scan

Organ perfusion

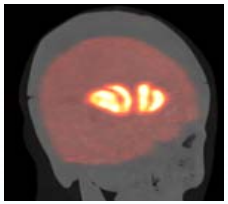




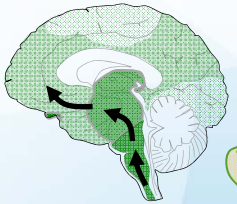
Striatum-specific aperture

Striatal phantom

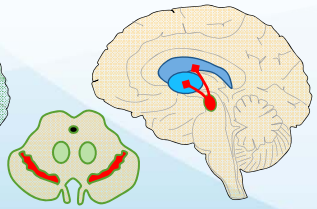
SPECT image



Disease spread

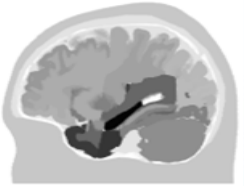


Nigrostriatal pathway

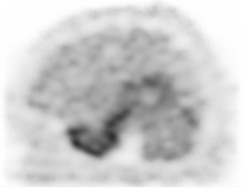


Cortex-specific aperture

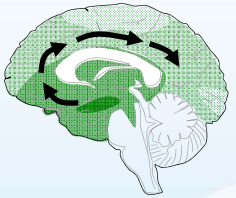
Alzheimer's phantom



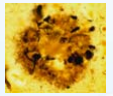
SPECT image



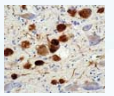
Disease spread



β-amyloid



Tau

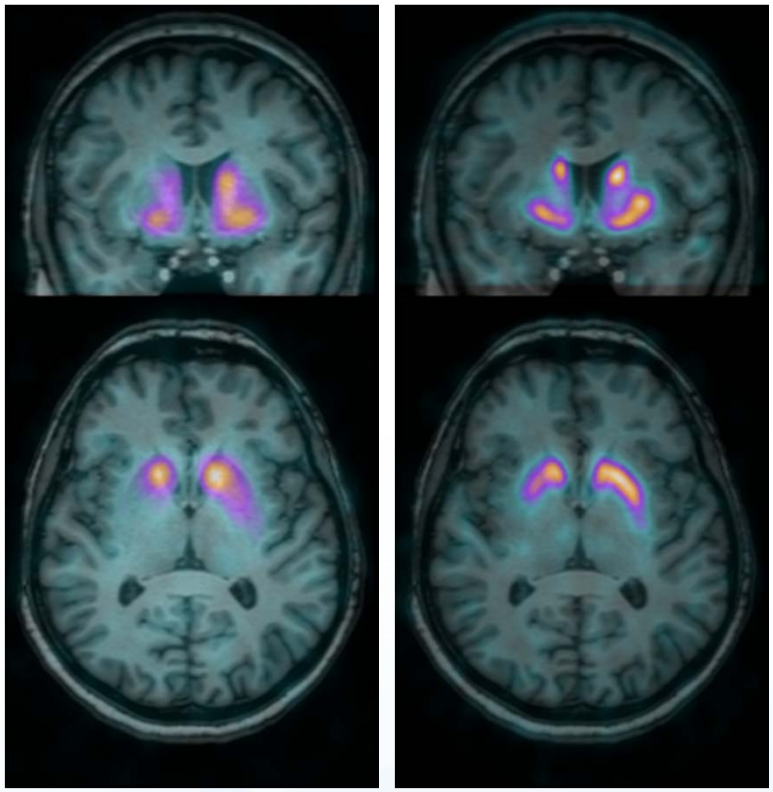


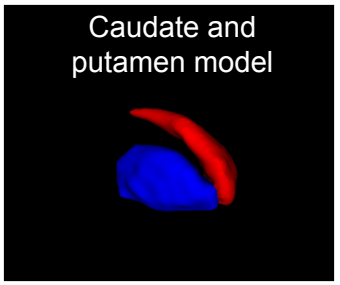
Application of high resolution SPECT imaging to Parkinson's disease

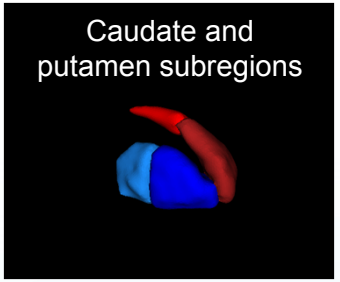
- Dopamine synapse loss determines Parkinson's motor symptoms
- BioSPECT improves accuracy and sensitivity of imaging dopamine synaptic terminals with SPECT probe (^{123}I-Ioflupane; DaTScan)
- Enhanced sub-region analysis of dopamine synapse loss could:
  - Enable earlier diagnosis
  - Increase diagnostic specificity
  - Allow faster disease modification hypothesis testing with fewer subjects

State of the art SPECT (DaTScan)

BioSPECT (DaTScan)







Data were acquired from the same scanning session in single patient with early Parkinson's disease

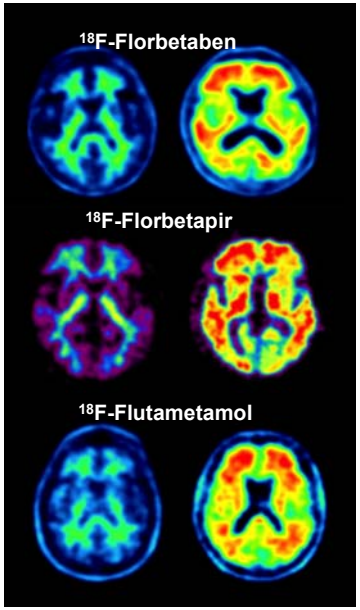
Biogen

Application of high resolution SPECT imaging to Alzheimer's disease

Current Amyloid tracers are sub-optimal for early detection

- PET availability limitations
- White matter background

Healthy Subject | Alzheimer's Disease

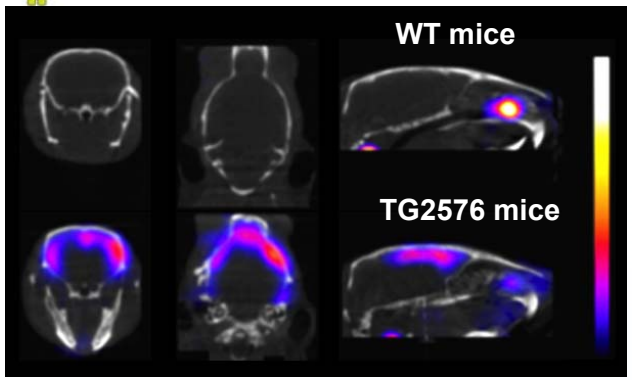


Courtesy of MNI

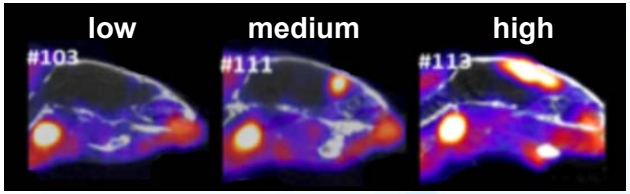
High-res SPECT facilitates development of biologics imaging agents: potential for new imaging approaches for early disease detection

- Higher specificity of biologics probes (mABs, Ab fragments)
- Longer SPECT isotope half-lives preferable for slow pharmacokinetics (mABs, ASOs)

^{125}I-12F6A (murinized aducanumab)



^{125}I-12F6A Fab2 fragment in TG2576 mice



Patel et al.,AD PD, Mar 2013

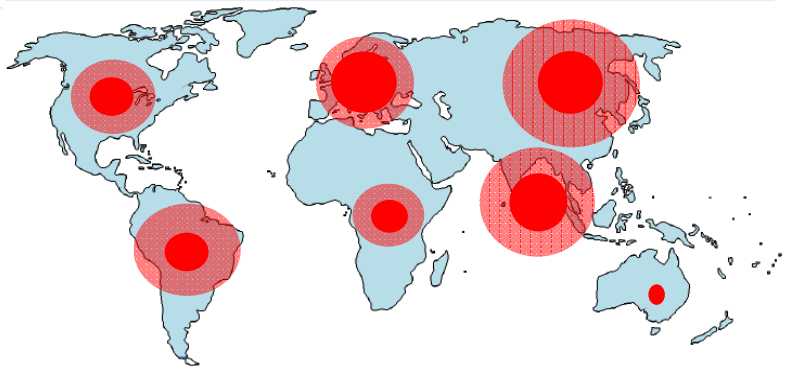
Alzheimer's phantom | SPECT image

Biogen

Addressing real world biomarker needs: new imaging solutions for growing demand

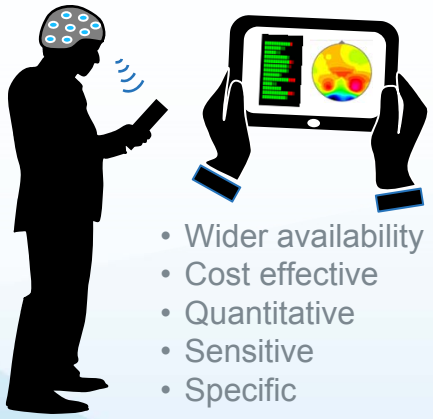
Map of US nuclear pharmacies

Growing world burden of dementia



~7500 Global PET scanners
~35,000 Global SPECT scanners

Novel solutions needed to meet growing world demand for molecular imaging



- Wider availability
- Cost effective
- Quantitative
- Sensitive
- Specific

Biogen

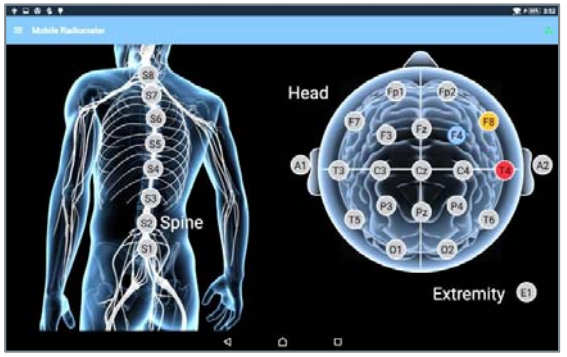
* Alzheimer's Research UK, 2015

Biogen mobile molecular scanner prototype

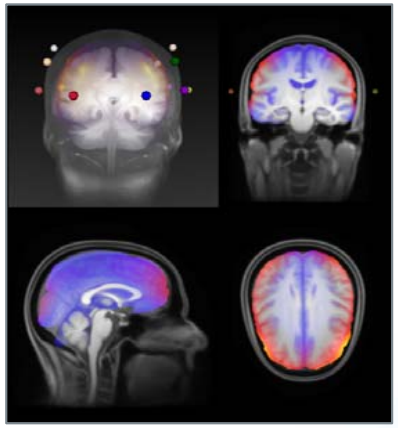
Functional prototype

Head and spine prototype

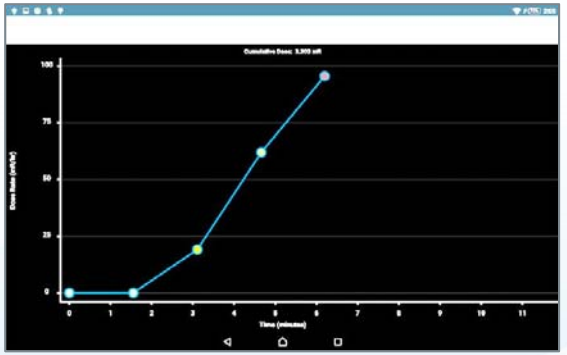
Wireless data transmission



Sensitivity map



Detector time activity curve



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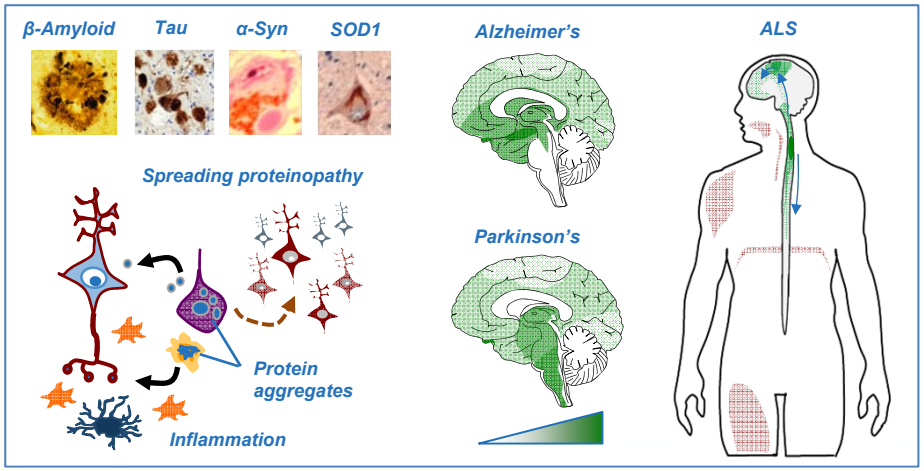
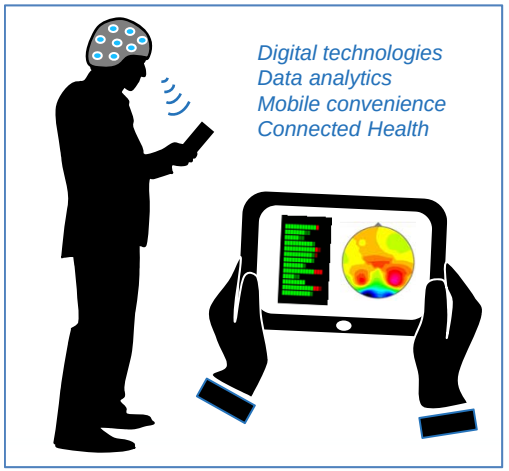
Biomarker innovations for smarter drug development

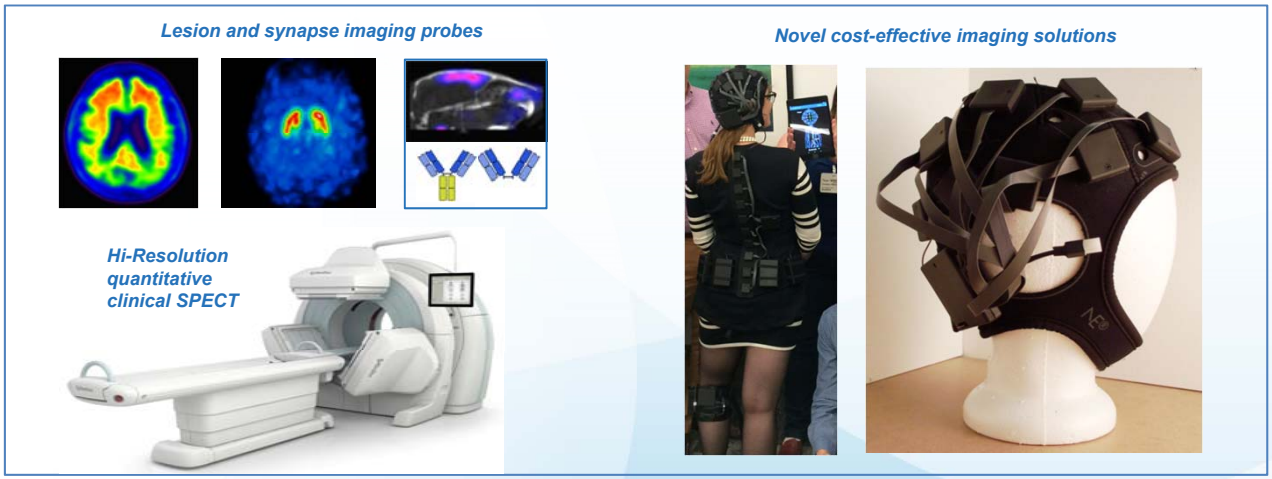
Emerging neurodegeneration knowledge



Emerging capabilities



Innovative biomarker technologies



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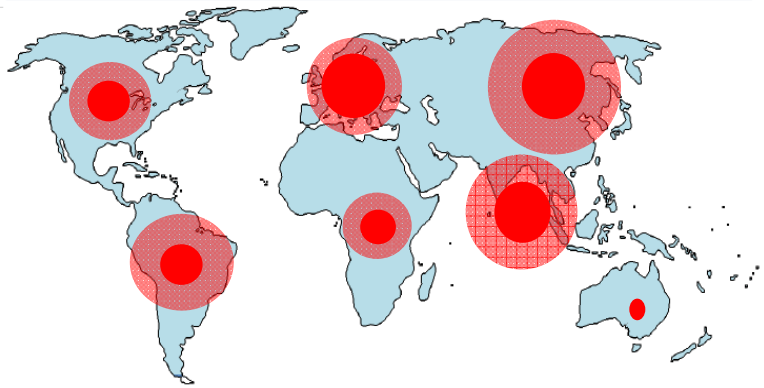
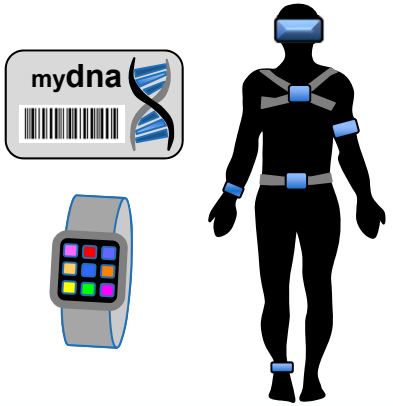
Biomarkers and the future of neurology drug development

Growing world burden of Dementia



Biomarkers for the masses



Novel solutions needed to meet growing world demand for molecular imaging

- Wider availability
- Cost effective
- Quantitative
- Sensitive
- Specific

Delivering value with biomarkers

Biogen

* Alzheimer's Research UK, 2015

Value based medicine

Richard A. Rudick, MD
VP Development Sciences

Biogen

Value based medicine

MS PATHS – A solution to outcomes-based reimbursement

Google Life Sciences Partnership – Biologic, genetic, and sensor technology to accelerate disease understanding

Biogen

Value based medicine

MS PATHS – A solution to outcomes-based reimbursement

Google Life Sciences Partnership – Biologic, genetic, and sensor technology to accelerate disease understanding

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Biogen is creating a technology-based solution to future outcomes-based reimbursement models

Pay for products, procedures & services

Pay for outcomes

New tools and methods are needed to measure outcomes in medical practice

Institute of Medicine has called for a learning healthcare system to continuously improve patient outcomes*

*Institute of Medicine of the National Academies. Best care at lower cost: The path to continuously learning health care in America. Available at http://books.nap.edu/openbook.php?record_id=13444. Accessed April 2, 2015.

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MS PATHS aims to enhance the standard of care through a Learning Health System

MS PATHS
Partners Advancing Technology and Health Solutions

- Biogen is collaborating with leading healthcare institutions to establish the first Learning Health System for MS
- Leverages new technology to standardize and collect outcomes data for every MS patient at their office visit
- Establishes a new core capability within Biogen that, if successful, can be deployed in other therapeutic areas

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Components of the MS PATHS Learning Health System

1 Standardized data collection

- Clinical data
- MRI data
- Biologic data

2 Data aggregation across healthcare institutions

Store, analyze, visualize data

3 Insights

- Research
- Point of care

Biogen

Multiple Sclerosis Performance Test (MSPT): An iPad®-based medical device

- Developed by Biogen in collaboration with the Cleveland Clinic
- Includes structured patient history, measures patient experience, and quantifies walking, dexterity, vision, and cognition
- Designed for patient self-administration
- Enables easy visualization of change over time and comparison to other patients

Note: At this time, the MSPT is not a commercially available product and is subject to change.

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MS patient conducting her own assessment

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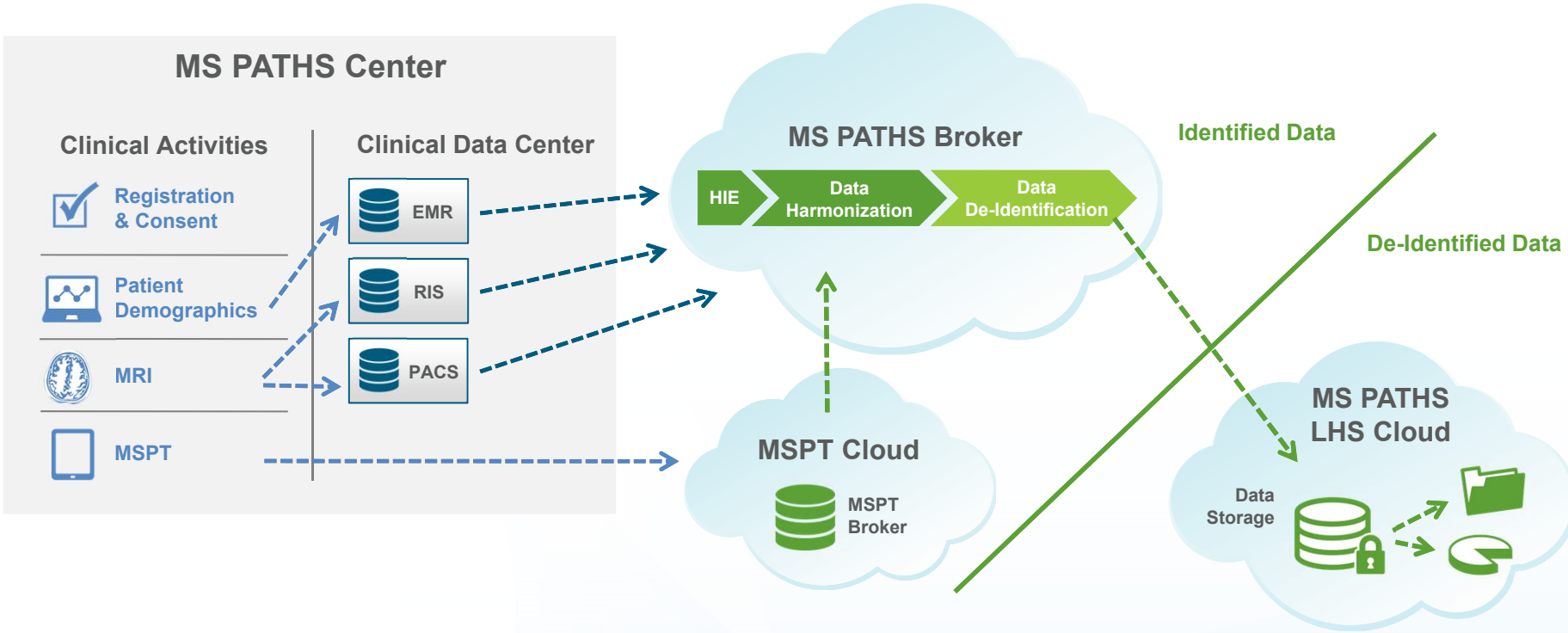
MS PATHS Informatics Solution: Designed to collect, de-identify, and aggregate data from a large volume of diverse patients



LHS = learning health system.

