Immunotherapy-Based Trials Will Lead Us To Our First Successful Disease Modifying Therapy

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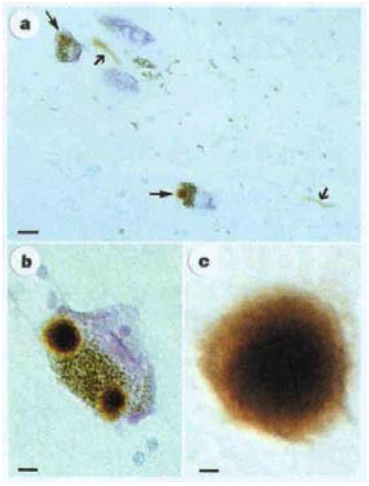
Overview

- Aggregates of misfolded proteins are the central molecular pathology underlying Parkinson's disease
  - Evidence from Human pathology
  - Evidence from Animal models
- Immunotherapy to remove misfolded proteins directly targets this pathology.
  - The first generation of anti-alpha synuclein monoclonal antibodies already exist
  - They bind specifically to aggregated alpha-synuclein
  - They slow disease progression in animal models
- Immunotherapy agents are currently in human trials
  - Alpha synuclein immunotherapy is being tested in phase I and large phase II trials.
  - There is emerging evidence of efficacy for immunotherapy in related disorders

Synuclein pathology in the substantia nigra

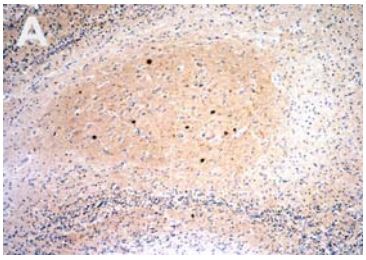


Substantia nigra from patients with Parkinson's disease (from the MRC Cambridge Brain Bank) immunostained for alpha-synuclein. a, Two pigmented nerve cells, each containing an alpha-synuclein-positive Lewy body (thin arrows). Lewy neurites (thick arrows) are also immunopositive. Scale bar, 20 micro m. b, A pigmented nerve cell with two alpha-synuclein-positive Lewy bodies. Scale bar, 8 micro m. c, alpha-Synuclein-positive, extracellular Lewy body. Scale bar, 4 micro m.

Courtesy of J. Trojanowski, MD, PhD

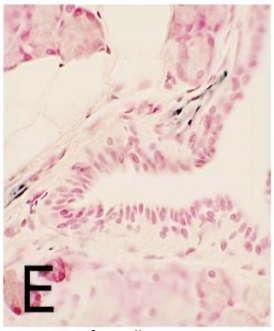
Evidence for widespread alpha-synuclein pathology

Olfactory bulb



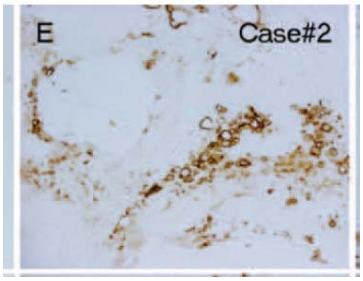
Courtesy of John Duda, MD, and J. Noorigian, MPH

Salivary gland



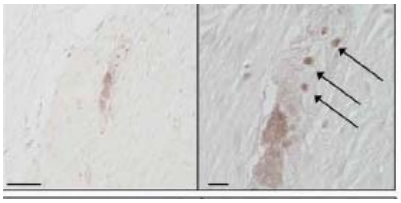
Courtesy of C. Adler MD

Colonic biopsy



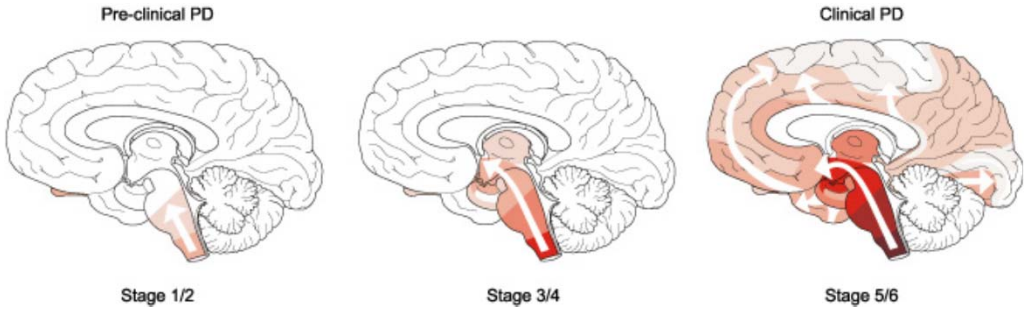
Shannon et al, Mov. Disorder. 2013

Appendix



Kilinger et al. Sci Trans Med 2018

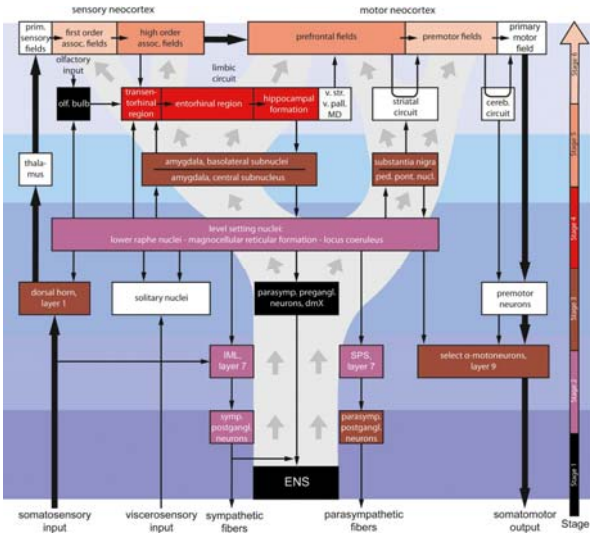
Braak staging of Lewy pathology in PD



PD-related Lewy body pathology evolves in predictable stages. According to the staging system of Braak, Lewy bodies (LB) first form within in the olfactory bulb and dorsal motor nucleus of the vagal nerve (Stage 1). In Stages 2 and 3, LB pathology expands from these induction sites into additional brain stem nuclei (e.g., locus coeruleus and substantia nigra) and then into the amygdala. In Stages 5 to 6, the pathology extends into the cerebral cortex. Clinical symptoms arise during Stages 4 to 6 when the pathology involves significant regions of the substantia nigra and related brain areas.

From Braak et al, Neurobiology of Aging 2003

Sporadic Parkinson's disease: development and distribution of α-synuclein pathology



Neuropathology and Applied Neurobiology, Volume: 42, Issue: 1, Pages: 33-50, First published: 13 December 2015, DOI: (10.1111/nan.12298)

Examples of genetically determined forms of PD related to alpha-synuclein mutations

Mutation in the α-Synuclein Gene Identified in Families with Parkinson's Disease

Mihael H. Polymeropoulos,* Christian Lavedan†, Elisabeth Leroy†, Susan E. Ide, Anindya Dehejia, Amalia Dutra, Brian Pike, Holly Root, Jeffrey Rubenstein, Rebecca Boyer, Edward S. Stenroos, Settara Chandrasekharappa, Aglaia Athanassiadou, Theodore Papapetropoulos, William G. Johnson, Alice M. Lazzarini, Roger C. Duvoisin, Giuseppe Di Iorio, Lawrence I. Golbe, Robert L. Nussbaum

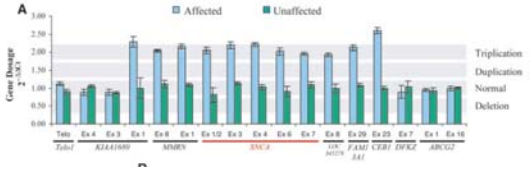
Parkinson's disease (PD) is a common neurodegenerative disorder with a lifetime incidence of approximately 2 percent. A pattern of familial aggregation has been documented for the disorder, and it was recently reported that a PD susceptibility gene in a large Italian kindred is located on the long arm of human chromosome 4. A mutation was identified in the α-synuclein gene, which codes for a presynaptic protein thought to be involved in neuronal plasticity, in the Italian kindred and in three unrelated families of Greek origin with autosomal dominant inheritance for the PD phenotype. This finding of a specific molecular alteration associated with PD will facilitate the detailed understanding of the pathophysiology of the disorder.