Biogen

MS PATHS: Returning Value to Biogen While Driving Innovation in Healthcare

- Create the first Learning Health System in neurology
- Improve the MS standard of care
- Demonstrate the effectiveness of Biogen MS therapies
- Stem reimbursement pressure
- Establish a new mechanism to accelerate translational research
- Drive toward personalized medicine for MS

Biogen

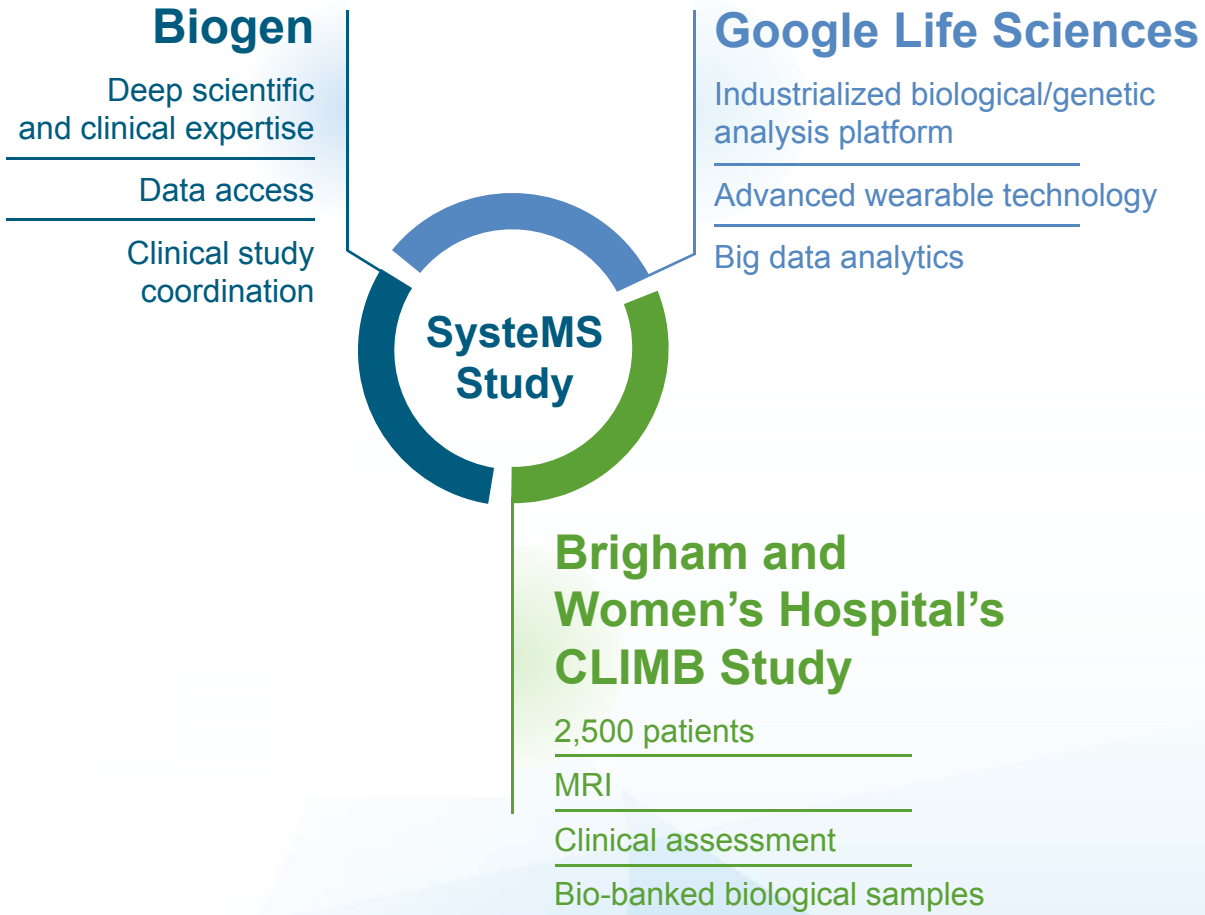
Value based medicine

MS PATHS – A solution to outcomes-based reimbursement

Google Life Sciences Partnership – Biologic, genetic, and sensor technology to accelerate disease understanding

Biogen

Google Life Sciences partnership



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SysteMS Study (Sensor Technology Component)

Evaluate participant behavioral and environmental factors using Google Life Science's advanced wearable sensor technology as they live in their own environment

In-clinic pilot study → **At-home pilot study**

Optimize assessment of mobility, gait, and dexterity with Google's sensors in the clinic and home environment

Compare device data, in clinic and home, with physician-assessed clinically validated measures of MS function

Expansion to full CLIMB population

Combine behavioral, environmental, genetic, biologic, imaging, and neurologic data to better understand MS disease progression

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Google Life Sciences Partnership

Future Implications

Biogen

Afternoon Plenary

Biogen 2015 R&D Day

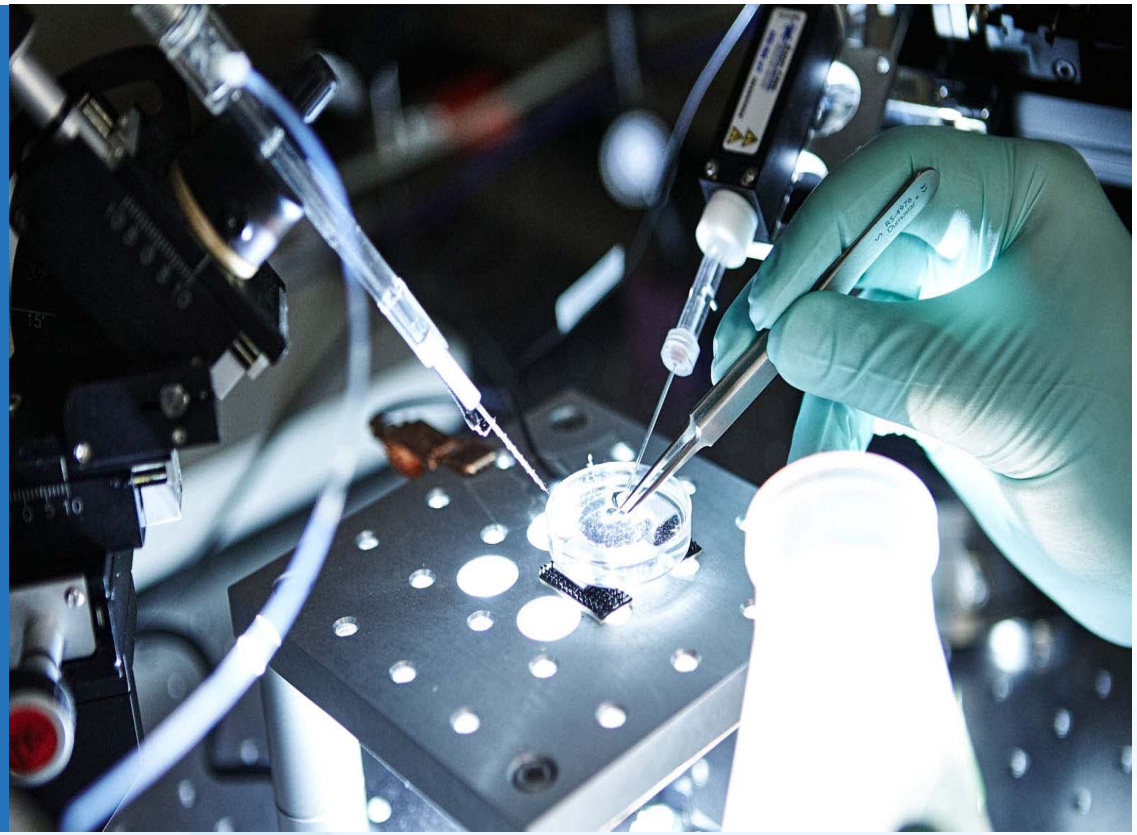
Advancing the Next Wave of Potential Therapies

November 3, 2015

Biogen

Raxatrigine in neuropathic pain

Simon Tate, PhD
VP Pain Research Therapeutic Area



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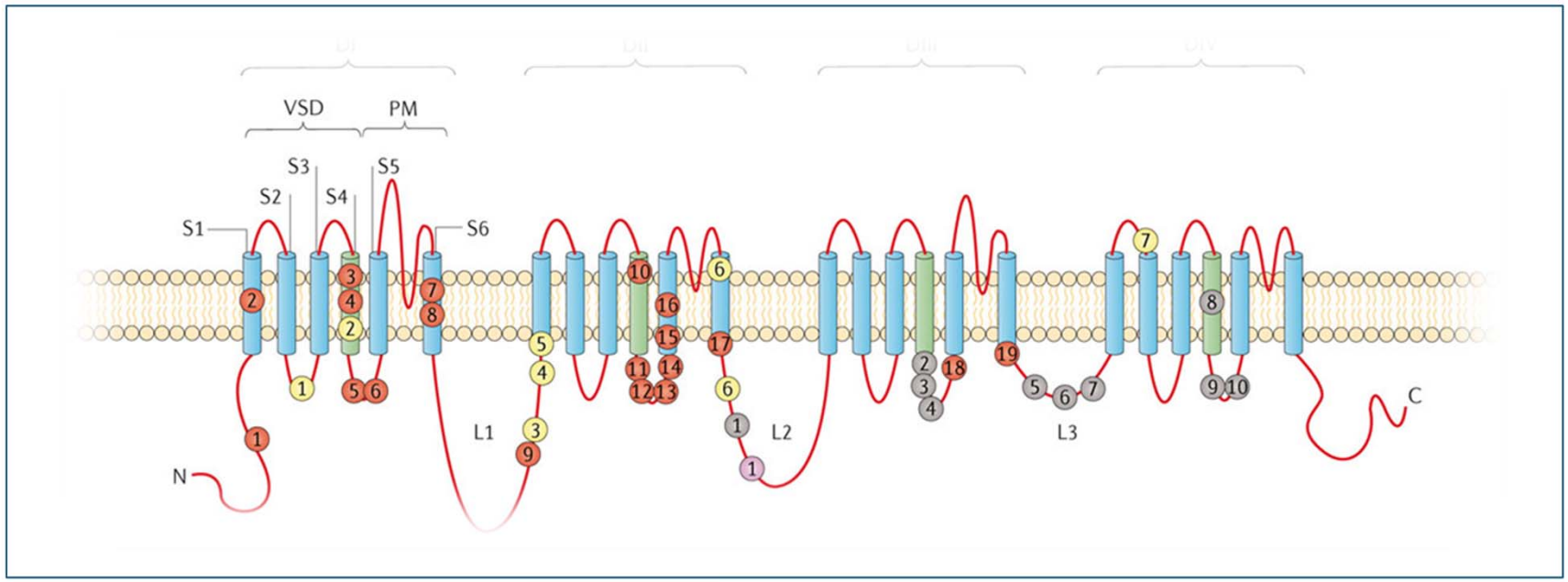
Pain is a large market with high unmet need and an improved scientific understanding

- Neuropathic Pain affects more than 12 million adults in the US (*Decision resources Oct 2014*)
- Continued and significant unmet need
  - Limited drug efficacy and substantial side effects
  - Need for innovative therapies with increased efficacy and improved safety/tolerability
- Now delivered successful phase 2 proof of concept studies with $Na_v1.7$ blocker, raxatrigine in neuropathic pain associated with trigeminal neuralgia and sciatica
- Initiating phase 3 in 2016

Biogen

Targeting sodium channel (Nav) dysfunction in pain



- Voltage-gated sodium channels, play a key role in the initiation of action potentials and subsequent propagation of pain signalling
- Genetics link SCN9A ***($Na_v1.7$ channel)*** with a variety of painful clinical syndromes, such as ***Erythromelalgia*** and ***Small Fibre Neuropathy***

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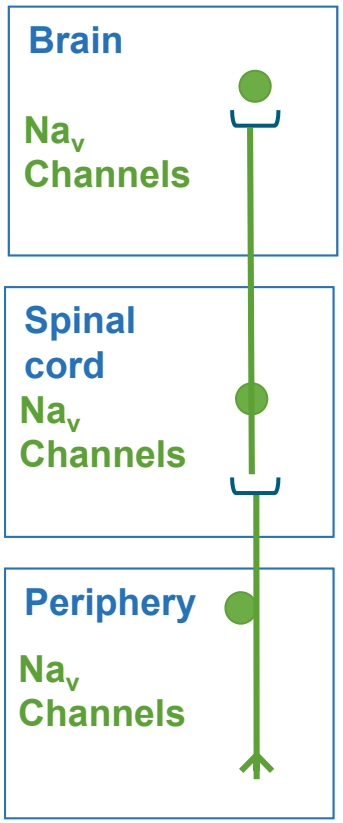
Biogen Nav channel pipeline: Targeting convergent points in pain pathway



The FDA has assigned raxatrigine orphan drug status for the treatment of trigeminal neuralgia

Pre-Clinical	Phase 1	Phase 2
Raxatrigine (CNV1014802) Na$_V$1.7 Blocker Trigeminal Neuralgia, Sciatica & Neuropathic Pain		
CNV1061436 Phase I ready Na$_V$1.7 blocker		
CNV3000223/CNV3000164 Na$_V$1.7 Candidates		

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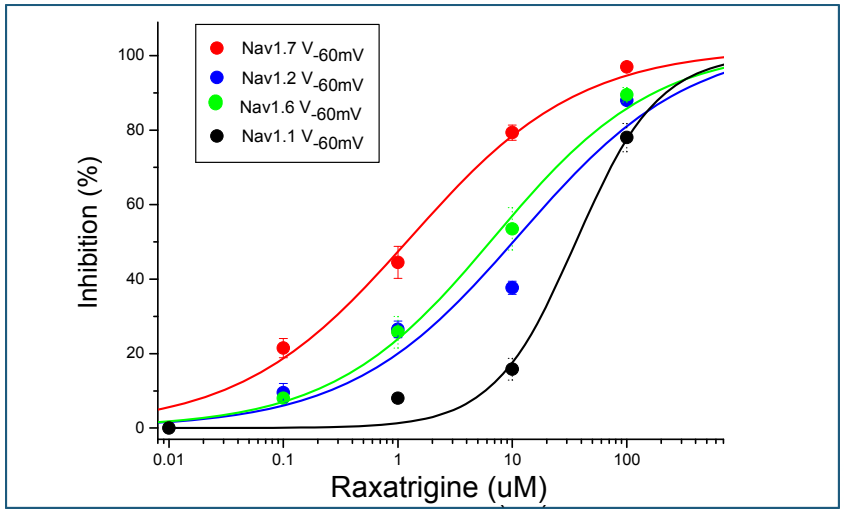
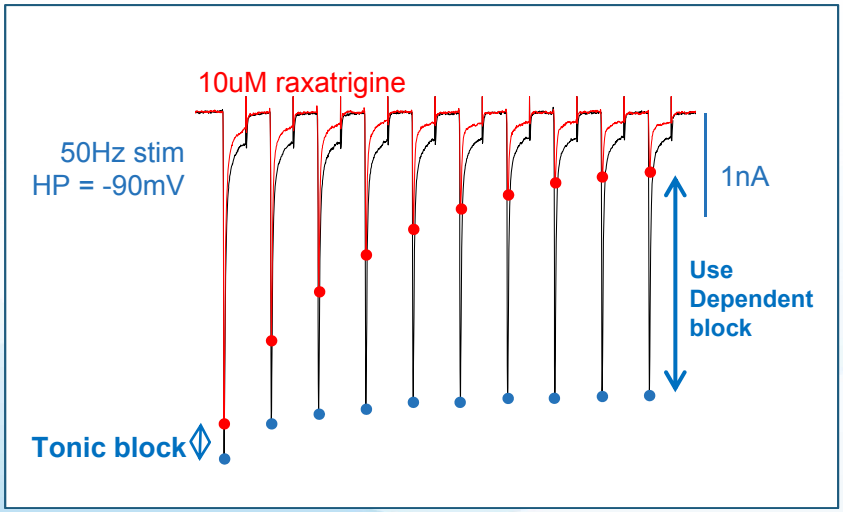
Raxatrigine is a selective Nav1.7 blocker with a differentiated mechanism of action



Orally available, CNS penetrant, $Na_v1.7$ selective blocker

Greater level of block as the pain network becomes more active (use-dependent block)



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Tremendous unmet need in trigeminal neuralgia

- Attacks of facial pain (paroxysms) - usually associated with entrapment of the trigeminal nerve with a blood vessel
  - "..sudden, severe, brief, stabbing pain occurring in attacks lasting at the most a few seconds usually only on one side of the face and provoked by light touch"
  - "an electric shock"
  - "stabbing, shooting, burning, excruciating.."
  - "unlike any other pain previously experienced" reference

  (quotes above taken from trigeminal neuralgia association - 'facing pain together')
- Paroxysm frequency depends on severity of disease
  - Range: a few times a month to several times each day
- Treatment options are limited: anticonvulsants or surgery

Only one drug licenced for this condition (Carbamazepine)
UK 1965, USA 1974

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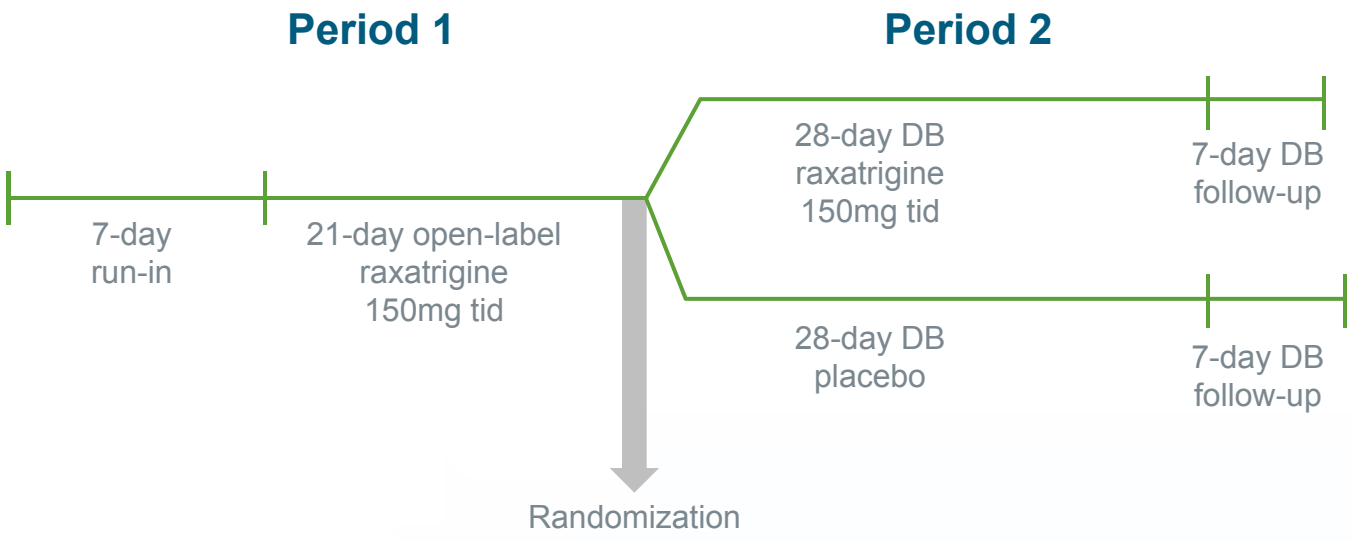
Successful Phase 2 completed in trigeminal neuralgia*



70.5% (31/44 pts) completing open-label treatment had a significant response

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* Presented at World Pain Congress 2014 and American Pain Society 2015.

Favourable efficacy outcomes on all endpoints

- Fewer patients experienced treatment failure (33.3%) versus placebo (64.3%) (p=0.0974)
- Longer time to treatment failure versus placebo (p=0.0306; KM analysis)
- After 4 weeks, pain intensity NRS values were 50% lower versus placebo (p=0.0009)
- Clinicians and patients reported greater improvement rates versus placebo
  - CGIC: improvement rate for raxatrigine was 80% vs 35% for placebo (p=0.0051)
  - PGIC: improvement rate for raxatrigine was 73% vs 50% for placebo (p=0.0265)

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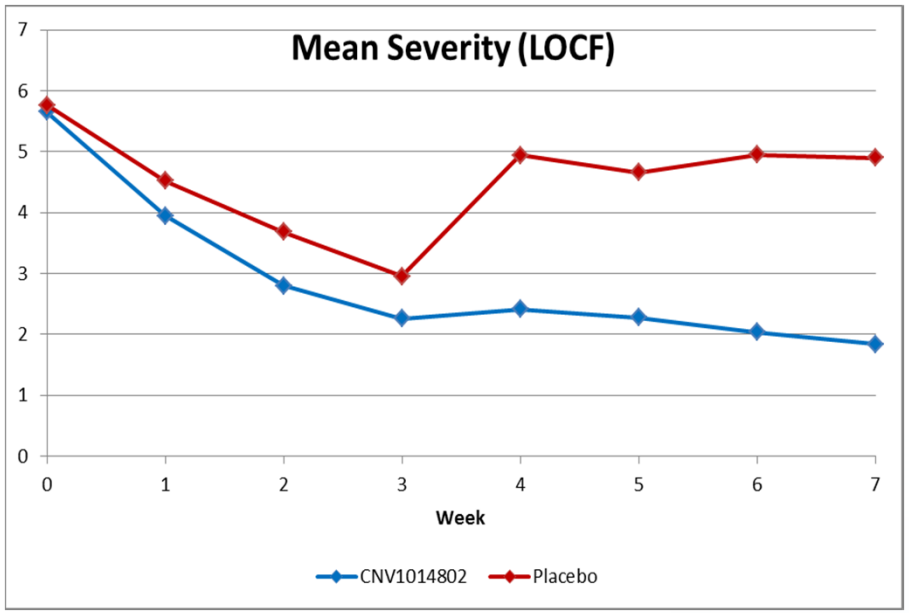
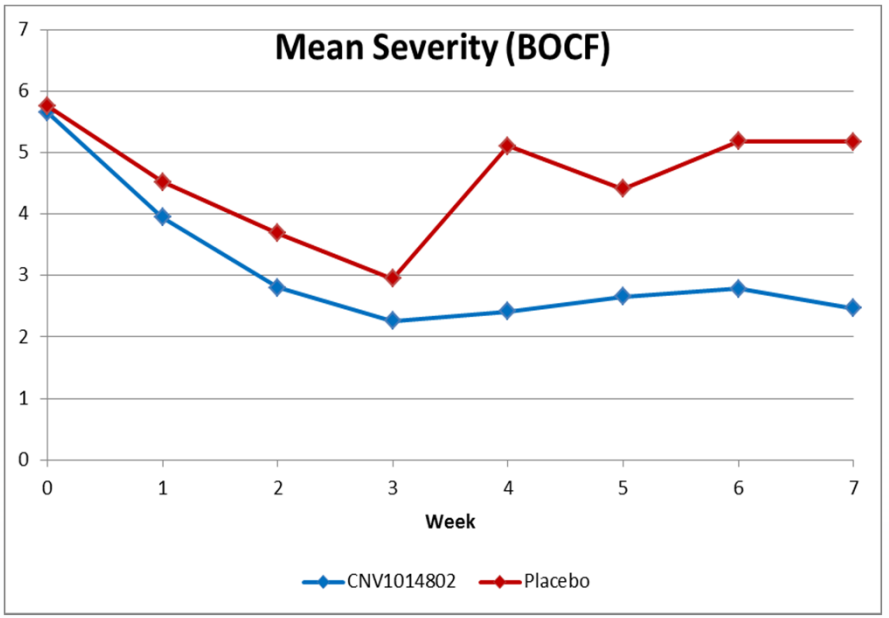
Post-hoc analysis reveals clinically significant benefit in average daily pain score





Analysis	Least Square Means		Comparison (Raxatrigine – Placebo) (95% CI)	p-value
	Placebo (N=14)	Raxatrigine (N=15)		
BOCF*	-0.74	-3.05	-2.31 (-3.78, -0.83)	0.0035
LOCF**	-1.10	-3.59	-2.50 (-4.16, -0.84)	0.0048

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** BOCF = Baseline observation carried forward*
*** LOCF = Last observation carried forward*

Phase 3 plans

Objective
To investigate the efficacy of raxatrigine in treating pain experienced by patients with trigeminal neuralgia

Design
12 weeks double blind

First Patient Dosed
Anticipated in 2016

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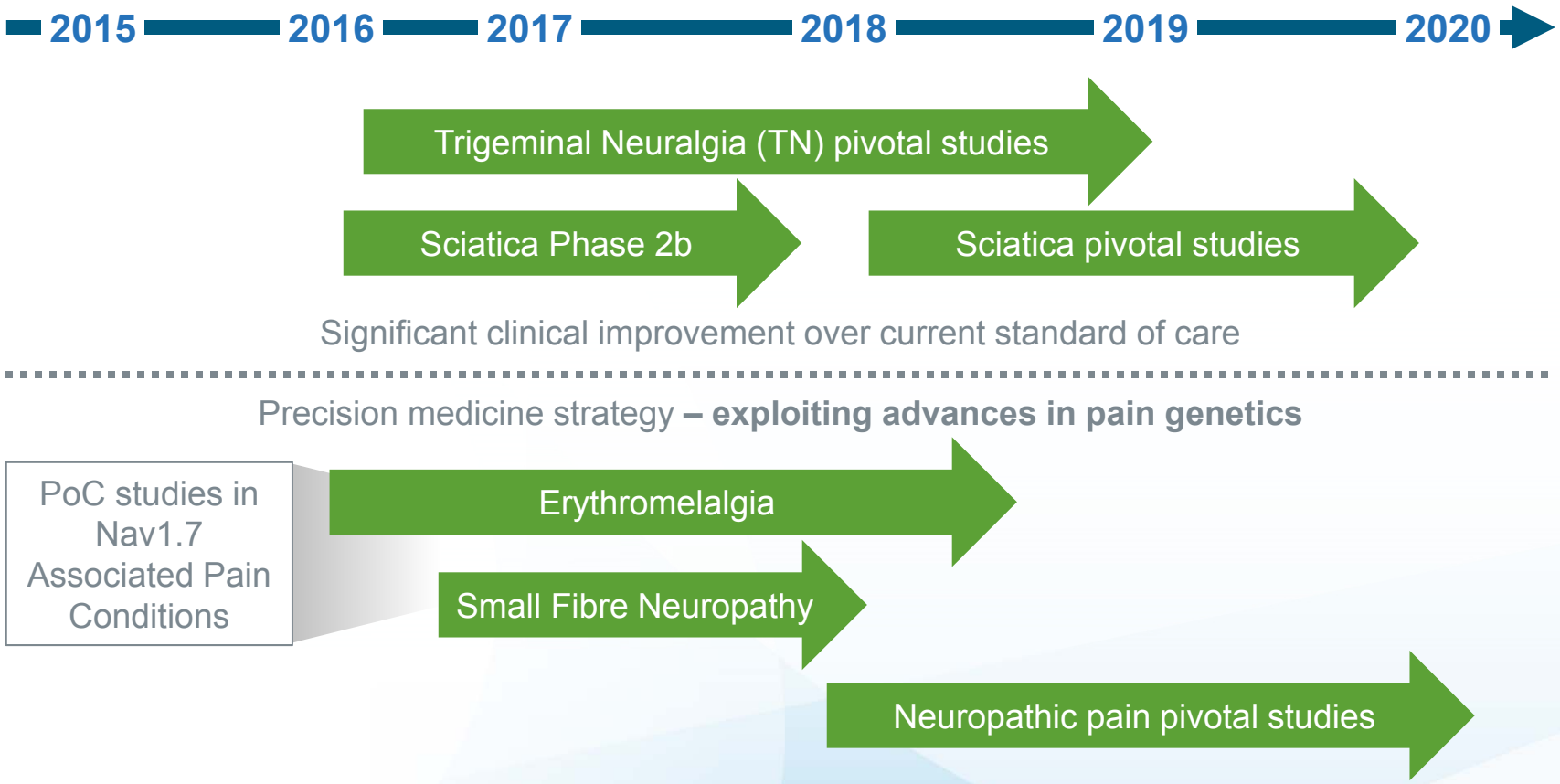
Integrated development plan

Deconstructing pain therapeutic area into populations of pharmacologically and genetically defined patient groups



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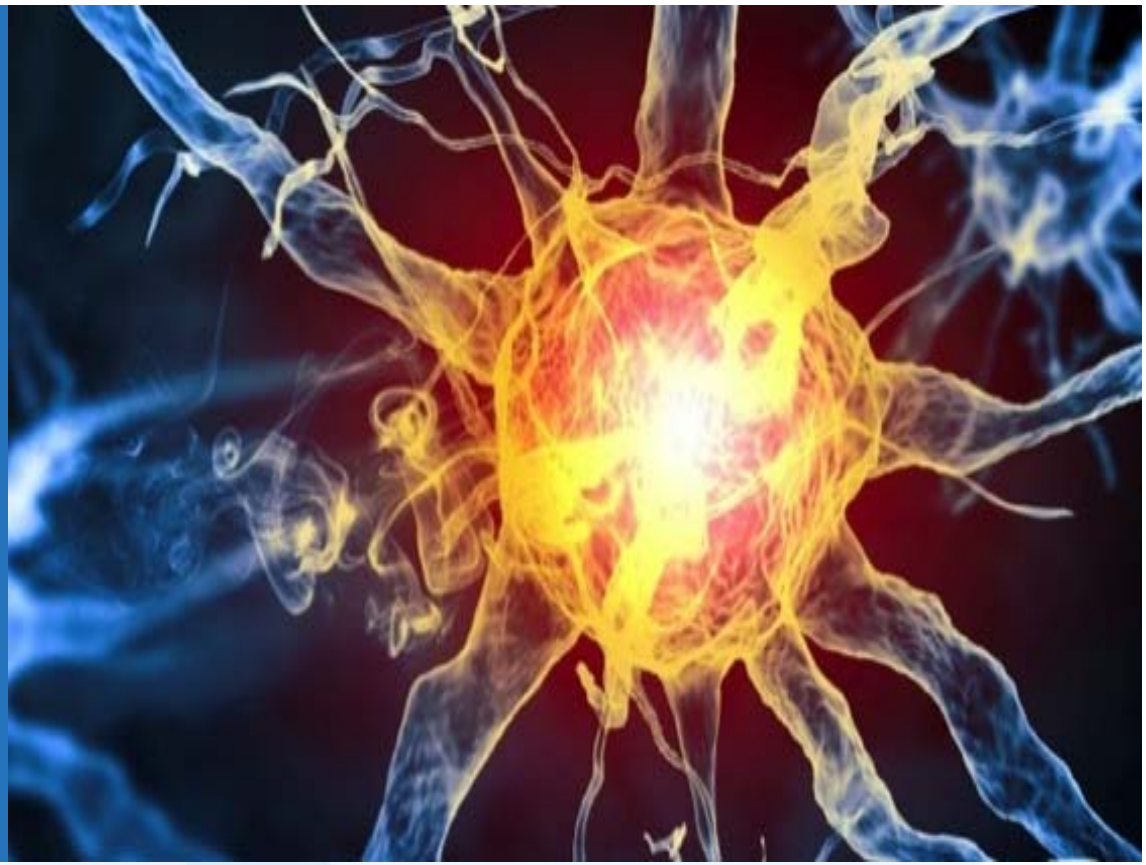
Tysabri in stroke

Jake Elkins, MD
Senior Medical Director



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TYSABRI for acute ischemic stroke

Significant Limitations with Current Tx

- Over 1.7M first-time ischemic strokes occur each year, common cause of death and disability
- High need for new treatments that can be used alone or as add-on to current therapies over extended time window

Phase 2 Demonstrated Clinical Benefit

- No effect of TYSABRI on MRI-defined infarct volume
- TYSABRI resulted in benefit on key clinical measures of stroke recovery and functional independence

Well-Characterized Safety Profile

- Phase 2 single dose administration - no safety concerns identified

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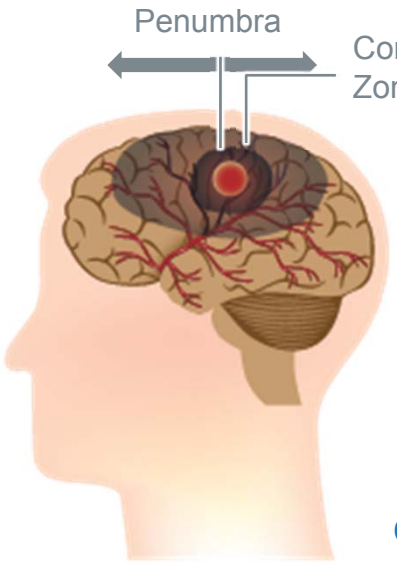
1 Biogen data on file; 2 AHA Heart Disease and Stroke Statistics, 2015 Update.3 Schichita, Nature medicine 2012, 4. Doyle J Neurosci 2015, Relton Stroke 2001.

TYSABRI targets key mediators of post-ischemic inflammation and neurotoxicity



After neuronal ischemia, damage-associated molecular patterns[1] activate innate and adaptive immune system

Acute (days)
Innate arm of the immune system: γδ T cells[2]
Acute infarct volume expansion: Measure with MRI

Subacute (weeks)
Adaptive arm of the immune system: CD4+T-cells, B-cells[3]
Peri-infarct – stroke recovery: Measure with clinical outcomes

[1] Shichita et al, Peroxiredoxin family proteins are key initiators of post-ischemic inflammation in the brain, Nature Medicine, 2012.
[2] Shichita et al, Pivotal role of IL-17 producing γδ T cells in the delayed phase of ischemic brain injury, Nature Medicine, 2008
[3] Doyle et al, B-lymphocyte-mediated delayed cognitive impairment following stroke, J Neurosci 2015.

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ACTION proof-of-concept trial: Single IV 300mg dose of TYSABRI in Acute Ischemic Stroke

- Acute Ischemic Stroke
- 0-9 Hours from onset
- NIH Stroke Scale > 5 points

Placebo (N=82)

TYSABRI 300mg IV x 1 dose (N=78)

Baseline	24±6hrs	Day 5	Day 30	Day 90 FINAL VISIT
Infarct Volume NIHSS	Infarct Volume NIHSS	Infarct Volume NIHSS; mRS; Barthel Index	Infarct Volume NIHSS; mRS; Barthel Index	NIHSS; mRS; Barthel Index;

*Single dose ** Change from baseline

AE=adverse event; AIS=acute ischemic stroke; FLAIR=Fluid attenuated inversion recovery; LKN=last known normal; MRI=magnetic resonance imaging; mRS=modified Rankin scale; NIHSS=National Institute of Health Stroke Scale; SAE=serious adverse event.

Protocol 101SK201.

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Clinical endpoints in ACTION

Modified Rankin Scale	• Functional Independence • 6-point scale ranging from death to no disability
Barthel Index	• Activities of Daily Living • E.g. walking, dressing, eating
NIH Stroke Scale	• Focal neurologic exam findings • E.g. arm / leg weakness, speech impairment
Stroke Impact Scale - 16	• Patient-reported stroke impact • E.g. difficulty completing daily tasks
Montreal Cognitive Assessment	• Cognitive screening test • Similar to Mini-Mental State Exam (MMSE) used in Alzheimer's disease

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Well-balanced baseline demographics

ACTION: Baseline Characteristics	Placebo N=82	TYSABRI N=77
Age, Mean (SD)	71.6 (12)	70.4 (13)
Gender (male)	59%	51%
Weight (kg), Mean (SD)	75.6 (16)	77.8 (17)
Baseline DWI volume in mL, Mean (SD)	40 (39)	42 (46)
Baseline NIHSS, Mean (SD)	13.2 (5.8)	12.9 (6.0)
Pre-stroke modified Rankin Scale, Mean (SD)	0.9 (1.45)	0.5 (1.00)
tPA use	79%)	73%
Time from stroke onset to study drug in hours, Mean (SD)	6.40 (1.7)	6.49 (1.5)

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Clinically meaningful benefit of TYSABRI at Days 30 and 90 on clinical and cognitive function, not on MRI volume

Clinical Outcome Scale	Odds Ratio for Favorable Outcome at Day 30	Odds Ratio for Favorable Outcome at Day 90	t-PA 3-4.5h Reference OR (95% CI) from ECASS3 Trial at Day 90
Clinical Function			
mRS score of 0 or 1	**2.88****	**1.48^**	**1.34 (1.02-1.76)**
Barthel Index ≥ 95	1.13	**1.91****	**1.23 (0.93-1.62)**
Stroke Impact Scale - 16 > median		**1.80***	**NA**
Montreal Cognitive Assessment ≥ 26		**2.03***	**NA**
Focal Clinical / MRI			
NIHSS score 0 or 1	0.69	1.10	**1.33 (1.01-1.75)**
MRI-defined Infarct Volume (1°EP)	1.09 (Day 5) 1.05 (Day 30)	NA	**NA**

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**1-sided P<0.05 ; *1-sided P <0.10; ^1-sided P <0.20

Clinical treatment effect of TYSABRI strongest in moderate size infarcts

Clinical Outcome Scale	Odds Ratio for Favorable Outcome at Day 90 Infarct volume < median	Odds Ratio for Favorable Outcome at Day 90 Infarct volume > median
Clinical Function		
mRS score of 0 or 1	**2.57****	0.52
Barthel Index ≥ 95	**3.22****	1.20
NIHSS score 0 or 1	0.90	1.36

****1-sided P<0.01**

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ACTION – Acceptable safety observed

Treatment Emergent Adverse Event	Placebo (n=82)	TYSABRI (n=78)
Death	13	14
Serious Adverse Events	38 (46%)	36 (46%)
Infections	36 (44%)	36 (46%)
Depression	15 (18%)	9 (11%)

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Conclusions and next steps

- A single-dose of TYSABRI did not reduce infarct volume but meaningfully improved functional outcomes at 90 days
- Pattern of clinical/MRI effects consistent with peri-infarct inflammation impacting functional recovery without focally expanding infarct core
- Overall, clinical profile and treatment window supports potential to complement existing therapies both as stand-alone and add-on therapy to reperfusion treatments
- Plan to confirm clinical effect and perform dose-ranging in Phase 2b trial. FPI anticipated in 2016

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Research in Biogen: Why and how

Spyros Artavanis-Tsakonas, PhD
Chief Scientific Officer

Biogen

Why ?

- **Research is the innovation engine that drives and sustains our growth over the long term**
- Research depends on world class researchers: we have been quite successful in recruiting such people from academia and industry
- We are conscious that we cannot solve everything inside. Quality of internal hires determines the quality of external collaborations
- Our research must be as good as any top level academic institution, perhaps better. Importantly we must link discovery to creative translation

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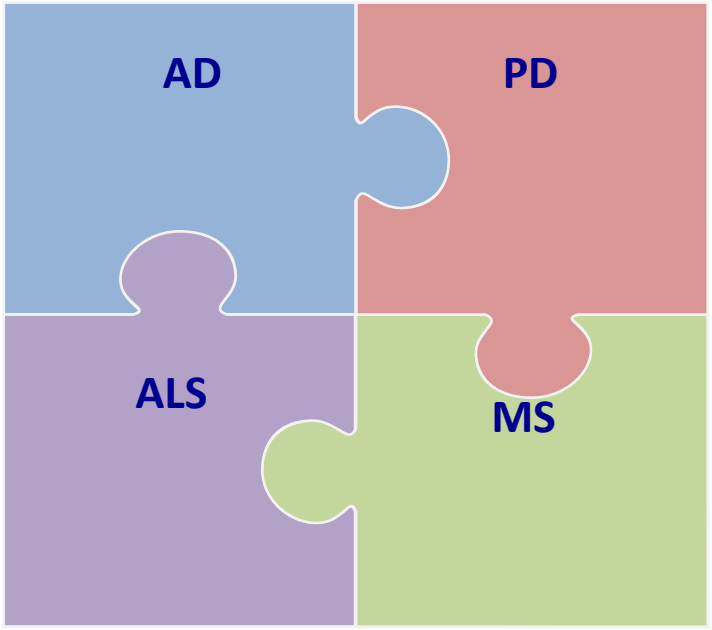
Our target discovery approach

Capitalize on Links within Neurodegeneration

An ALS target may address PD etc!



- Multifaceted approaches:
  - *Genetics, cell biological, physiological, molecular biological, biochemical, model system biology, imaging , novel preclinical models*

Exploratory freedom tightly integrated with drug development in core areas

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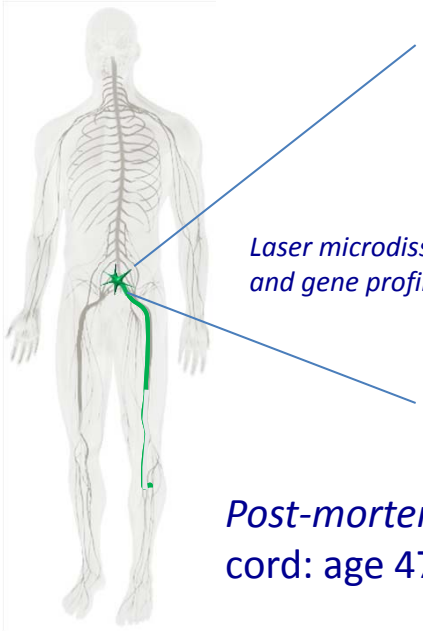
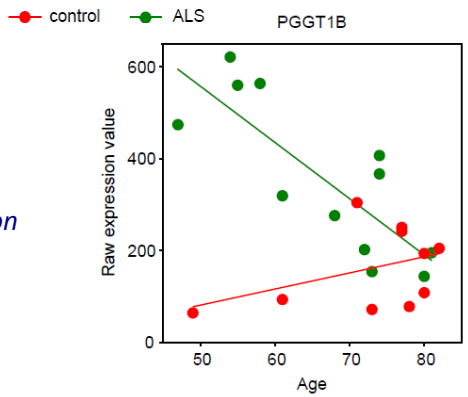
Novel disease modifiers in fly and human provide validated therapeutic targets



Laser microdissection and gene profiling



40 genes show tight correlation with early-onset ALS: candidate disease modifiers?

Post-mortem ALS spinal cord: age 47 to 81

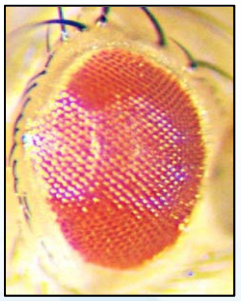
Henderson lab, Columbia;
Rabin et al., 2010

75% overlap !!

1 target relevant to both ALS and AD already in drug discovery pipeline

ALS fly eye

genetic screen



ALS fly eye with suppressor mutation

List of genes that slow or prevent ALS phenotype

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Artavanis lab, Biogen

Genetic screens identify a phospholipase (PL) as a modifier of ALS phenotypes

ALS | **AD**

Drosophila

- Knockdown protects ALS-related NMJ phenotypes
- Knockdown of PL pathway members also protect ALS-related

Mouse

- PL knockout protects a SOD.G93A model (preliminary data)
- PL ablation confers protection in a transgenic model of AD

Genetically Engineered Mouse

- PL knockout mice have no deleterious effects

Human

- High PL levels correlates with earlier onset ALS
- PL upregulation in AD patient-derived brains

Small Molecules

We have small molecule inhibitors

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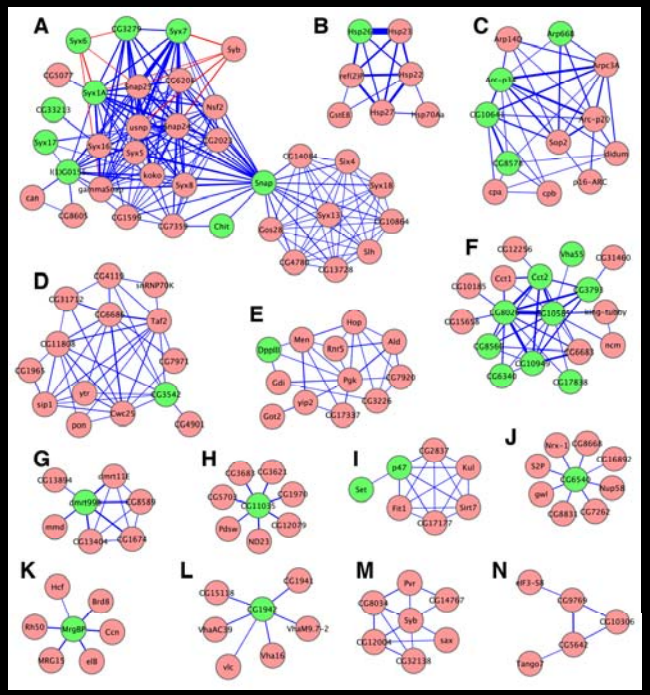
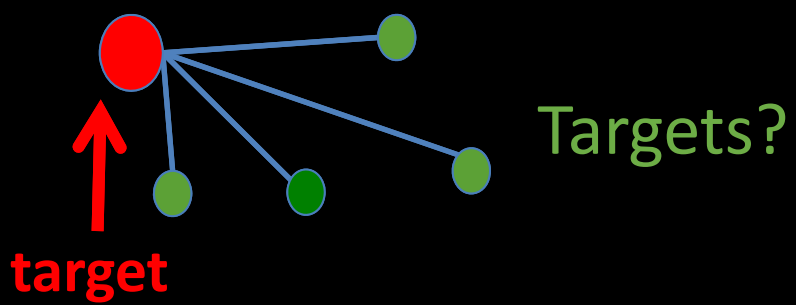
PL as an exploratory Target!