SCIENCE • VOL. 276 • 27 JUNE 1997

α-Synuclein Locus Triplication Causes Parkinson's Disease

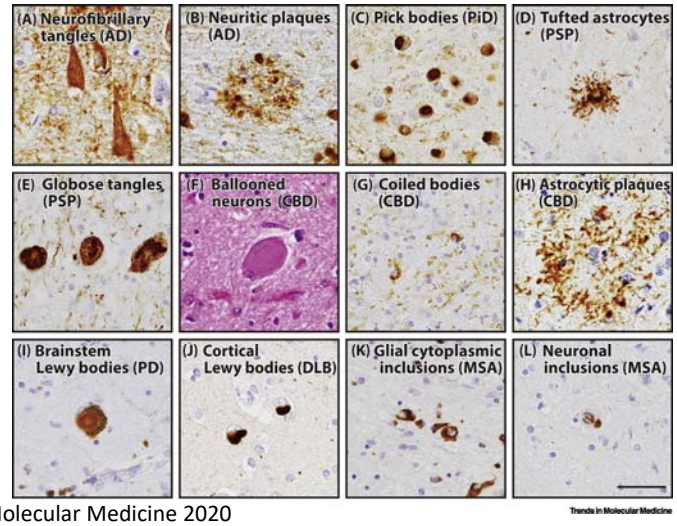
A. B. Singleton,[1*†] M. Farrer,[4†] J. Johnson,[1] A. Singleton,[2] S. Hague,[1] J. Kachergus,[4] M. Hulihan,[4] T. Peuralinna,[1] A. Dutra,[3] R. Nussbaum,[2] S. Lincoln,[4] A. Crawley,[2] M. Hanson,[1] D. Maraganore,[5] C. Adler,[6] M. R. Cookson,[1] M. Muenter,[6] M. Baptista,[1] D. Miller,[1] J. Blancato,[7] J. Hardy,[1] K. Gwinn-Hardy[2]

Mutations in the α-synuclein gene (*SNCA*) in the Contursi kindred (*1*) implicated this gene in Parkinson's disease (PD). Subsequently, α-synuclein was identified as the major component of Lewy bodies, the pathological hallmark of PD, and of glial cell cytoplasmic inclusions (*2*). eM (*D4S2367–D4S1560*), with a multipoint LOD of 3.50 at *D4S2460*. The *SNCA* genotypes were inconsistent with previous data, leading to initial exclusion; re-evaluation of the original linkage revealed a sample swap. Resequencing of *SNCA* failed to reveal pathogenic mutations.



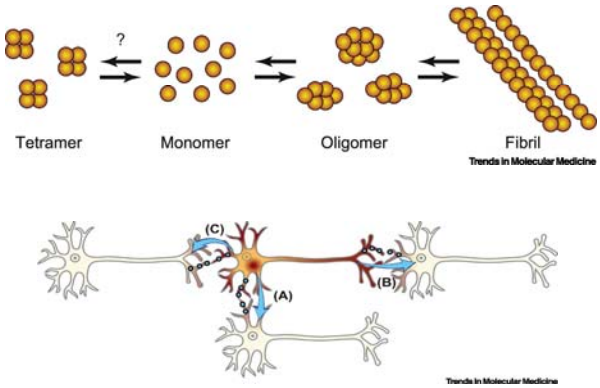
SCIENCE VOL 302 31 OCTOBER 2003

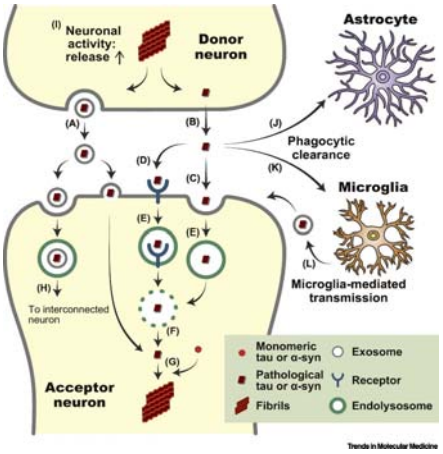
Tau and a-syn aggregates in various neurodegenerative disorders