Exploring the target "space" : Proteomics

Proteins do not act alone



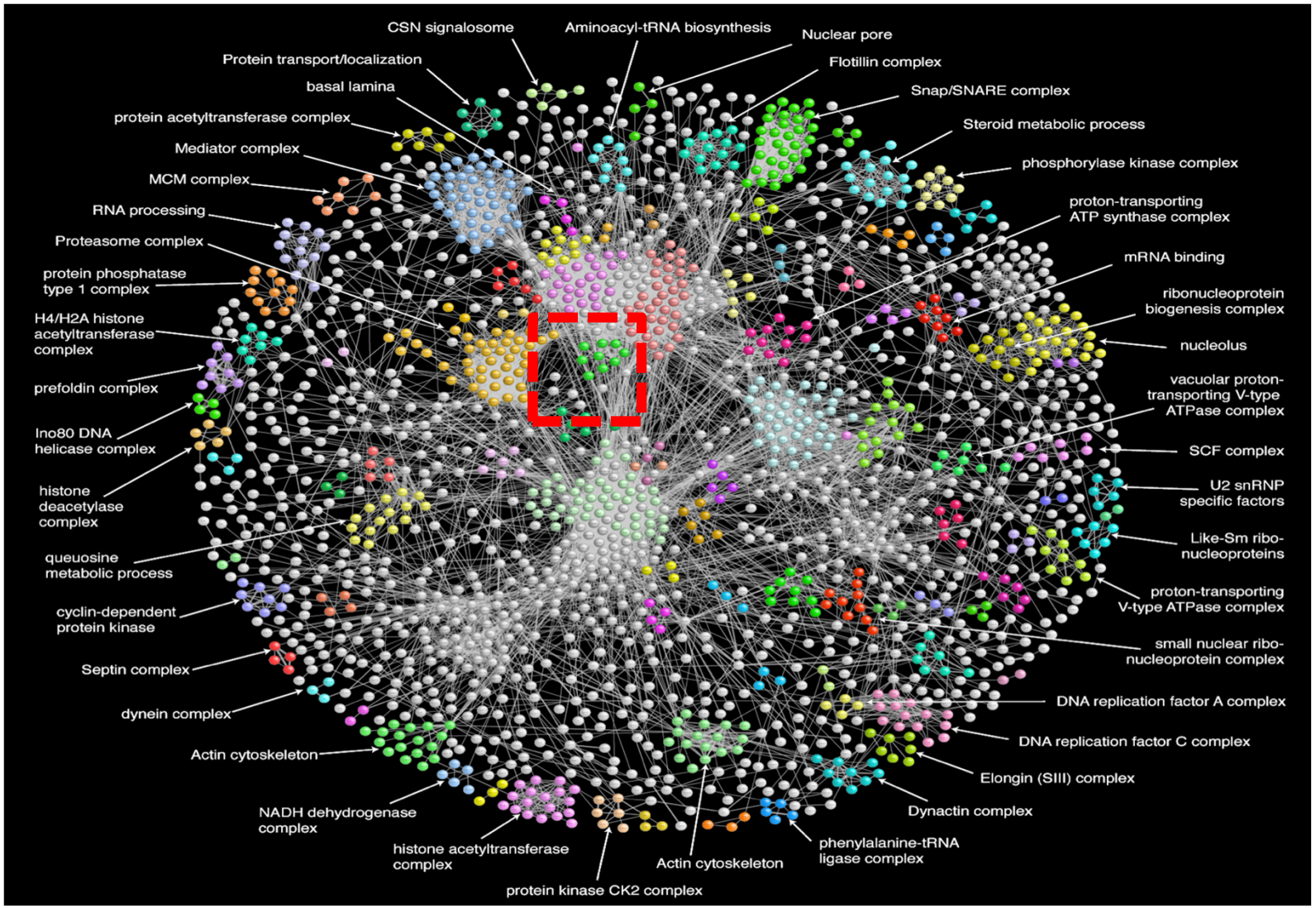
Defining protein complexes is important both for **function** as well as novel **target identification**



Define all protein interactions in a cell: Drosophila and Human

From one target to target (multiple !) alternatives

Defining the human and the Drosophila proteome



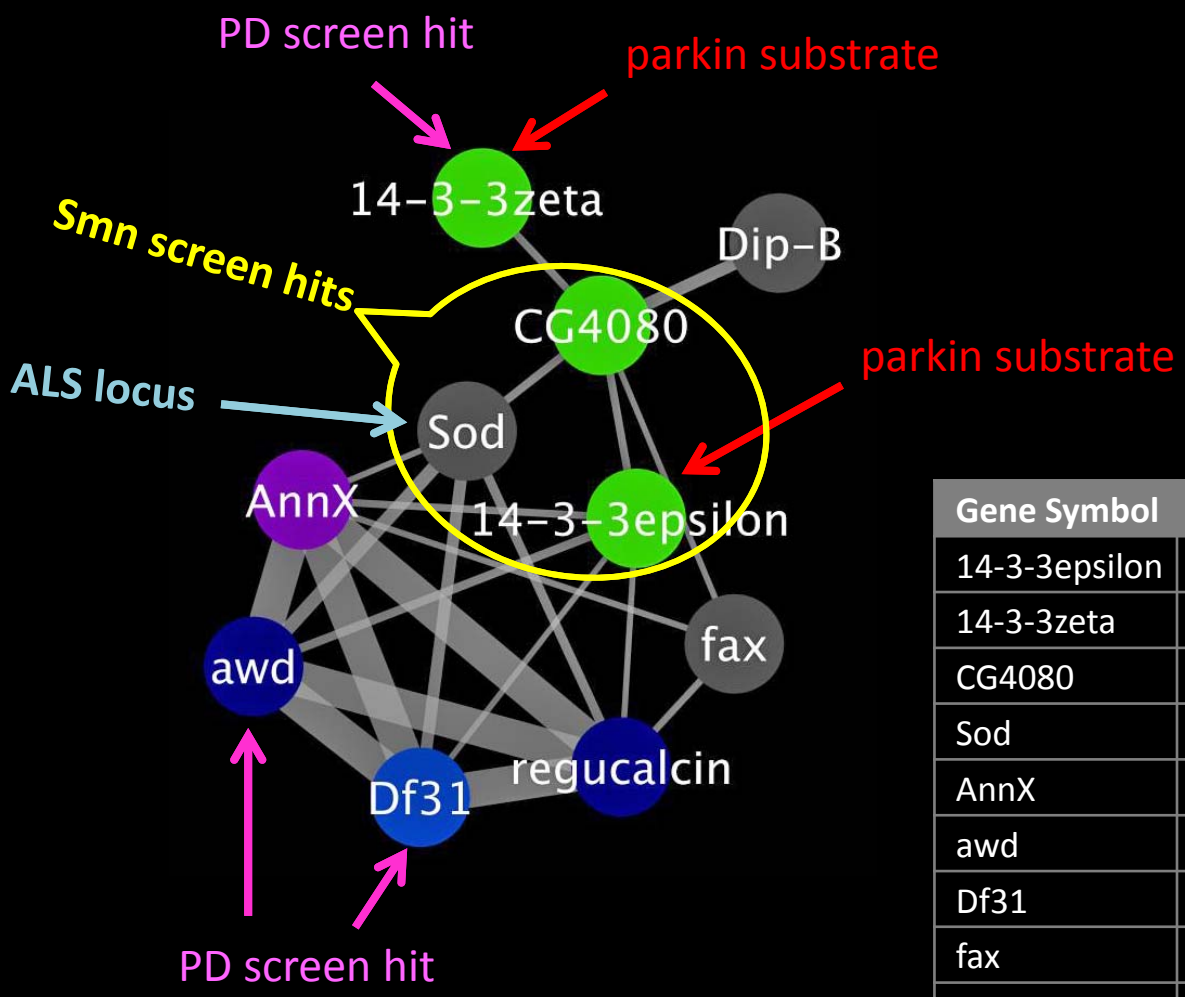
Q4 2015 Completion of both Proteomes

Collaboration with the Gygi and Harper Labs at Harvard

Guruharsha et al., 2011. *Cell*
Hutlin et al. 2015. *Cell*

Cluster 213

protein kinase C inhibitor activity, Ras protein signal transduction



Gene Symbol	Function
14-3-3epsilon	Ras protein signal transduction ;
14-3-3zeta	Ras protein signal transduction ;
CG4080	wing disc development ;
Sod	removal of superoxide radicals ;
AnnX	calcium-dependent phospholipid binding ;
awd	microtubule-based process ;
Df31	nucleosome assembly ;
fax	axonogenesis ;
Dip-B	proteolysis ; aminopeptidase activity
regucalcin	Intracellular calcium homeostasis

Our future depends on a successful innovation engine which can be efficiently and creatively translated

An innovation engine uniquely relies on the quality and originality of our research

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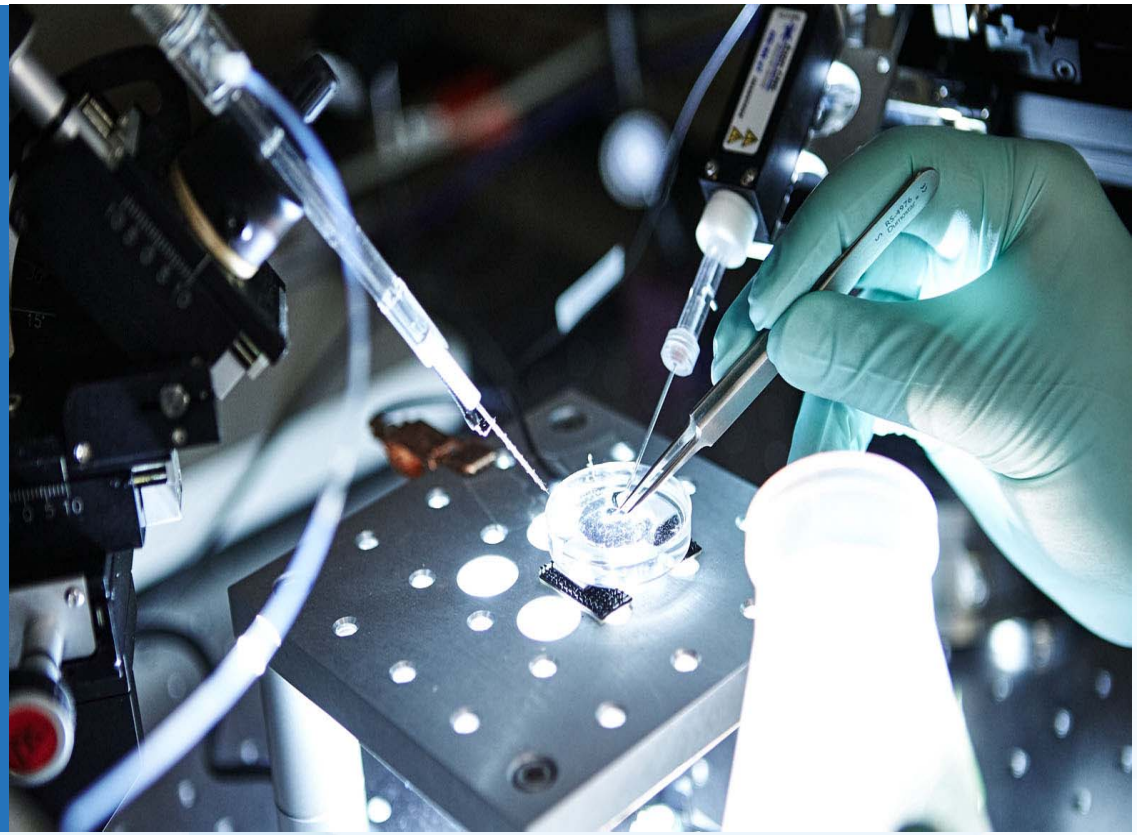
The new neurology at Biogen

Chris Henderson, PhD
VP Neurology Research



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Exciting times for neurodegenerative disease

1) Broadening AD research: Tau and beyond
2) A concerted assault on familial and sporadic ALS
3) Testing new and better targets in people with AD, PD, ALS and MS

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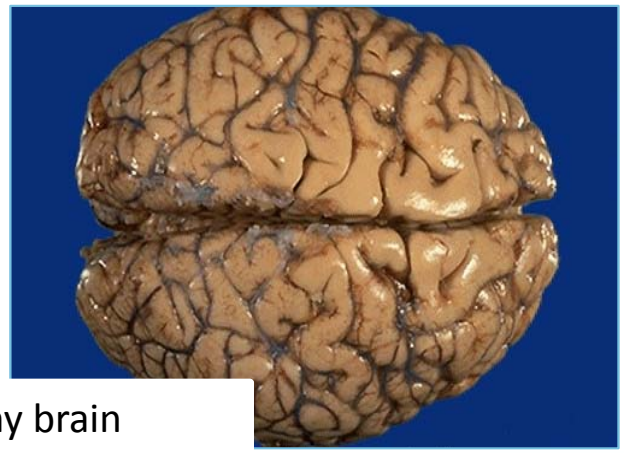
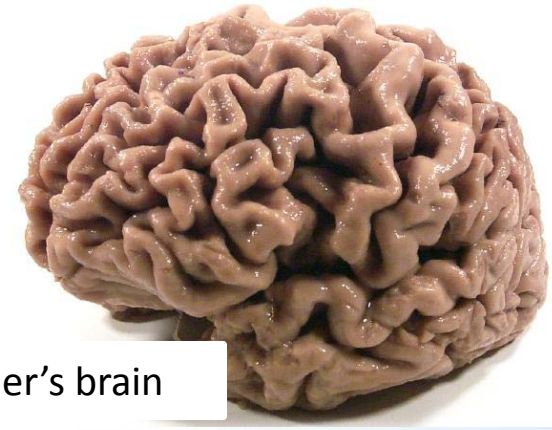
Neurodegenerative diseases have both specific and shared underlying mechanisms: future drugs may target either



Healthy brain



Alzheimer's brain

- Protein misfolding
- Altered RNA metabolism
- Glial dysfunction
- Synaptic dysfunction
- Axonal degeneration
- Cell death
- Inflammation

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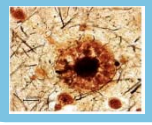
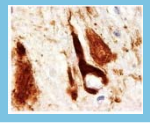
AD research strategy: thinking beyond aducanumab

Protein misfolding and aggregation

 Aβ

 Tau

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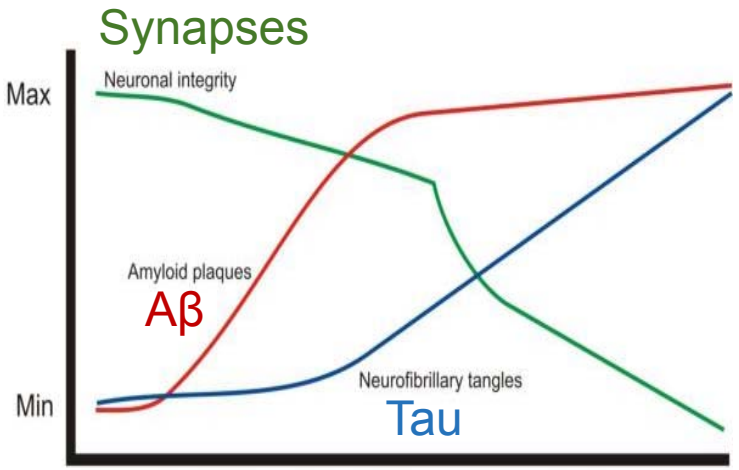
At risk → prodromal → mild → moderate → severe

Why tau?

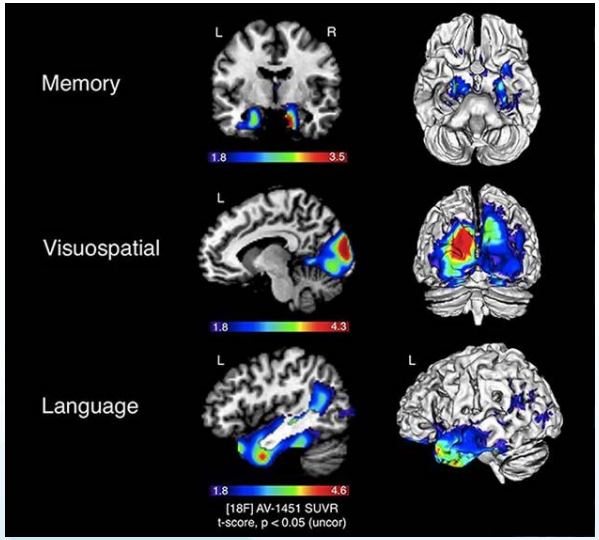
Temporal correlation with cognitive decline



disease progression

Perrin et al., 2009

Regional correlation with cognitive deficit



Schonhaut, Rabinovici labs (Alzforum AAIC report 2015)

Both AD and tauopathies

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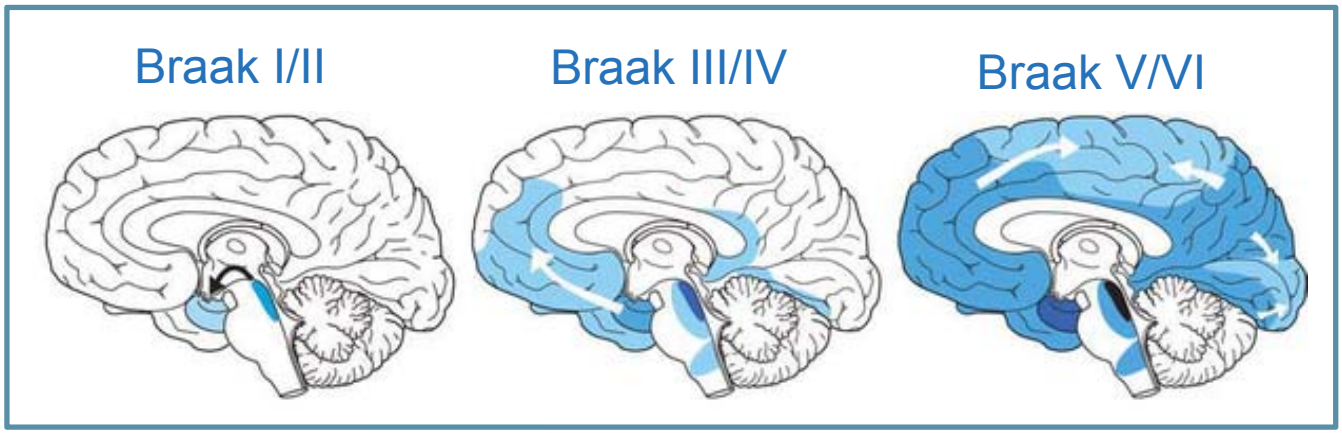
Spreading of tau pathology is correlated with progression of symptoms and may self-perpetuate



Jucker and Walker 2013

- Human imaging and postmortem data indicate that **Aβ initiates tau spreading**
- However, once triggered, **tau spreading can self-perpetuate** in the absence of Aβ pathology, at least in animal models

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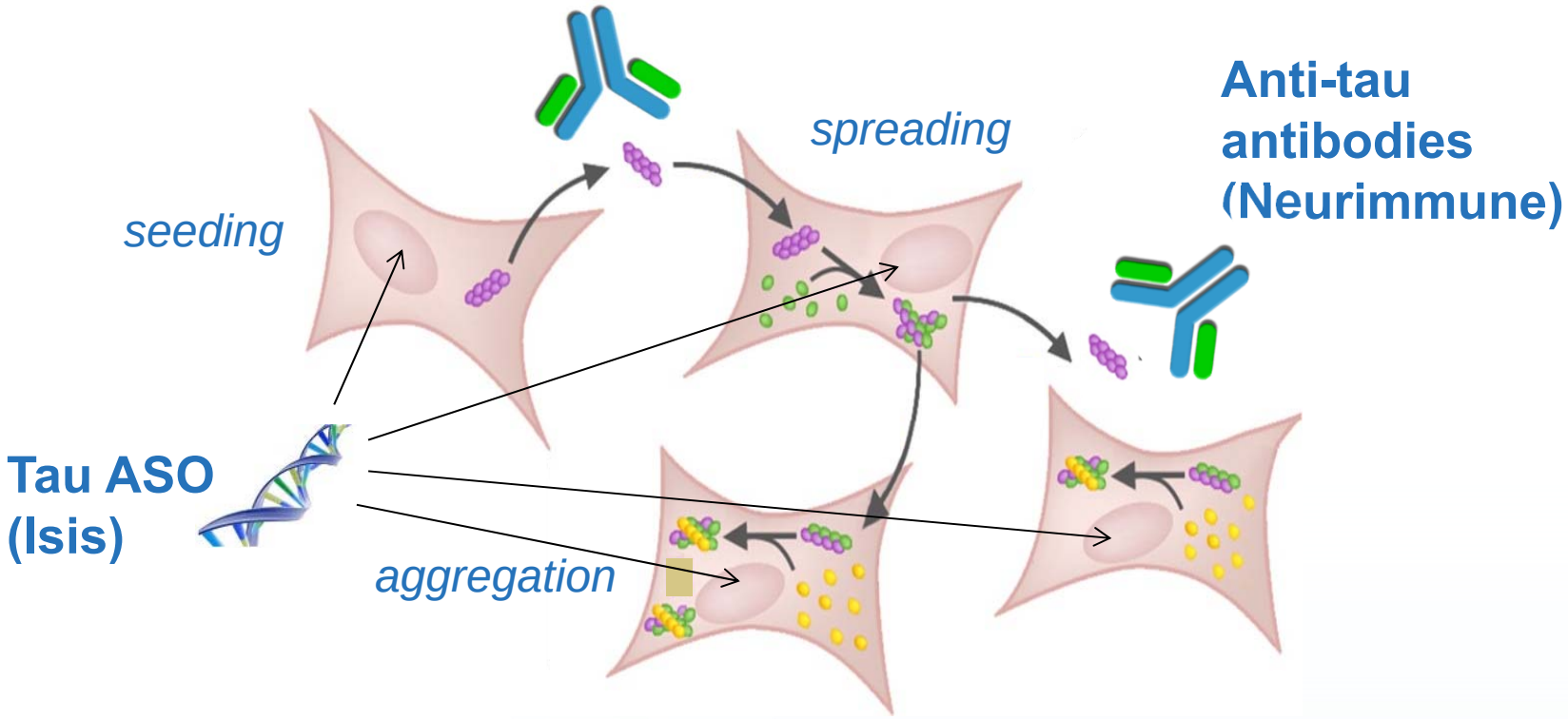
Aβ/tau combination therapy may be required to prevent progression in later stages of AD

Tau spreading as a target in AD and other tauopathies



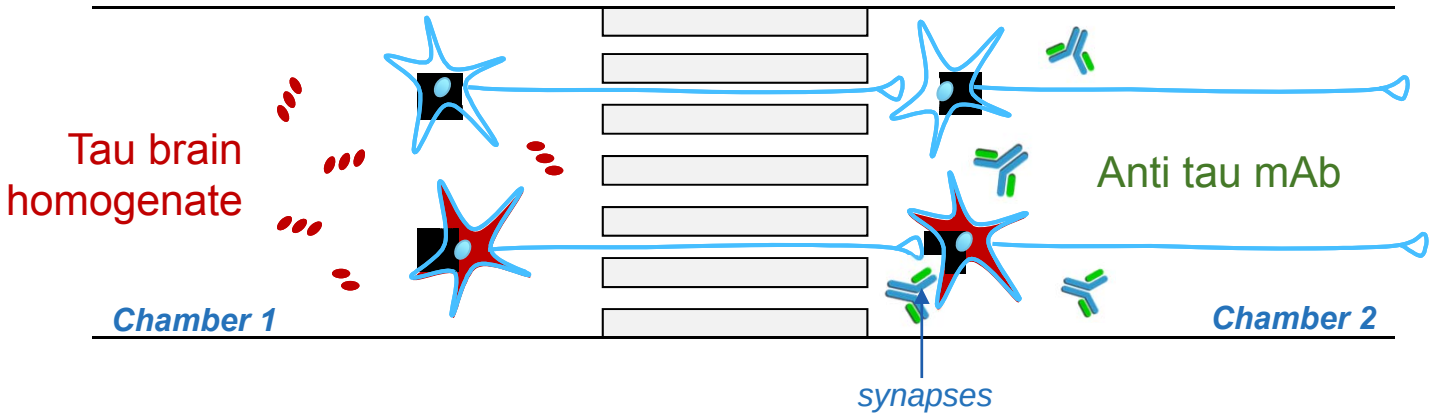
Challenge for all antibody approaches

The toxic and spreading tau species in human patients are unknown: phosphorylated? truncated? oligomeric? disease-specific strain?