Uemura et al. Trends in Molecular Medicine 2020

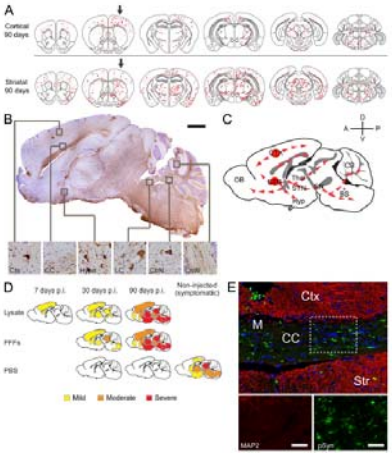
How do pathologic protein aggregates spread?

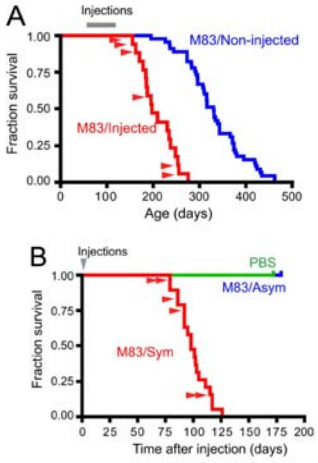




From Trends in Molecular Medicine 2020

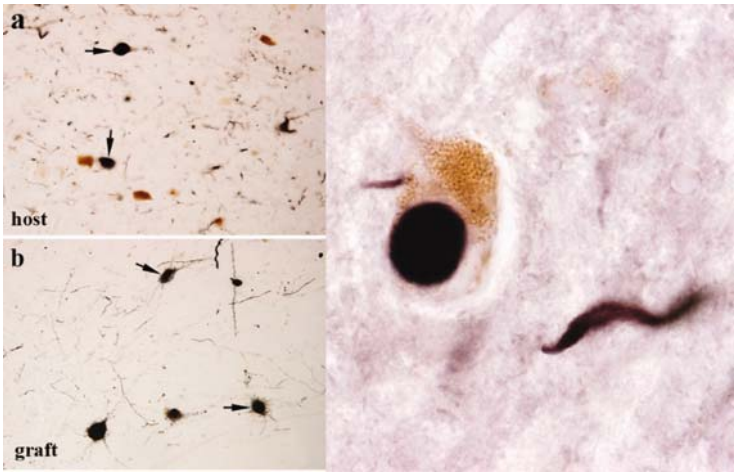
Experimental transmission of α-synuclein pathology





From Luk et al. JEM. 2012

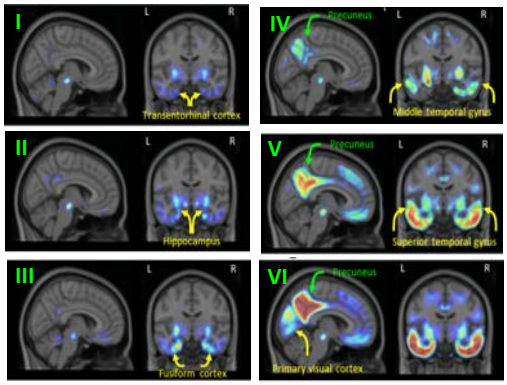
Lewy pathology in fetal grafts may represent host-to-graft transmission of asyn pathology



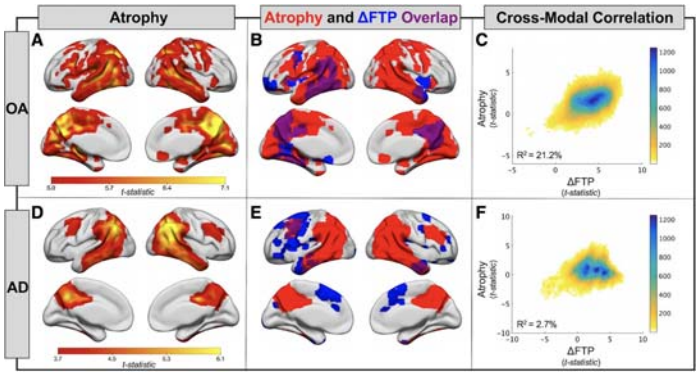
Movement Disorders, Volume: 28, Issue: 1, Pages: 31-40, First published: 06 February 2013, DOI: (10.1002/mds.25373)

Longitudinal tau accumulation and atrophy in aging and Alzheimer's disease

***In vivo* estimate of Braak stage from AV-1451 images**

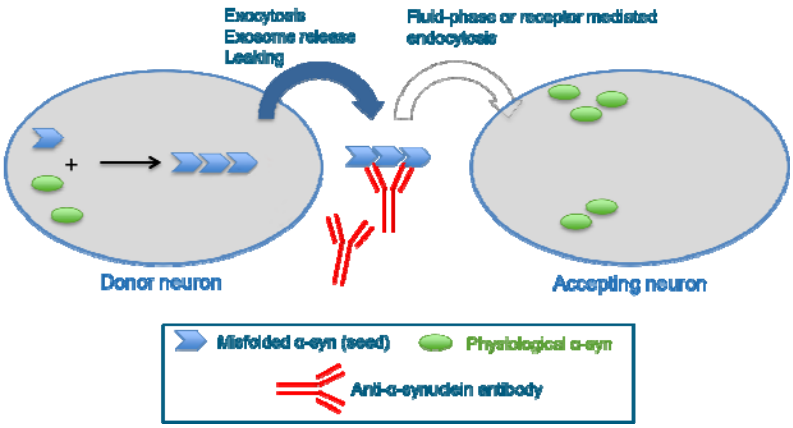


Schwarz AJ et al. (2016) Brain



Harrison TM et al. Annals of Neurology, Volume: 85, Issue: 2, Pages: 229-240, First published: 31 December 2018, DOI: (10.1002/ana.25406)

Targeting Aggregated α-Syn in PD with Immunotherapy



Anti-synuclein antibody treatment reduces α-Syn pathology and ameliorates behavioral deficits in animal models

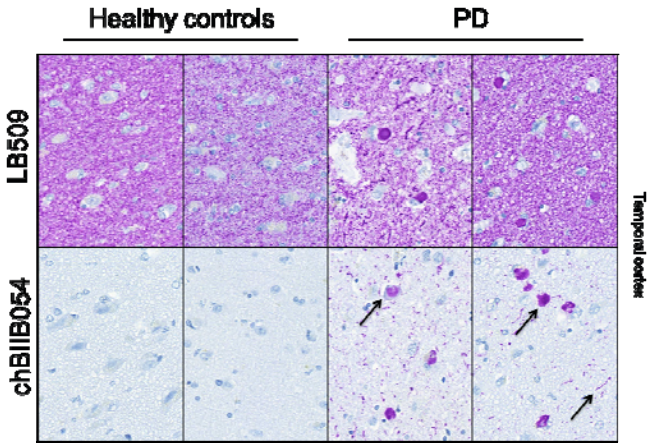
[Masliah, 2005, Masliah, 2011, Lindstrom 2014, Bae 2012, Hien 2014, Shahaduzzaman 2015, Mandler 2015]

Development status of anti-alpha-synuclein immunotherapies

	MEDI1341	Lu AF82422	ABBV-0805	Prasinezumab PRX002	Cinapanemab BIIB054
Company	AstraZeneca/Takeda	Lundbeck	Abbvie/Bioarctic	Prothena/Roche	Biogen
Phase	Phase I	Phase I	Phase I	Phase II	Phase II
Trial completion date	Nov 2019	March 2020	Jun 2020	Feb 2021	April 2022
Antibody type	Full human IgG1 agly	Human IgG1	Humanized IgG1	Humanized IgG1	Full human IgG1
Epitope	102-130	112-117	121-127	115-126	1-10
Affinity for monomer	7nM (Biacore)	16 nM (Biacore)	50-120nM (Biacore)	3nM (Biacore)	100nM (ITC)
Affinity for aggregate	Not reported	100 fold selectivity over monomer	200 fold selectivity over monomer	48pM	120pM