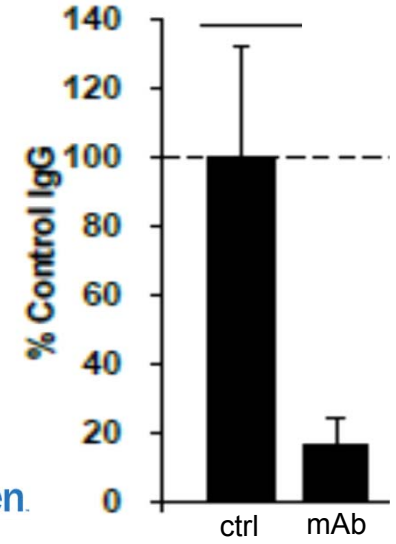
Potential solution

Lowering levels of *Tau* messenger RNA should reduce all toxic forms

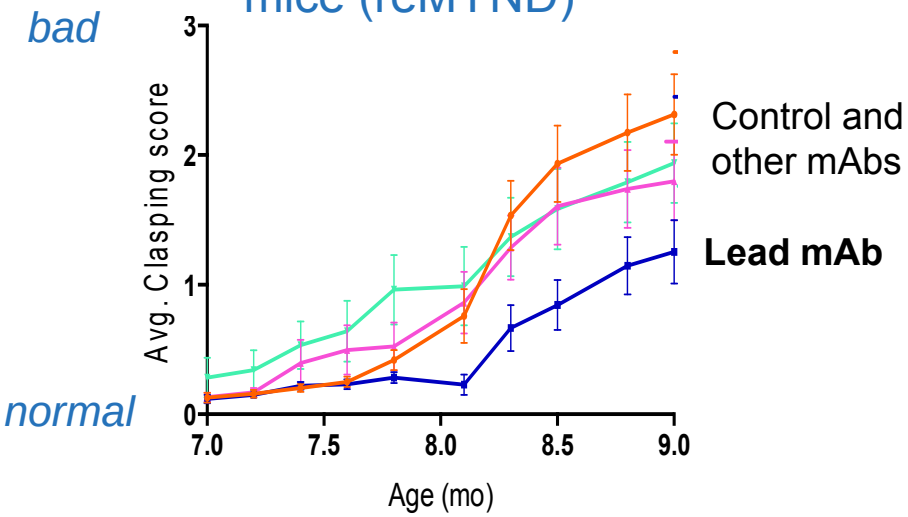
Tau mAbs block neuron-to-neuron spreading *in vitro* and improve behavior in transgenic mice *in vivo*



In vitro: Lead mAb **blocks tau spreading**



In vivo: Lead mAb **improves motor symptoms** in P301L mice (reMYND)



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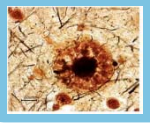
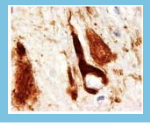
AD research strategy: an expanding focus

Novel targets from exploratory research

Risk factors (e.g. ApoE)

Biomarker-based outcomes

Protein misfolding and aggregation

 Aβ  Tau

Synapse dysfunction / loss – Neuronal death

Glial dysfunction

Novel targets from human genetics

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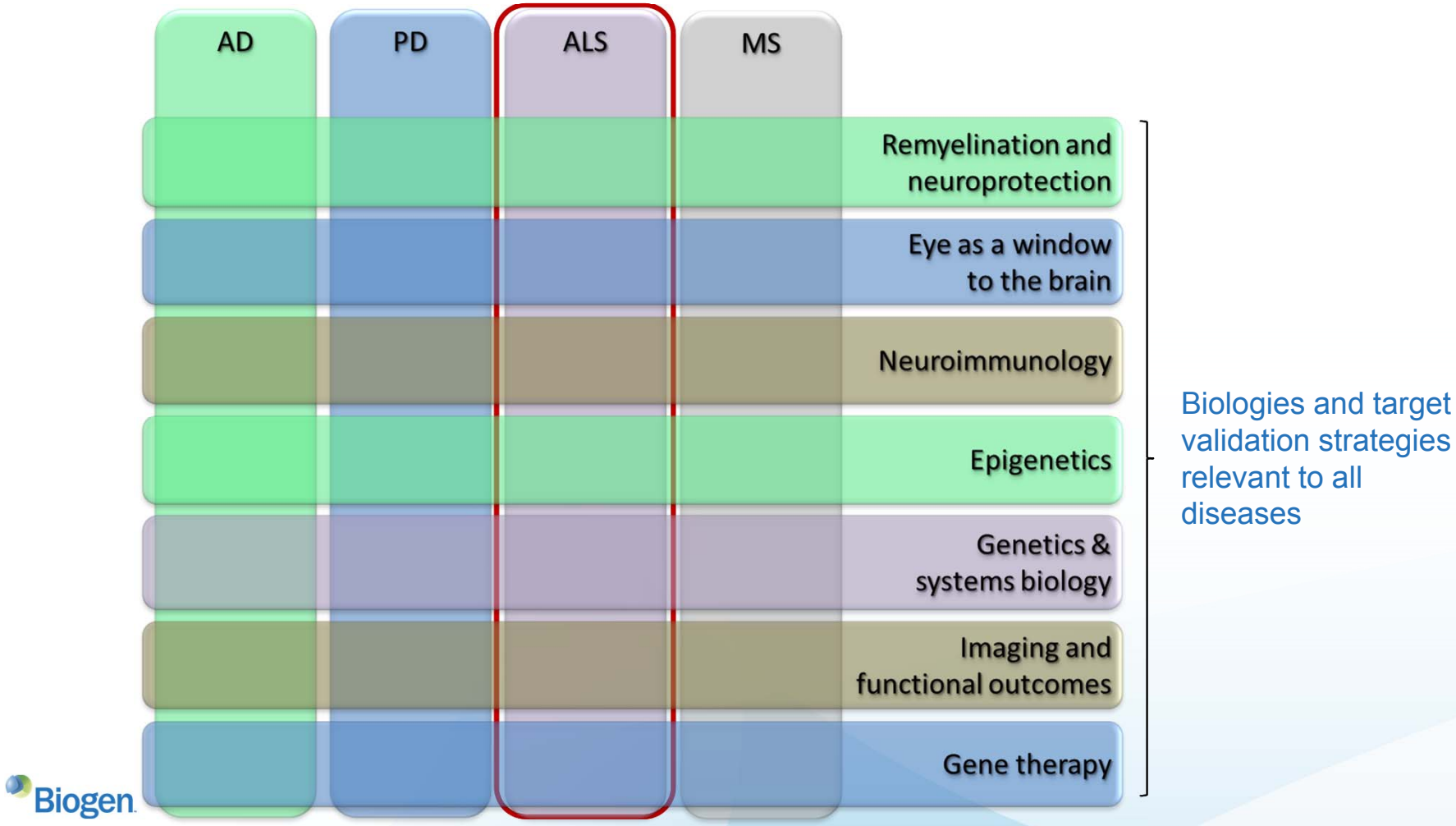
At risk prodromal mild moderate severe

A neurology discovery-to-development engine for multiple diseases and pathways



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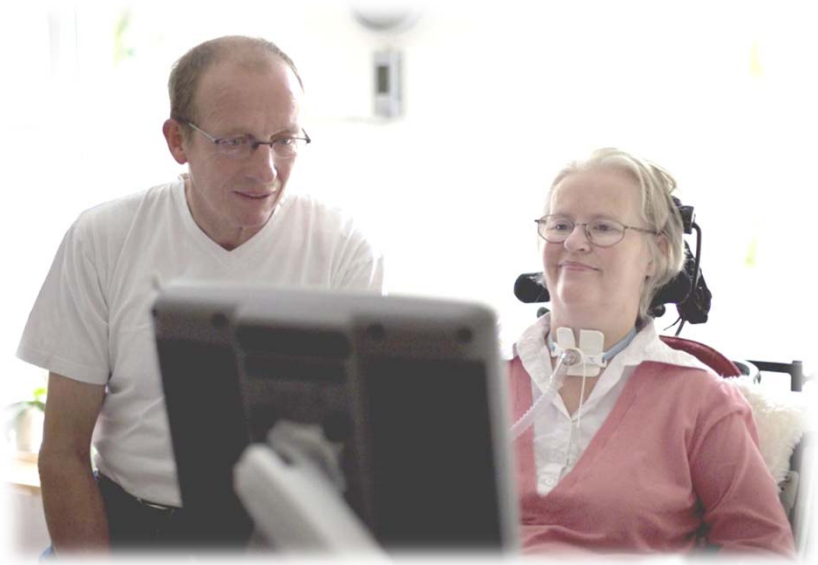
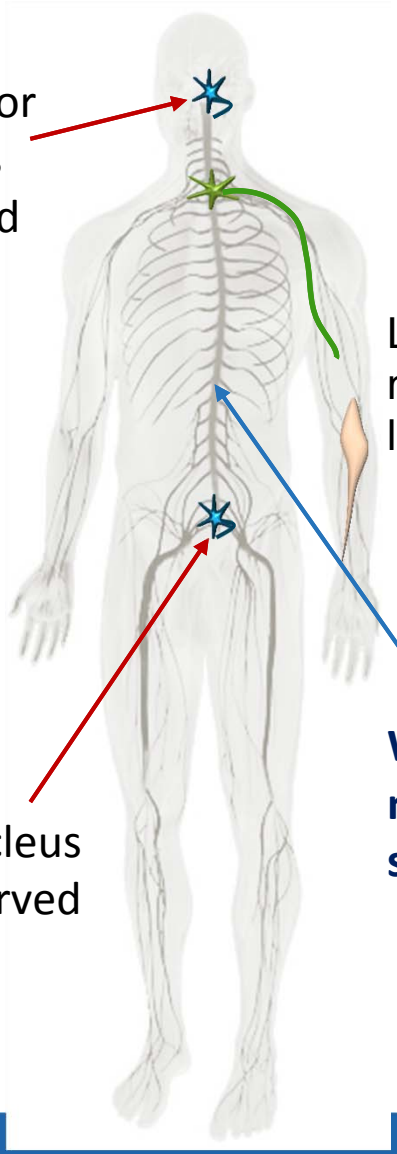
Learning from nature: Using selective resistance to discover targets for sporadic ALS





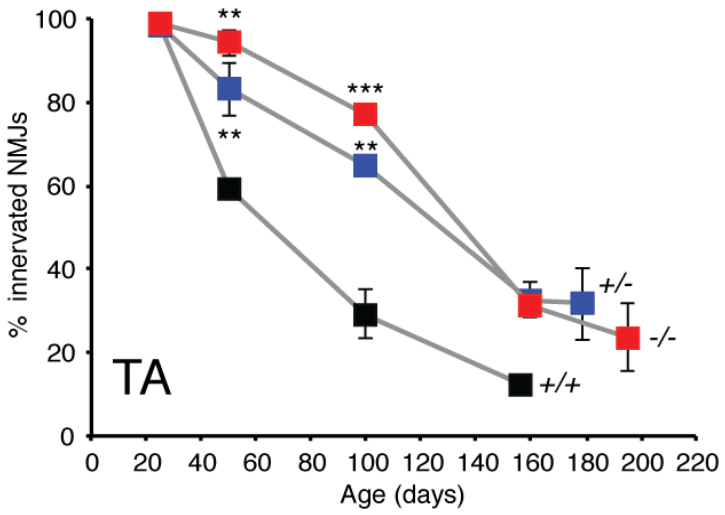
What makes spinal motor neurons selectively vulnerable?

They are the only motor neurons to express MMP-9

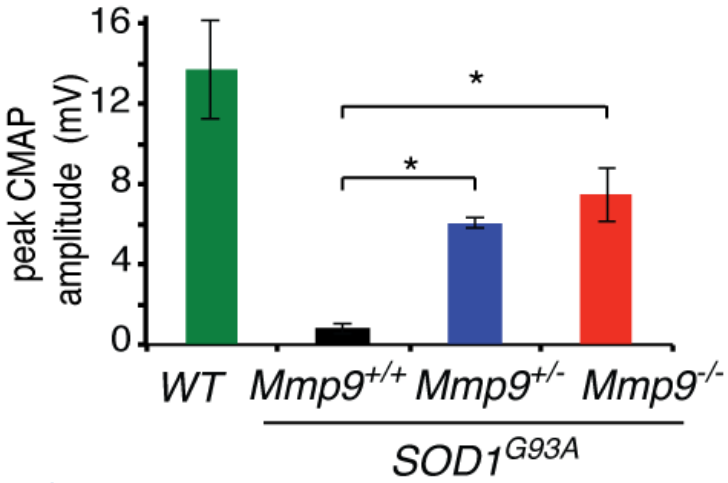
Biogen

Reducing MMP-9 delays loss of neuromuscular synapses and enhances muscle strength in ALS model mice

Nerve-muscle synapses last 80 days longer



Muscle strength preserved when MMP-9 levels low

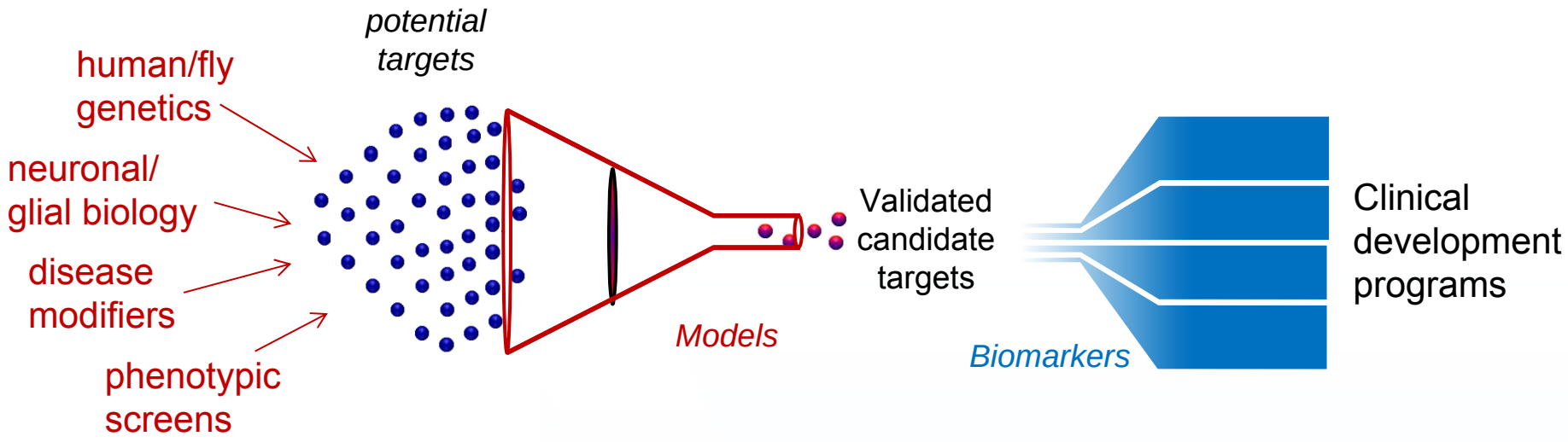


Kaplan et al., 2014

- **Reducing MMP-9 may be therapeutic for patients with both familial and sporadic ALS**
- **Tens of other targets have strong rationale in ALS and other diseases but have not been validated**

Biogen

Accelerating target validation in patients with neurodegenerative diseases



Filters:

human genetics and expression

high-throughput evaluation in animal models

sensitive human proof-of-concept trials

see Johns (ALS)

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Exciting times for neurodegenerative disease

1) Broadening AD research: Tau and beyond
2) A concerted assault on familial and sporadic ALS
3) Testing new and better targets in people with AD, PD, ALS and MS

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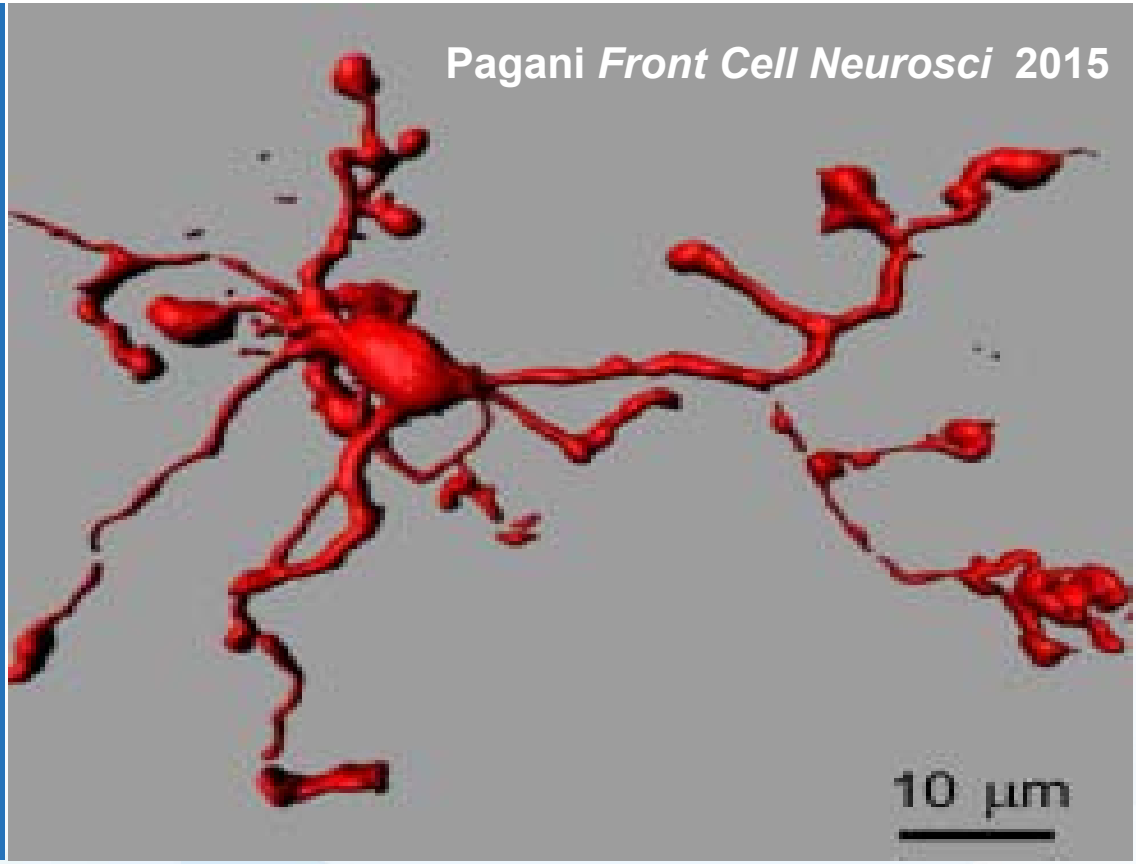
Vision for neuroimmunology in neurodegeneration

Richard M. Ransohoff, MD
Senior Research Fellow &
VP Neuroimmunology



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Four takeaway points

- Neuroinflammation is integral to neurodegeneration.
- At Biogen Neuroimmunology Research, we study how the brain's local environment regulates neuron failure or death in neurodegenerative disease.
- This research is carried out by a deep, talented team, tightly integrated with Biogen Neurology and Pathway Research.
- Identifying neuroimmunological molecular mechanisms enables us to attack neurodegeneration on multiple fronts.

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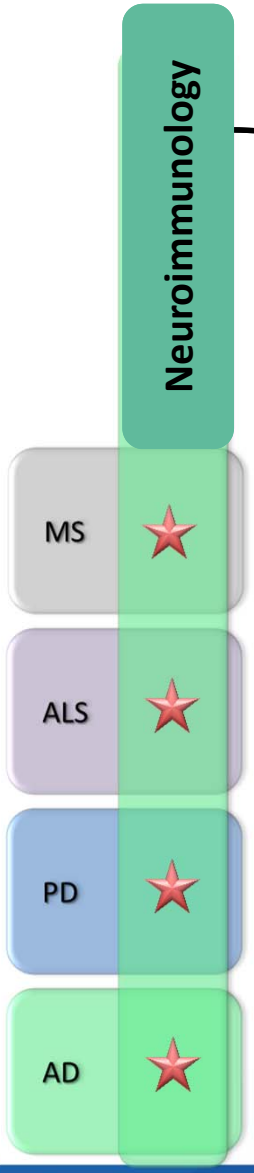
Neuroimmunology research affects all therapeutic areas

Richard M. Ransohoff and team



Focus for today: Microglia, BBB

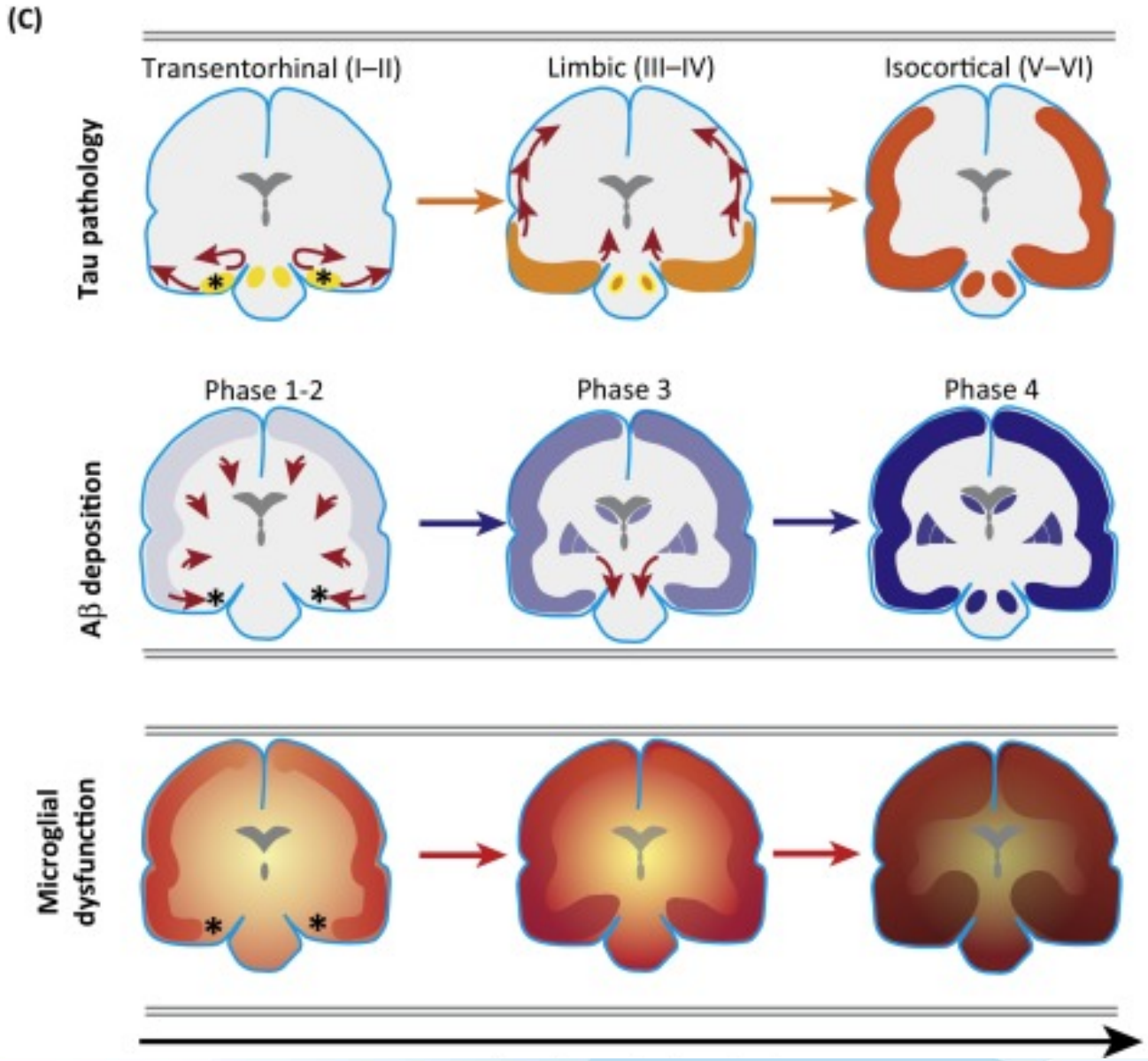
Attenuate MS tissue injury, promote BIIB37 BBB transit

Promote axon repair and NMJ reinnervation

Lessen striatal motor neuron loss by modulating microenvironment, promote BIIB054 BBB transit

Reduce synapse loss, foster synapse formation, neurogenesis. Enhance Aβ clearance and interdict tau pathology; address ARIA

Tau and Amyloid Pathologies: Synchronous with the Neuroinflammatory Reaction



Andreasson *TiNS* 2015

Who is Biogen Neuroimmunology?

Bench scientists and scientist-managers

Largest single site group in the U.S.

Uniformly talented; deep, diverse, experienced

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Why Neuroimmunology?

- CNS neurodegenerative diseases selectively degrade and destroy neurons and oligodendrocytes. Pathogenesis is not cell autonomous.
  - CNS local environment includes reactive cells (microglia and others) and the BBB which determine outcomes of disease process
  - The systemic environment (infection, chronic inflammation, metabolic state, microbiome) also contributes to disease or health

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Why Microglia?

- Most reactive cells in CNS
  - Myeloid origin endows them with toxic effector functions
  - Myeloid origin endows them with repair capacity.

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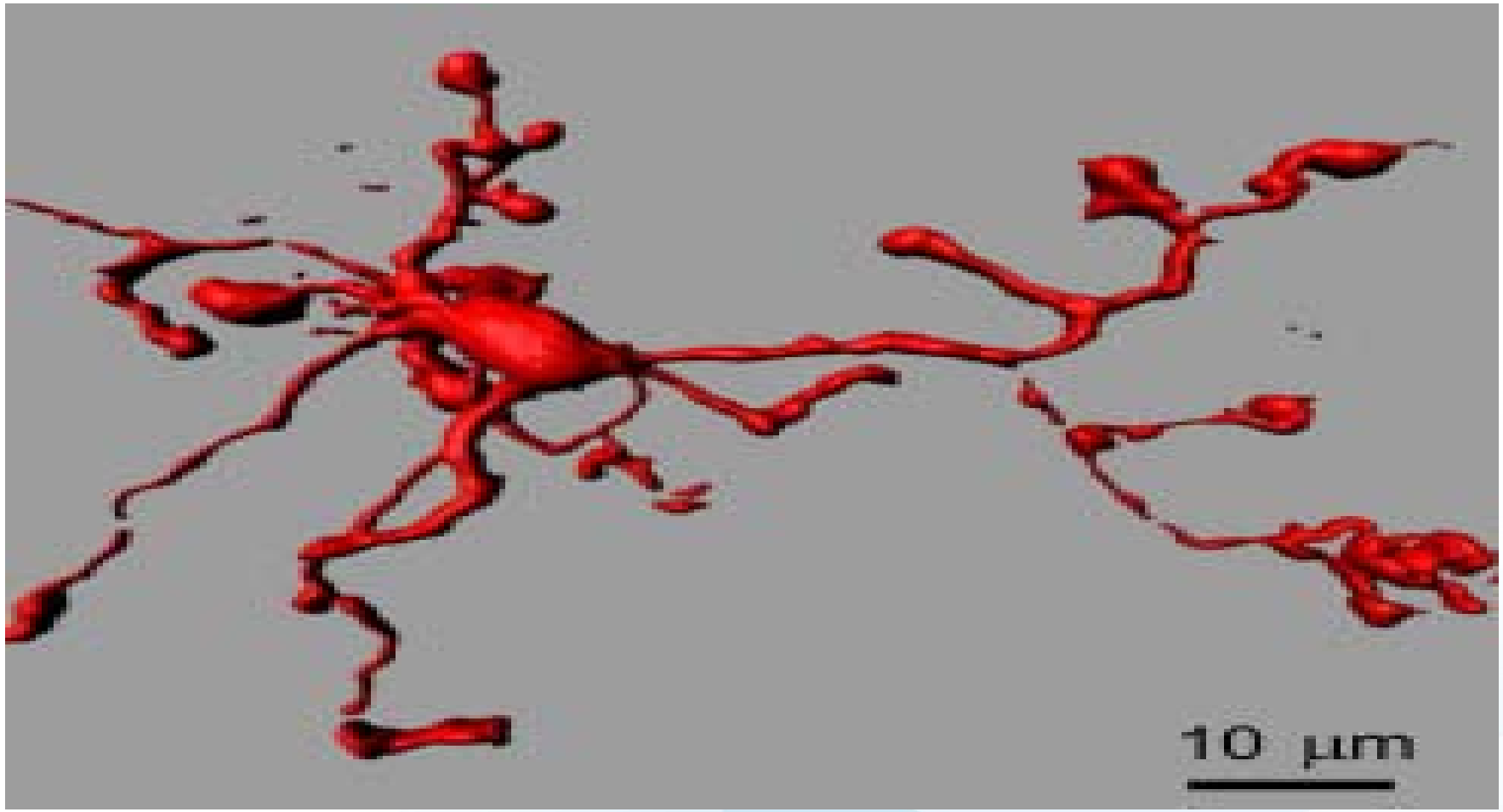
Why Microglia?



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Why Microglia?

- Most reactive cells in CNS
  - Myeloid origin endows them with toxic effector functions
  - Myeloid origin endows them with repair capacity.
  - Loss of essential function in reactive state mandates urgent restoration of physiological abilities.

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Why Microglia?

- Most reactive cells in CNS
  - Myeloid origin endows them with toxic effector functions
  - Myeloid origin endows them with repair capacity.
  - Loss of essential function in reactive state mandates urgent restoration of physiological abilities.
- Ripe for therapeutic application:
  - Numerous clinical stage compounds and agents which modify myeloid cell function
  - Problem: Role(s) in disease are complex, largely unknown.

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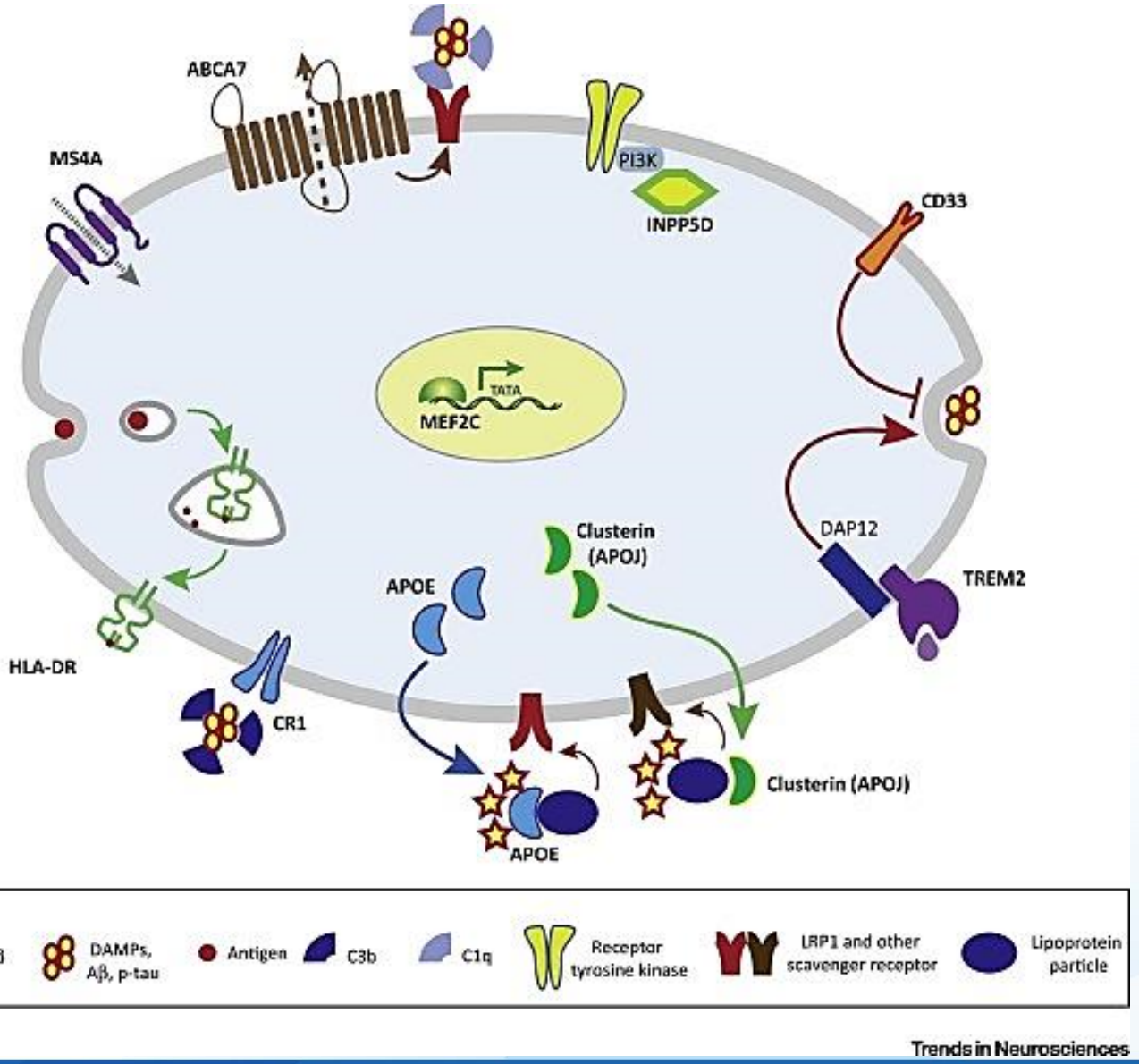
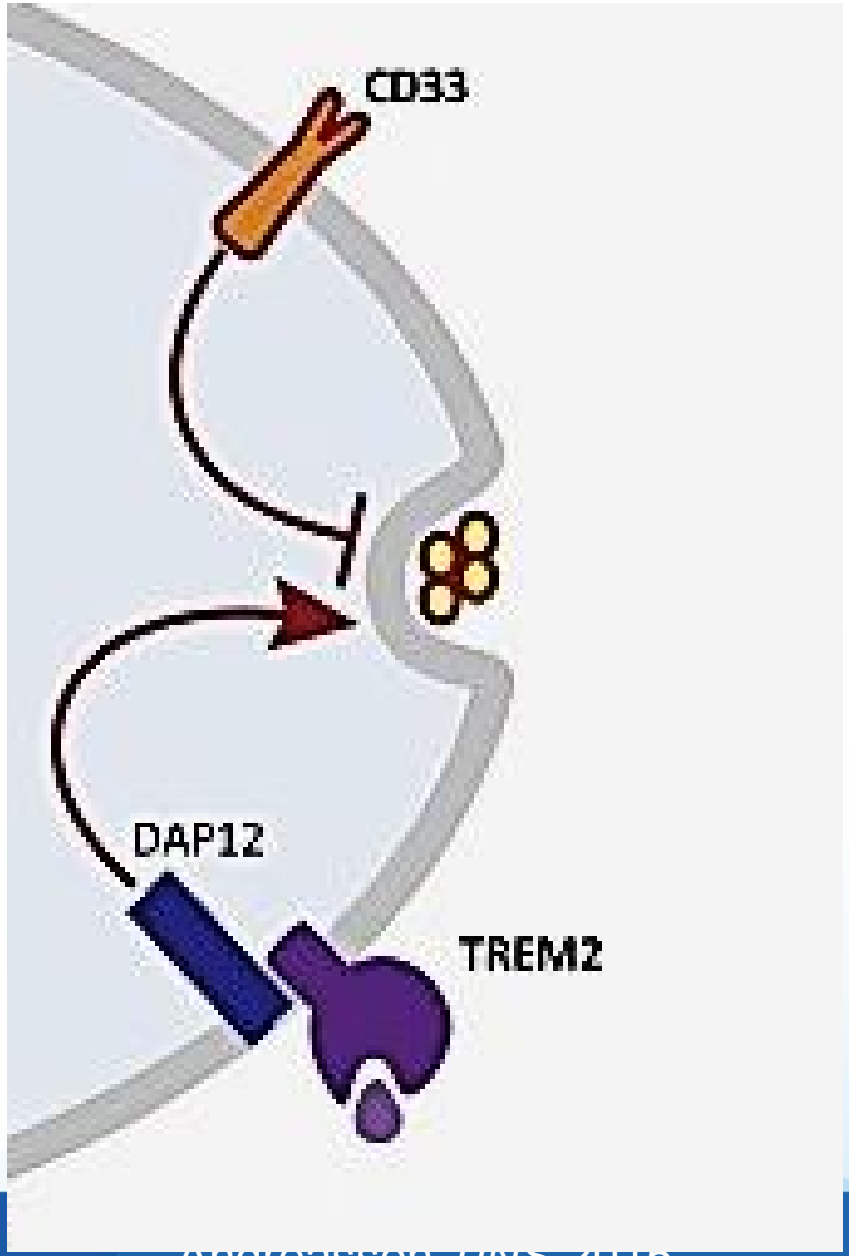
GWAS* AD Variants crowd together in Microglia!

*GWAS: Genome-Wide Association Studies



Andreasson *TiNS* 2015

GWAS AD Variants crowd together in Microglia!



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TREM2 variant R47H implicated in multiple neurodegenerative diseases

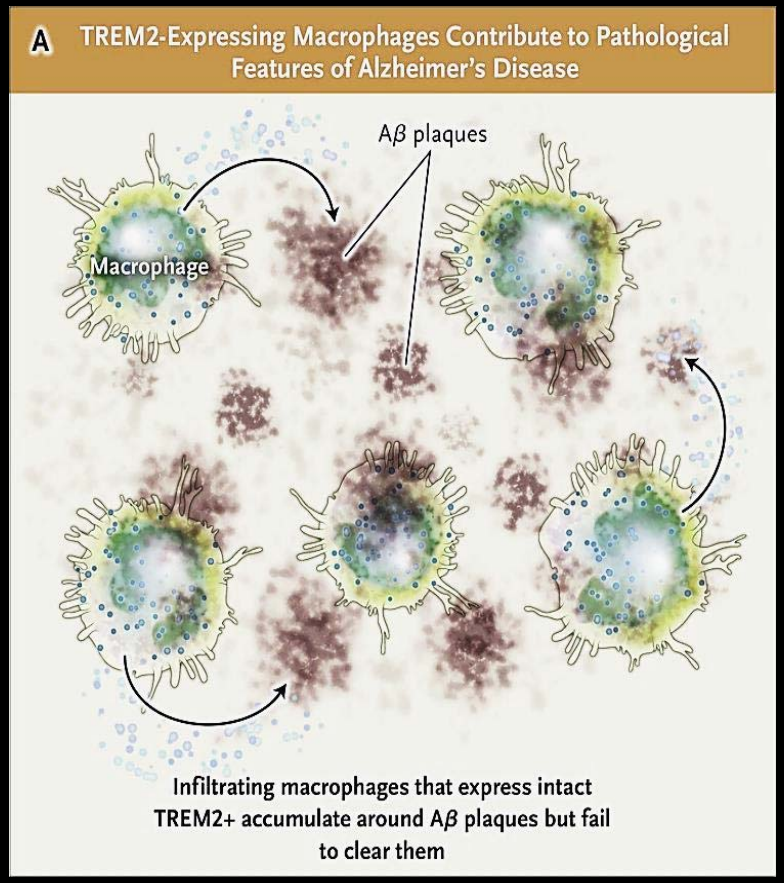
Table 1

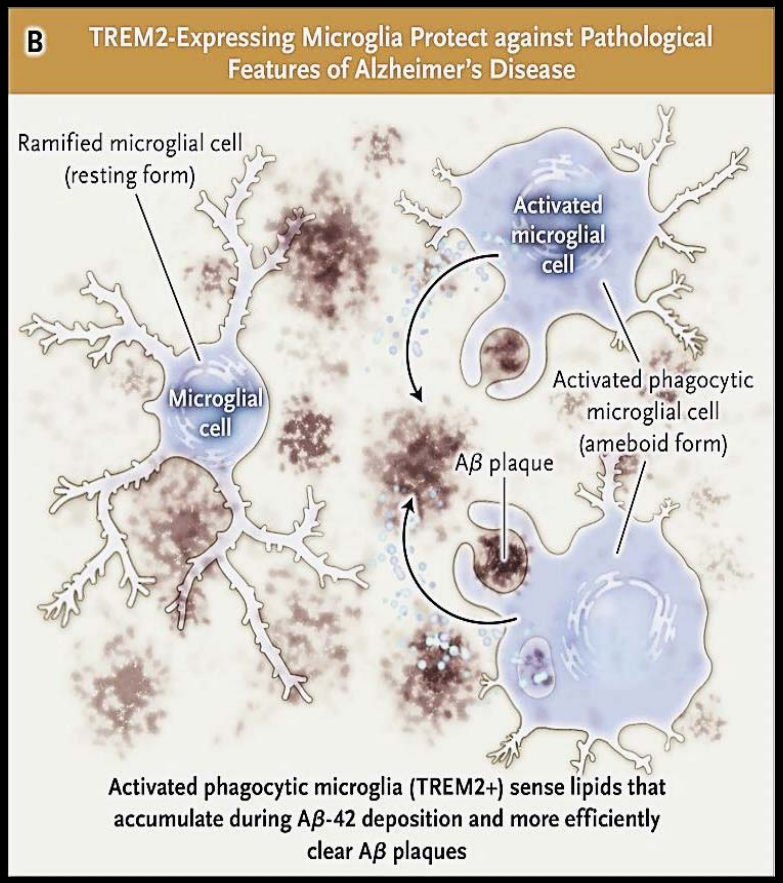
Association analysis of *TREM2* variant c.140G>A (rs75932628; p.R47H) in disease

Disorder (*n*)		Patient, *n* (%)		Control, *n* (%)		OR (95% CI)		p-value[a]
Controls	(1324)			6	(0.45)			
FTD	**(609)**	**13**	**(2.1)**	**6**	**(0.45)**	**5.064**	**(1.9, 13.51)**	**0.0012**
ALS	(765)	5	(0.7)	6	(0.45)	1.466	(0.43, 4.94)	0.5378
PD	**(683)**	**9**	**(1.3)**	**6**	**(0.45)**	**3.144**	**(1.1, 9.03)**	**0.0333**
PSP	(722)	5	(0.6)	6	(0.45)	1.537	(0.41, 5.78)	0.5249
Ischemic Stroke	(448)	3	(0.7)	6	(0.45)	1.506	(0.37, 6.17)	0.5689

Rayaprolu *Mol Neurodegen* 2014

TREM2 and amyloid pathology: Two distinct hypotheses

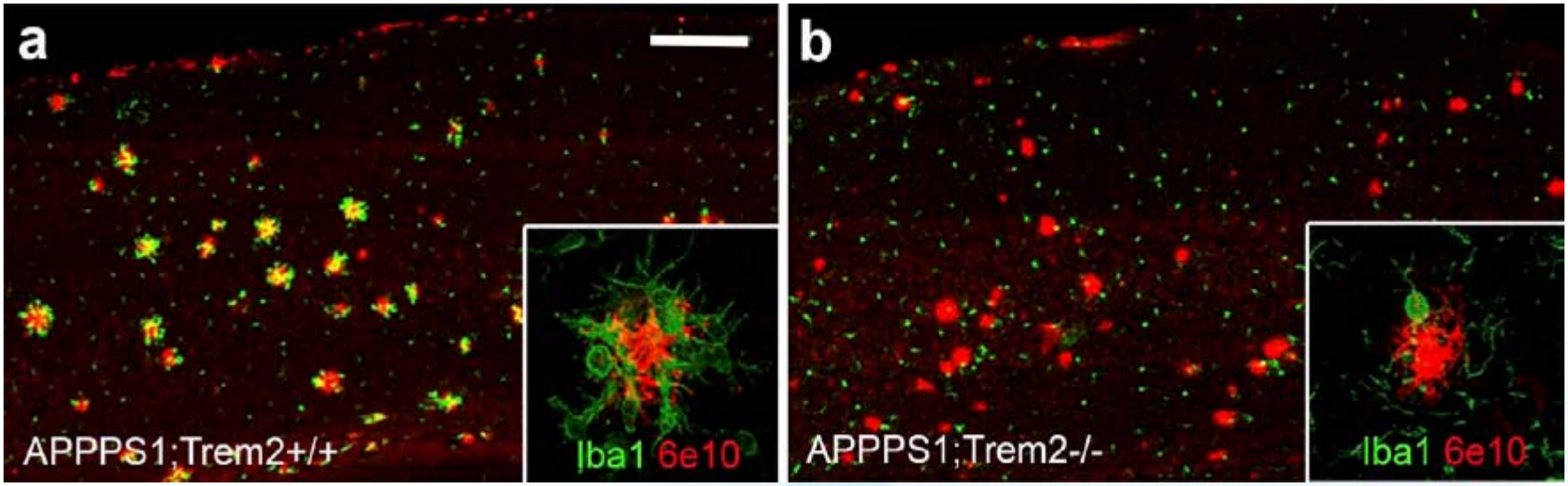




Tanzi RE. *N Engl J Med* 2015; 372:2564

The NEW ENGLAND JOURNAL of MEDICINE

Loss of plaque-associated macrophages in TREM2-KO APPPS1 mice



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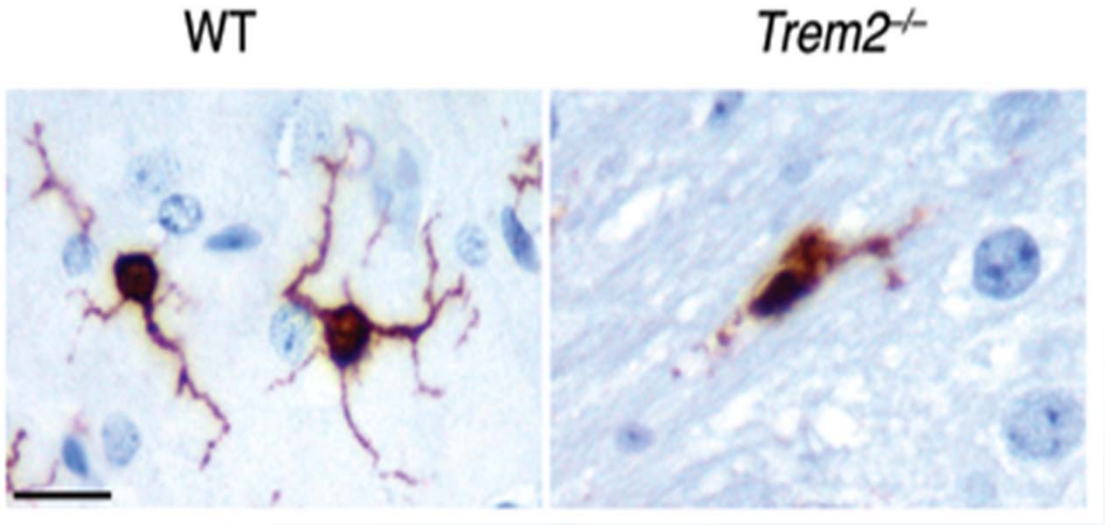
TREM2 supports microglial homeostasis