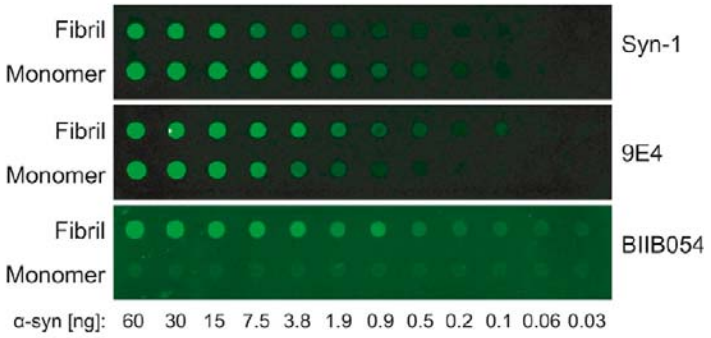
BIIB054: Background

- BIIB054 is a human monoclonal antibody generated using Neurimmune's Reverse Translational Medicine™ platform
- Selected based on affinity for aggregated vs. monomeric a-syn
- BIIB054 Selectively targets pathologic, aggregated α-Syn; much lower affinity for more abundant, physiological, monomeric α-Syn
- Efficacy demonstrated in multiple preclinical models

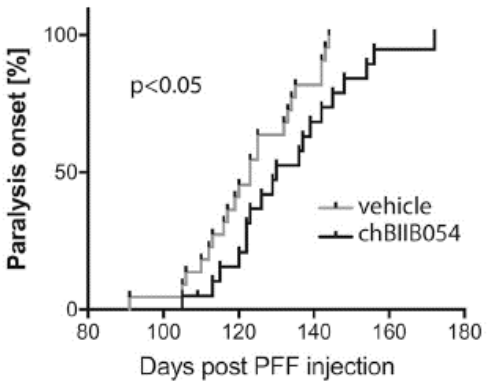


BIIB054 selectivity and impact in animal behavior model

Selectivity for pre-formed fibrils relative to other mAbs

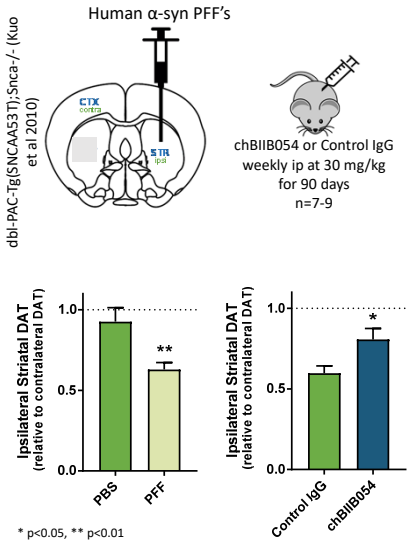


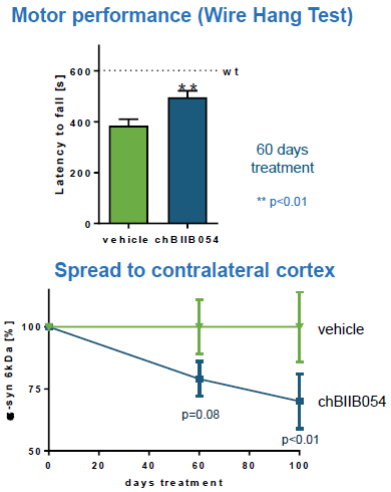
A53T mutant mice treated after PFF injection