TREM2 deficiency:
Microglial dystrophy in old mice



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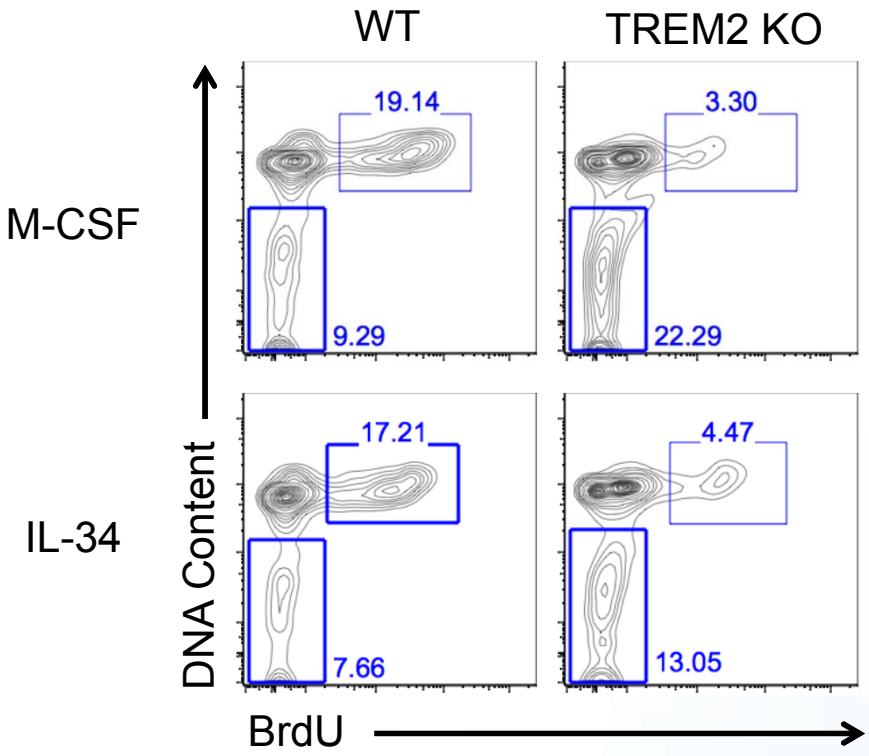
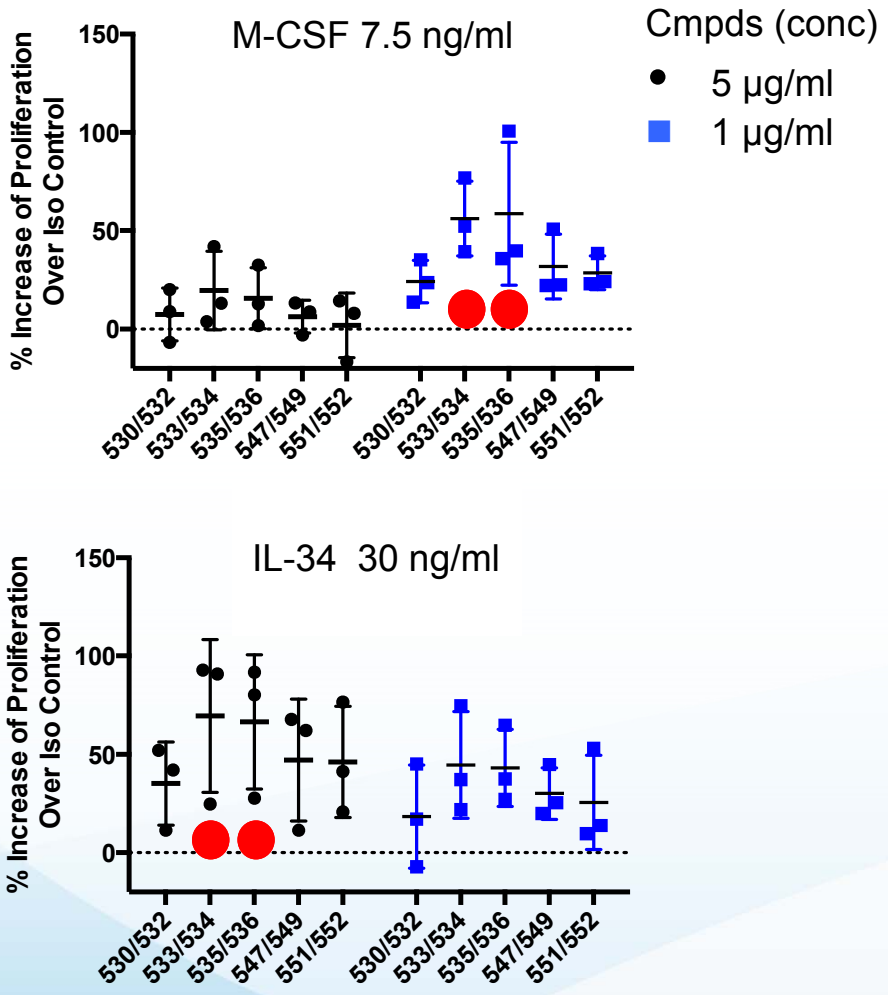
Poliani *J Clin Invest* 2015

Macrophage proliferation to CSF1-R ligands:

Impaired by TREM2 deficiency, increased by BIIB TREM2 compounds





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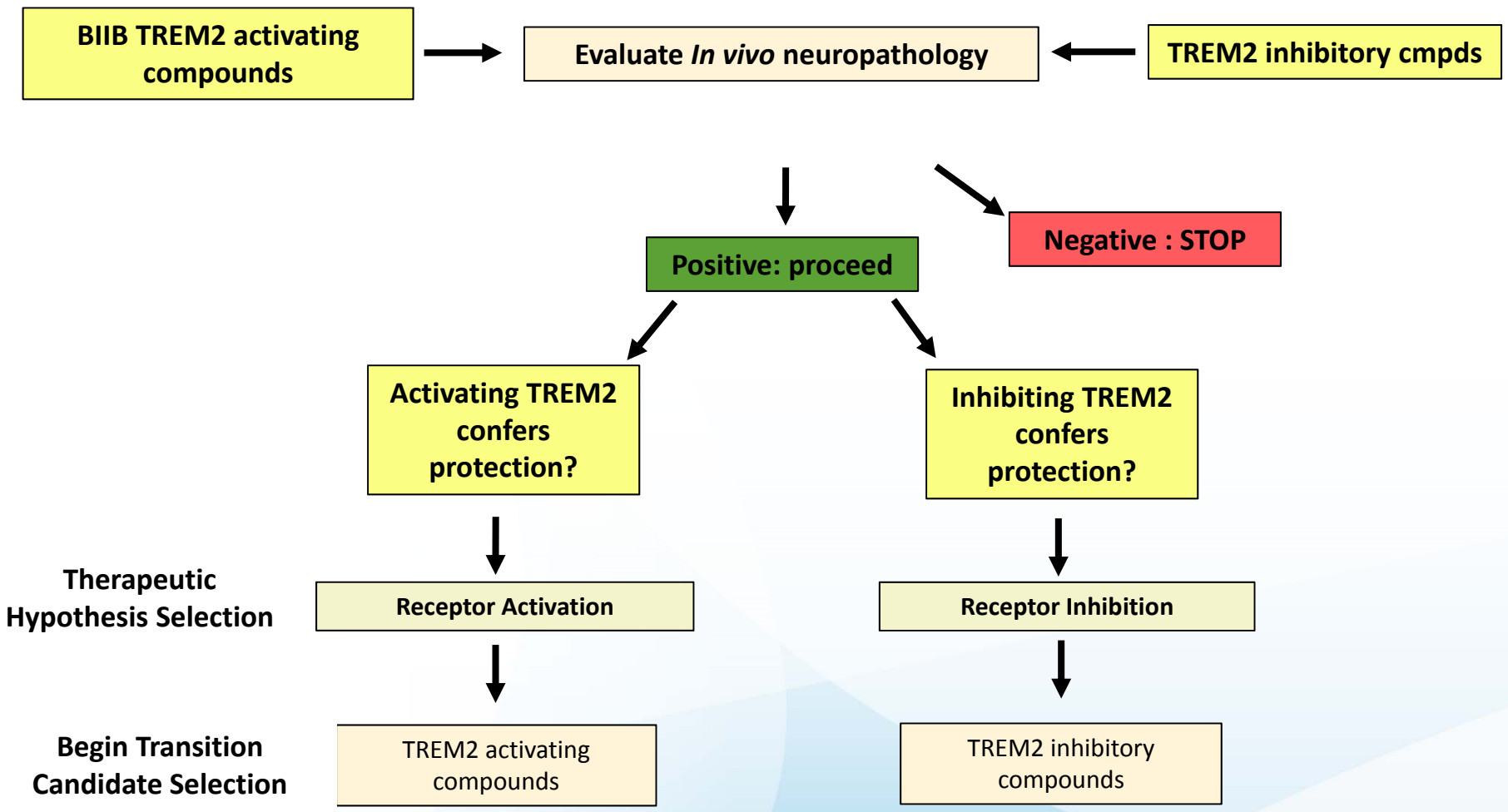
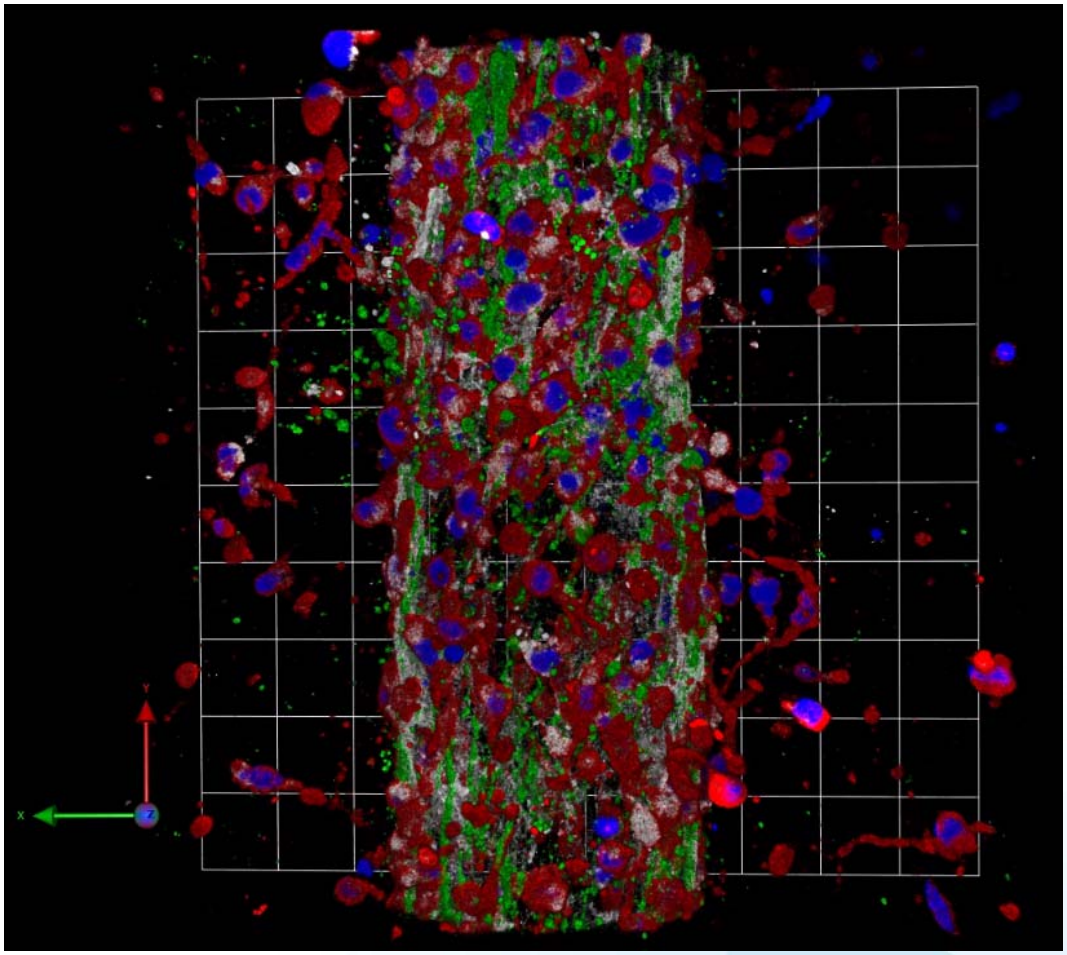
Triage Scheme/ Decision Tree to elucidate the TREM2 Targeting Strategy



Biogen's BBB model: A brain capillary *in vitro*



- Test strategies for delivery across BBB
- Test effects of (for example) amyloid on BBB integrity
- Mechanisms of leukocyte invasion across BBB

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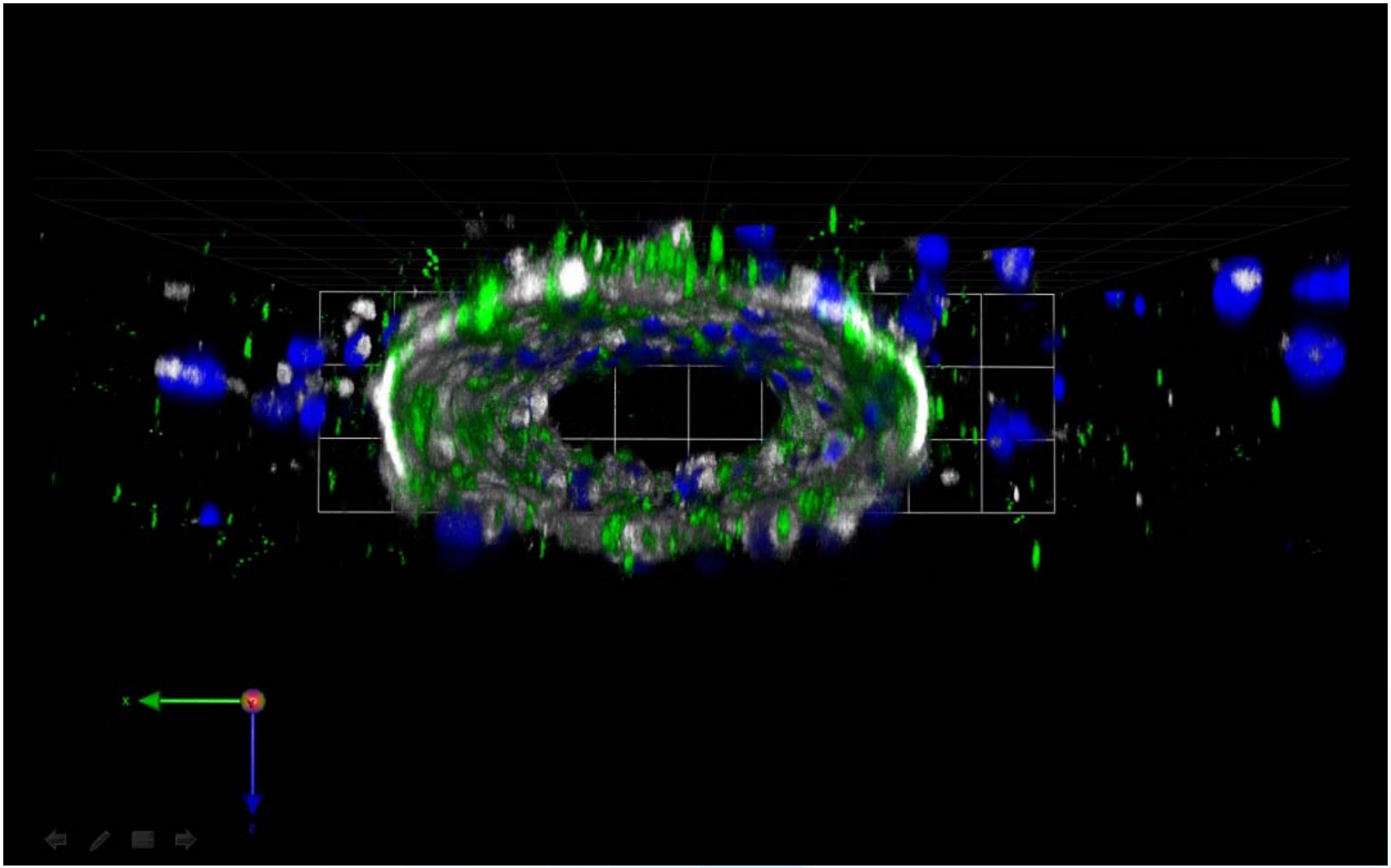

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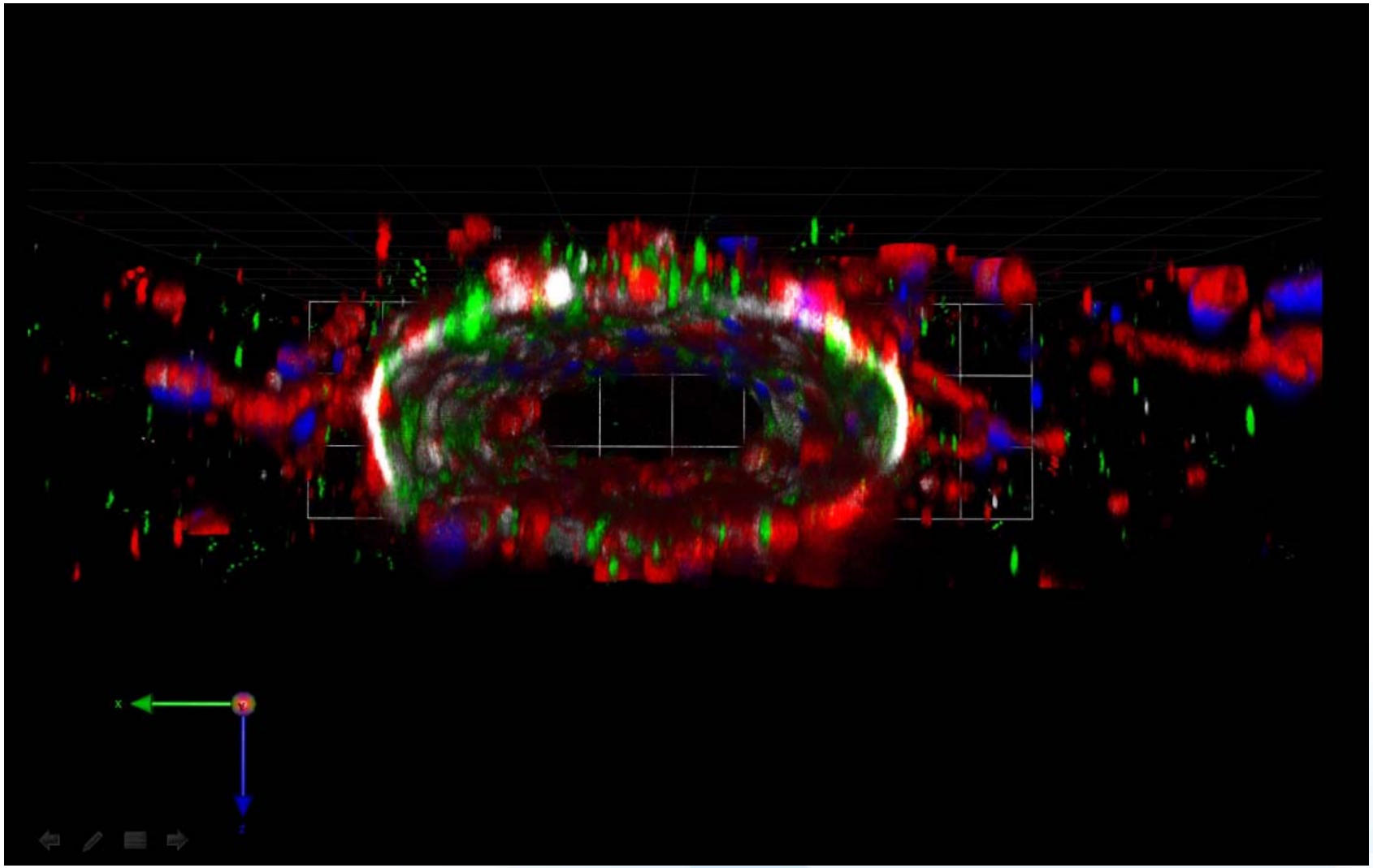

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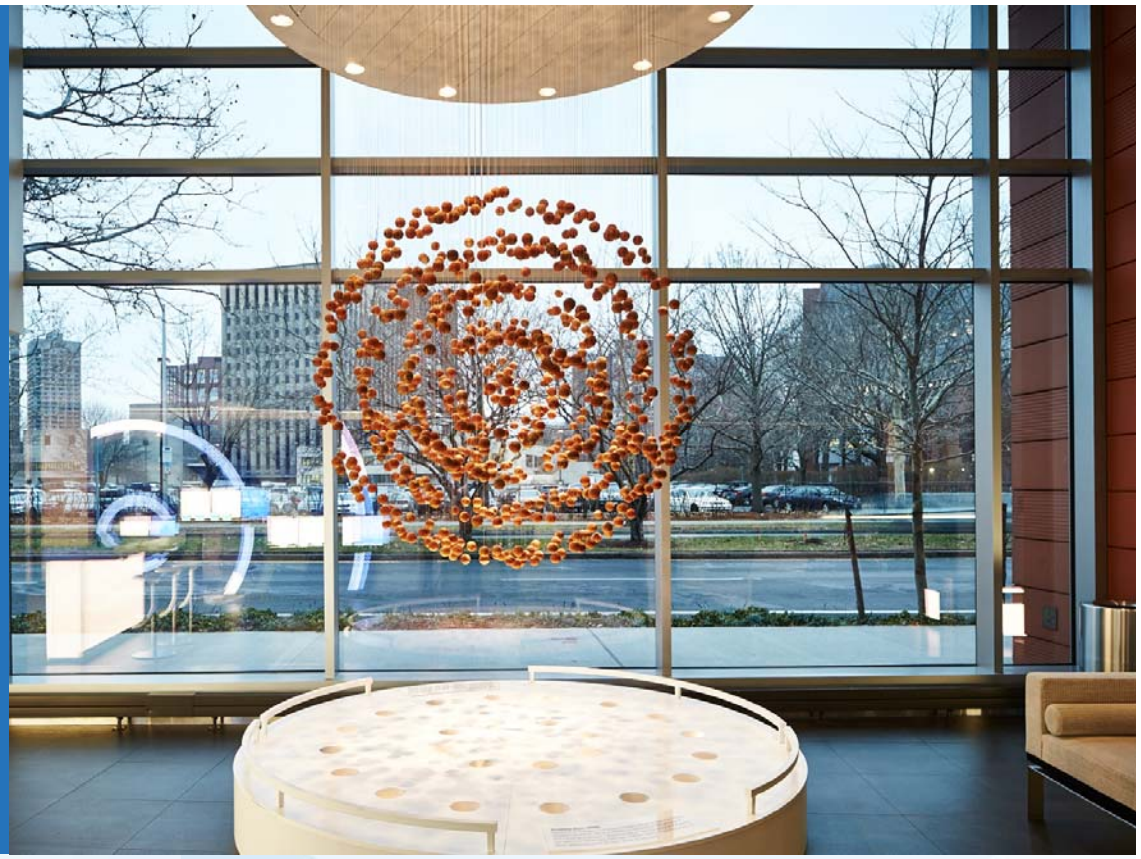
Vision for neuroimmunology in neurodegeneration

Biogen 2015 R&D Day
3rd November, 2015

Thanks for your attention!

Biogen 2015 R&D Day

Q&A



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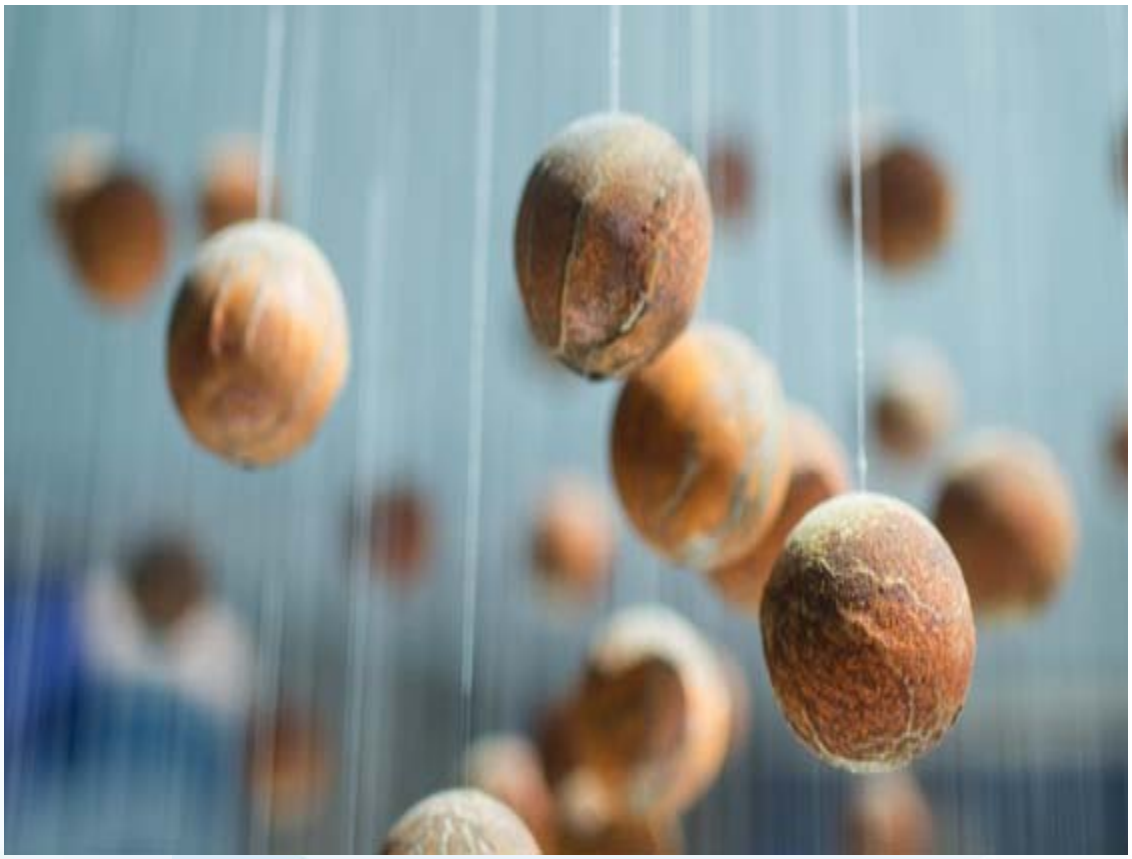
Presenter Biographies



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Biogen Investor R&D Day 2015

George A. Scangos

George A. Scangos, Ph.D., is our Chief Executive Officer and has served in this position and as a member of our Board of Directors since July 2010. From 1996 to July 2010, Dr. Scangos served as the President and Chief Executive Officer of Exelixis, Inc., a drug discovery and development company, where he continues to serve on the board. From 1993 to 1996, Dr. Scangos served as President of Bayer Biotechnology, where he was responsible for research, business development, process development, manufacturing, engineering and quality assurance of Bayer's biological products. Before joining Bayer in 1987, Dr. Scangos was a professor of biology at Johns Hopkins University for six years, where he is still an adjunct professor. Dr. Scangos served as non-executive Chairman of Anadys Pharmaceuticals, Inc., a biopharmaceutical company, from 2005 to July 2010 and was a director of the company from 2003 to July 2010. He also served as the Chair of the California Healthcare Institute in 2010 and was a member of the board of the Global Alliance for TB Drug Development until 2010.

Dr. Scangos is Chairman-Elect of the Board of Directors of Pharmaceutical Research and Manufacturers of America (PhRMA), a member of the Boards of Trustees of the Boston Museum of Science and the Biomedical Science Careers Program, and a member of the National Board of Visitors of the University of California, Davis School of Medicine. Dr. Scangos is also on the Board of Directors of Agilent Technologies, Inc., a provider of bioanalytical and electronic measurement solutions.

Alfred W. Sandrock

Alfred W. Sandrock, Jr., M.D., Ph.D., is our Group Senior Vice President and Chief Medical Officer and has served in this position since May 2013. From February 2012 to April 2013, Dr. Sandrock served as our Senior Vice President, Chief Medical Officer. Since joining us in 1998, Dr. Sandrock has held several senior executive positions, including Senior Vice President of Development Sciences, Senior Vice President of Neurology Research and Development, and Vice President of Clinical Development, Neurology. Dr. Sandrock received his B.A. in human biology from Stanford University, an M.D. from Harvard Medical School, and a Ph.D. in neurobiology from Harvard University. He completed an internship in medicine, a residency and chief residency in neurology, and a clinical fellowship in Neuromuscular Disease and Clinical Neurophysiology (electromyography) at Massachusetts General Hospital.

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Biogen Investor R&D Day 2015

Spyros Artavanis-Tsakonas

Spyros Artavanis-Tsakonas is Senior Vice President and Chief Scientific Officer at Biogen, and has served in this position since May 2013. In 1998, Dr. Artavanis-Tsakonas joined the Harvard Faculty as Professor of Cell Biology at the Harvard Medical School, where, since 2015, he continues his affiliation as a Professor Emeritus of Cell Biology. From 1999 to 2007, Spyros was the K.J. Isselbacher–P. Schwartz Professor at the Massachusetts General Hospital Cancer Center, and is the founding Director of the Developmental and Regenerative Biology Program at Harvard Medical School. During 1983-1998, Dr. Artavanis-Tsakonas was at Yale, where his most recent appointment was as Professor of the Departments of Cell Biology and Biology, and a Howard Hughes Medical Institute Investigator. Spyros also served as the Director of the Biological Sciences Division at Yale. In 1999, he was elected Professor at the Collège de France, holding the Chair of Biology and Genetics of Development. Since 2012, Dr. Artavanis-Tsakonas is Professeur honoraire at the same Institution, and he is also the Founding Director (2007-2009) of the Department of Genetics and Developmental Biology at the Institut Curie, Paris.
Dr. Artavanis-Tsakonas is a co-founder of Exelixis Pharmaceuticals, Inc., Cellzome (acquired by GlaxoSmithKline in 2012), and Anadys Pharmaceuticals, Inc. (acquired by Hoffman-La Roche in 2011). He is also President and co-founder of Fondation Santé.

Diego Cadavid

Dr. Cadavid studied Medicine and Surgery at the Pontificia Universidad Javeriana in Bogotá, Colombia, Microbiology and Immunology at The University of Texas Health Science Center in San Antonio, Texas, Clinical Neurology at Georgetown University and Neuropathology at the Armed Forces Institute of Pathology, both in Washington, DC. He was for nearly 10 years a Faculty Member in the Department of Neurology and Neuroscience at Rutgers-New Jersey Medical School in Newark, NJ and since 2008 he has been a member of the Neurology Clinical Development Group at Biogen and between 2008 and 2015 a Consultant at the Center for Immunology and Inflammatory Diseases at Massachusetts General Hospital in Boston. The main focus of his research career has been on Borrelial infections and multiple sclerosis. He has published over 70 peer reviewed papers and over 10 book chapters. He is currently the Medical Director of the anti-LINGO-1 (BIIB033) clinical development program for CNS remyelination and Senior Director of the CNS Repair Group at Biogen in Cambridge, MA. He is licensed to practice Medicine in Massachusetts, and a Fellow Member of both the American Academy of Neurology and the American Neurological Association.

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Biogen Investor R&D Day 2015

Samantha Budd Haeberlein

Samantha Budd Haeberlein, Ph.D., is our Vice President, Neurology Clinical Development.
Samantha has more than fifteen years of pharmaceutical industry experience across Research, Translational Science/Medicine and Clinical Development. Samantha is a results oriented and successful leader of global, multi-disciplinary project teams and line-managed functions. She is currently leading Global Clinical Development for Alzheimer's disease at Biogen, while overseeing the Pain portfolio through an externalized model. Previously, she held roles at AstraZeneca in the US, Canada and Sweden most recently as Vice President of the Translational Science & Global Program Lead in Alzheimer's disease. Samantha helped build the Neuroscience Virtual R&D group an experimental business model, and successfully led an Alzheimer's project through to Ph3 in the virtual setting. Prior to that Samantha led multi-disciplinary teams in Research, Strategy, Diagnostic and Clinical Development. Samantha has served on the Board for the Stockholm Brain Institute, and currently serves as an Advisory Board Member to Quartet Medicine, and AlzForum. Samantha has a BSc and PhD in Biochemistry from the University of Dundee in Scotland, and conducted research at Brigham & Women's Hospital Harvard Medical School in Boston, and at The Burnham Institute in San Diego.

Jeffrey Sevigny

Dr. Jeffrey Sevigny is a Senior Medical Director at Biogen Idec in Cambridge, MA. Dr. Sevigny's research focuses on the development of biomarkers and therapeutics for neurodegenerative disorders. Dr. Sevigny earned his MD from Tufts University and completed Neurology residency and fellowship in Aging & Dementia and Neuro-epidemiology at Columbia University. Dr. Sevigny previously worked at Novartis AG and Merck and Co, and prior to joining industry was Assistant Professor of Neurology at Albert Einstein School of Medicine and at Columbia University.

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Biogen Investor R&D Day 2015

Wildon Farwell

Wildon Farwell, MD, MPH, is Senior Medical Director in Clinical Development at Biogen. In his role, Dr. Farwell currently oversees the clinical development program for Spinal Muscular Atrophy (SMA) at Biogen. Dr. Farwell was also a Medical Director in the Safety and Benefit Risk function at Biogen where he participated in the Hemophilia and ALS programs. Prior to coming to Biogen in 2010, Dr. Farwell was Assistant Professor of Medicine at Harvard Medical School and on faculty at Brigham and Women's Hospital and the VA Boston Healthcare System. In his research career, Dr. Farwell has explored novel risk factors and developed and conducted innovative, large-scale clinical trials in cardiovascular disease, diabetes mellitus, and cancer. He also exhibited leadership as an Associate Director of the Harvard Medical School Fellowship in General Medicine and Primary Care. Wildon holds a medical degree from University of Missouri, Columbia and has a MPH in Clinical Effectiveness from Harvard School of Public Health. He completed his residency in internal medicine at Indiana University, Indianapolis and fellowship training in general internal medicine at Harvard Medical School.

Jeff Bornstein

Jeff Bornstein is currently overseeing the clinical development of MT-1303 in inflammatory bowel disease. Jeff was born and raised in Montreal, Canada, and he received his MD and completed an Internal Medicine residency at McGill University. He then completed a Gastroenterology fellowship at Duke University. After fellowship, Jeff remained at Duke as an assistant professor, focusing on hepatitis C and liver transplantation. In 2002, Jeff left Duke to join Maxim Pharmaceuticals, when he was responsible for a hepatitis C development program. Next, he served as a Director, Clinical Development at Elan Pharmaceuticals, where he was the lead physician for the phase 3 natalizumab program in Crohn's Disease. After his time at Elan, Jeff served as Vice President of Clinical Development at both Tioga pharmaceuticals and Ocera Therapeutics, before joining Gilead Sciences as a Senior Director in Liver Disease Therapeutics in 2010. At Gilead, Jeff played a role in the development of sofosbuvir for hepatitis C, contributed to the advancement of tenofovir for hepatitis B, helped launch the MMP-9 program for ulcerative colitis and lead the development of simtuzumab for liver fibrosis. Jeff joined Biogen as a Senior Director in Fibrosis and Tissue injury in 2014. He initially worked on the IPF program, and has now transitioned to immunology and the IBD program.

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Biogen Investor R&D Day 2015

Jesse Cedarbaum

Jesse M Cedarbaum, MD obtained his medical degree from Yale Medical School, where he is currently Professor (Adjunct) of Psychiatry. He trained in Neurology at New York Hospital-Cornell Medical Center and, after residency, led the Parkinson's and Movement Disorders program there from 1983-1990. In 1990 Dr. Cedarbaum joined Regeneron, where he led the establishment of the Clinical Development function and served as Program Director and later Vice President of Clinical Affairs from 1990-2007. He subsequently held senior positions in Clinical Development at Elan, Cytokinetics, and Bristol-Myers Squibb. He joined Biogen in April 2014. Dr. Cedarbaum has authored or co-authored over 90 peer-reviewed scientific publications, most in the area of neurotherapeutics. He is a Fellow of both the American Academy of Neurology and the American Neurological Association. Dr. Cedarbaum was the 2014-15 chair of the Alzheimer's Disease Neuroimaging Initiative (ADNI) Private Partner Scientific Board, and currently chairs the Industry Scientific Advisory Board for the Michael J. Fox Foundation's Parkinson Progression Marker Initiative (PPMI).

Donald R. Johns

Donald R. Johns, MD is Vice President and Head of the Amyotrophic Lateral Sclerosis innovation Hub (ALS iHub) in the Development Sciences organization at Biogen. The ALS iHub team works with both internal and external collaborators to catalyze innovative and effective drug development to transform the lives of ALS patients. Donald joined Biogen in July 2014 after ten years as Vice President, Global Head, Neuroscience Translational Medicine at Novartis. He is a board-certified neurologist and scientific leader with 25+ years of experience with rare and orphan diseases. He was on the faculty in Neurology at Johns Hopkins University Medical School and Harvard Medical School. At HMS he was an Associate Professor of Neurology and Ophthalmology and was the founding Director of the Division of Neuromuscular Disease at Beth Israel Deaconess Medical Center, Department of Neurology. His scientific work focused on mitochondrial dysfunction and human disease. Donald graduated from Vanderbilt University and Yale Medical School and completed his residency and fellowship in Neurology at Massachusetts General Hospital.

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Biogen Investor R&D Day 2015

Olivier Danos

Olivier Danos is a pioneer in the field of gene therapy, and has dedicated his career to advancing the use of this technology to develop life-saving therapies for patients. Olivier joined Biogen in 2014 from Kadmon Pharmaceuticals, where he served as SVP, Molecular Medicine, Synthetic Biology and Gene Regulation. Over the past twenty years, he has played a number of leadership roles in cell and gene therapy as director of the Gene Therapy Consortium of the University College of London, at the Necker Hospital – Enfants Malades in Paris, as chief scientific officer of Genethon and as senior director of research at Somatix Therapy Corporation. He has held senior research positions at the French National Centre for Scientific Research (CNRS) and at the Institut Pasteur in Paris. Olivier is the former president and a founding member of the European Society of Gene and Cell Therapy. Olivier received a Master's in Genetics and Molecular Biology at University of Paris Orsay, and his Ph.D. in Biology at the Pasteur Institute and University of Paris Diderot.

Richard Hargreaves

Richard Hargreaves, Vice President, Neuropharmacology and Biomarkers- Extensive imaging, biomarker, drug discovery and development experience in neurosciences. VP Worldwide Head of Imaging (Merck Research Laboratories MRL) – built medical and preclinical imaging internally and externally for all therapeutic franchises across imaging modalities. VP Worldwide Discovery Head for Neuroscience (MRL) – responsible for strategic and scientific direction and prioritization including external scientific affairs, licensing and academic collaborations for the neuroscience drug discovery pipeline. Advanced drug candidates and novel PET imaging agents to the clinic for Alzheimer's disease, cognition, migraine headache, anxiety, depression, schizophrenia, chemotherapy palliation, pain and sleep wake circadian disorders. Led the discovery teams that contributed to the development and registration of MAXALT® (rizatriptan) for migraine, EMEND® (aprepitant) and IVEMEND® (fosaprepitant) for prevention of chemotherapy-induced nausea and vomiting and the department producing Belsomra ® (suvorexant) for insomnia. Published extensively with >200 papers and chapters and 3 books co-edited and on neuroscience drug discovery, translational biomarkers and the use of biomedical imaging in drug discovery and development. Scientific Research Fellowship (adjunct) Children's Hospital Boston, Harvard Medical School, Gary Neil Award for "Innovation in Drug Development" by the American Society of Clinical Pharmacology and Therapeutics for work on imaging in drug discovery and development and the first Sir James Black Award for Drug Discovery from the British Pharmacological Society.

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Biogen Investor R&D Day 2015

Ajay Verma

Ajay Verma is a Vice President at Biogen for Biomarkers and Experimental Medicine. Ajay leads efforts to develop, validate, and implement human experimental platforms and biomarker technologies for decision making in clinical trials. These include nuclear and MR imaging approaches, electrophysiology, organ physiology, functional measurements, and experimental human models. Prior to starting up the Experimental Medicine group Ajay was the therapeutic area head for Neurodegenerative diseases at Biogen. Ajay studied zoology at the University of Maryland and received his MD and PhD from The Johns Hopkins University. His neurology training and service was at the Walter Reed Army Medical Center and the National Naval Medical Center where he was a staff Neurologist for 11 years. He was also a tenured Professor at the Uniformed Service University of the Health Sciences, the US Military's Medical School, where he directed basic research in Neurology. Since leaving the Army as a Lt. Colonel in 2006, Ajay has worked at Merck & Co., Inc. and Novartis Pharmaceuticals prior to joining Biogen. Ajay also currently serves on the Innovation Board of the X Prize Foundation.

Rick Rudick

Dr. Rudick graduated from Case Western Reserve University School of Medicine in 1975. Following internship and residency in Medicine at the University of Connecticut, Dr. Rudick trained in Neurology at the University of Rochester. During a post-doctoral research fellowship and early career development at the University of Rochester, his studies focused on neurologic consequences of immune disease in animals and immunologic abnormalities in multiple sclerosis(MS) patients. In 1987, Dr. Rudick became Director of the Mellen Center for Multiple Sclerosis at Cleveland Clinic. Driven by a vision of compassionate multidisciplinary MS care integrated with clinical and translational research, the Mellen Center developed an international reputation for excellence in MS treatment, search, and education. Dr. Rudick's research has focused on experimental therapeutics, including innovative approaches to measuring immunologic, clinical, and imaging features of the disease for use in clinical research and practice. He played key roles in development of IFNß-1a (Avonex) and natalizumab (Tysabri) for relapsing forms of MS. For 30 years, his clinical practice focused on diagnosis and management of MS patients. In addition to directing the Mellen Center, Dr. Rudick was the Chief Clinical Research Officer at Cleveland Clinic from 2001 – 2007, Vice Chairman for Research and Development in the Neurological Institute at Cleveland Clinic from 2007 – 2014, and Co-Principal Investigator of the city wide NIH Clinical and Translational Science Collaborative (CTSA) from 2006 – 2014. In 2014, Dr. Rudick transitioned to Biogen, where he is Vice President, Development Science, and Director of the Value Based Medicine MS Innovation Hub. The VBM iHub is charged with enhancing MS care through technology, innovation, and continuous learning.

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Biogen Investor R&D Day 2015

Simon Tate

Simon Tate has 26 years of experience in drug discovery and development, 21 years of which in ion channels and pain. He is currently Vice President and Head of the Pain Therapeutic Area at Biogen. Simon transitioned to this role at Biogen following the acquisition of Convergence Pharmaceuticals, where he was the Chief Scientific Officer and one of the founders. Simon led Convergence to be widely recognized as a leading company in the field of pain and ion channel drug discovery and development. In 2014, Convergence reported successful clinical proof of concept studies with clinically significant efficacy and a good overall safety profile, in both trigeminal neuralgia and pain associated with radiculopathy. Simon was instrumental to the acquisition of Convergence Pharmaceuticals' clinical assets from GSK, where he was previously Vice President, Pain and Epilepsy Discovery Performance Unit. During his time at GSK, Simon was a member of the senior leadership teams in both Neurology and Psychiatry and led several cross functional departments in discovery and early development.

Jake Elkins

Dr. Elkins received his medical degree from Harvard Medical School and then completed residency and fellowship training in neurology and neurovascular medicine at the University of California, San Francisco (UCSF). After completing his medical education, Dr. Elkins joined the neurology faculty of UCSF in 2003 where he was principal investigator on grants sponsored by the NIH/NINDS and the American Heart Association focused on the effects of silent cerebrovascular pathology on cognitive function. He received a Master's degree in clinical research from UCSF and the Siekert award for new investigators from the American Stroke Association. Dr. Elkins joined Biogen in 2007 and has been the global clinical development lead for daclizumab, Tecfidera and the Tysabri Stroke programs. Dr. Elkins has published extensively on the subjects of cerebrovascular disease, cognition, multiple sclerosis, and clinical trial design. He is a member of the American Heart Association and the American Academy of Neurology.

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Biogen Investor R&D Day 2015

Christopher Henderson

Christopher E. Henderson, Ph.D.- After training in Cambridge (UK) and spending much of his career in France, Chris Henderson moved in 2005 to Columbia University in New York, where he co-founded the Center for Motor Neuron Biology and Disease, a new initiative in translational neuroscience that created a continuum from research on motor neurons through to clinical research on the motor neuron diseases ALS (amyotrophic lateral sclerosis) and SMA (spinal muscular atrophy). He was also director of the Columbia Stem Cell Initiative, a group of 120 laboratories across the university using stem cells to better understand or treat human disease. While still at Columbia he became director of Target ALS, a privately-funded consortium that has stimulated industry investment in ALS research by supporting cutting-edge translational research and nationwide core facilities in academia. In 2014, Trophos - a French biotech of which he was an academic founder - announced positive clinical trial data in patients with SMA. This provided major motivation to become more actively engaged in the biotech world and in October 2014, Henderson moved to Biogen (Cambridge, MA) to lead the neuroscience research program focused on Alzheimer's disease, Parkinson's disease, ALS and multiple sclerosis.

Richard Ransohoff

Richard M Ransohoff served at the Cleveland Clinic as Director of the Neuroinflammation Research Center in the Lerner Research Institute (2005-14); a professor of molecular medicine at the Cleveland Clinic Lerner College of Medicine (from 2003, now adjunct); and a staff neurologist in the Mellen Center for MS Treatment and Research (1984-2014). Dr Ransohoff joined Biogen (Cambridge, MA) in 2014 as Senior Biogen Research Fellow, Neuroimmunology. Among his awards are a Physician's Research Training Award from the American Cancer Society (1984-86); a Clinical Investigator Development Award from the National Institutes of Health (NIH; 1988-1993); the Harry Weaver Neuroscience Scholarship of the National MS Society (1987-1992); the John and Samuel Bard Medal in Science or Medicine (2002); the Cleveland Clinic Lerner Research Institute's Award for Excellence in Science in 2006; and the Cleveland Clinic's Scientific Achievement Award in Basic Science (2009). He was invited to give the FE Bennett Memorial Lecture to the American Neurological Association in 2009. He has been cited in *Best Doctors in America* for his expertise in the clinical care of patients with multiple sclerosis (MS). The American Academy of Neurology and the National Multiple Sclerosis Society awarded Dr Ransohoff the 2012 John Dystel Prize for MS Research. Dr Ransohoff served as regular member and chair on study sections of the NIH and NMSS and is currently a regular member of the CMBG Study Section. He is a member of the American Academy of Neurology, the American Neurological Association, and the American Association of Physicians and is a Fellow of the American Association for the Advancement of Science.

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Biogen Investor R&D Day 2015

Carmen Bozic

Carmen Bozic MD is Senior Vice President of Global Development at Biogen. Her department is responsible for developing and obtaining regulatory approvals. The functions in her department include global clinical development, regional clinical development in Japan and Europe, safety and benefit risk management, global clinical operations, biostatistics, medical writing, data management and statistical programming. Dr. Bozic is an experienced drug development leader with over 17 years of biopharmaceutical industry experience with progressively increasing responsibilities in multiple functions and therapeutic areas. As the former Global Head of Safety and Benefit-Risk Management at Biogen for several years, she led a world-class organization that was accountable for patient safety for the pre and post-approval pipeline and addressed complex issues in safety and benefit-risk management. Dr. Bozic has also overseen functions accountable for the regulatory filing and approvals of multiple therapies, including TECFIDERA (dimethyl fumarate) and PLEGRIDY (pegylated interferon beta-1a) for multiple sclerosis, as well as ELOCTATE (Factor VIII Fc fusion protein) and ALPROLIX (Factor IX Fc fusion protein) for the treatment of severe Hemophilia A and B in multiple countries. She led the development of the risk management plan for TYSABRI® (natalizumab) and presented on this topic at an FDA Advisory Committee, leading to the approval of TYSABRI for the treatment of multiple sclerosis. She has also served as the industry representative to the FDA's Risk Communication Advisory Committee and is a member of PhRMA's Clinical and Preclinical Development Committee. She received an MD degree and did her residency in internal medicine at McGill University in Montreal, Canada, completed a fellowship in Pulmonary and Critical Care Medicine at Brigham and Women's Hospital in Boston, and was an Associate Physician at Beth Israel Deaconess Medical Center and Harvard Medical School before joining the biopharmaceutical industry. Dr. Bozic is a frequent lecturer and speaker on benefit-risk and other drug development topics nationally and internationally.

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