Weihofen et al. Neurobiology of Disease 2019

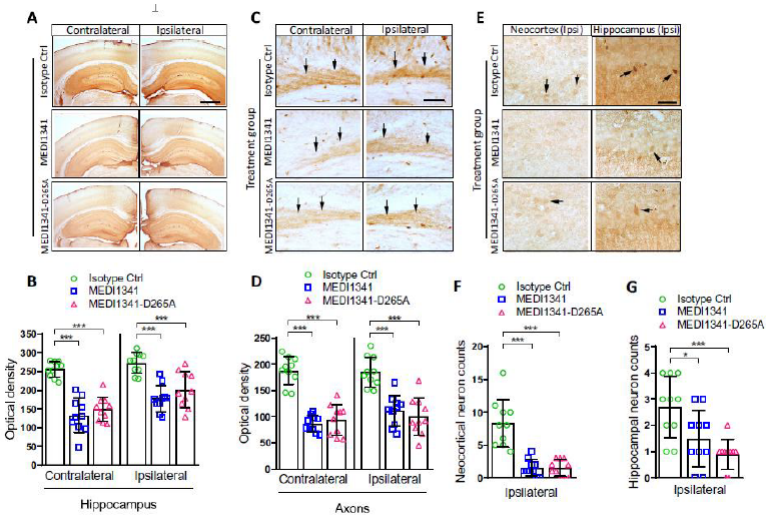
Peripheral Dosing with chBIIB054 Attenuates Loss of Striatal Dopamine Transporter in Humanized PFF Mouse Model





Weihofen et al, ADPD 2017

MEDI 1341 reduces a-syn spreading in mouse model



From Schofield et al. Neurobiology of Disease 2019

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Affinity for aggregate	Not reported	100 fold selectivity over monomer	200 fold selectivity over monomer	48pM	120pM

Update on Phase 2 PASADENA Study

- Powered to detect a 37.5% relative reduction in progression (MDS-UPDRS) at week 52
- Study did not meet its primary objective
- Signal was observed on multiple pre-specified secondary clinical endpoints
- Additional long-term follow-up is being conducted

Clinical trials of aducanumab for Alzheimer's disease

- Monoclonal anti-body that is selective for aggregated forms of amyloid-beta
- Studies 301 (n = 1,647) and 302 (n= 1,638)
  - Multi-center, global, placebo-controlled RTC
  - 78 week duration
  - Primary outcome measure CDR-SB
- Study 103 (n = 196)
  - Multicenter-RTC, phase 1B study (staggered, parallel group design)
  - 54 weeks duration
  - Primary outcome, safety and tolerability

Clinical studies of aducanumab are consistent with an effect on AD pathology and clinical features

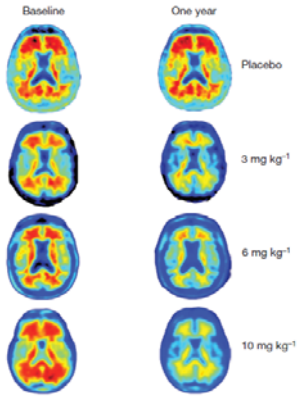

Figure 1 | Amyloid plaque reduction with aducanumab: example amyloid PET images at baseline and week 54. Individuals were chosen

Sevigny et al. Nature, 2016

	Study 301 Final Data			Study 302 Final Data		
	Week 78 Placebo decline (N=545)	Week 78 Difference vs. placebo (%) p-value		Week 78 Placebo decline (N=548)	Week 78 Difference vs. placebo (%) p-value	
		Low Dose (N=547)	High Dose (N=555)		Low Dose (N=543)	High Dose (N=547)
CDR-SB	n=333 1.56	n=331 **-0.18 (-12%)** 0.2250	n=295 **0.03 (2%)** 0.8330	n=288 1.74	n=290 **-0.26 (-15%)** 0.0901	n=299 **-0.39 (-22%)** 0.0120
MMSE	n=332 -3.5	n=334 **0.2 (-6%)** 0.4795	n=297 **-0.1 (3%)** 0.8106	n=288 -3.3	n=293 **-0.1 (3%)** 0.7578	n=299 **0.6 (-18%)** 0.0493
ADAS-Cog 13	n=331 5.140	n=332 **-0.583 (-11%)** 0.2536	n=294 **-0.588 (-11%)** 0.2578	n=287 5.162	n=289 **-0.701 (-14%)** 0.1962	n=293 **-1.400 (-27%)** 0.0097
ADCS-ADL-MCI	n=331 -3.8	n=330 **0.7 (-18%)** 0.1225	n=298 **0.7 (-18%)** 0.1506	n=283 -4.3	n=286 **0.7 (-16%)** 0.1515	n=295 **1.7 (-40%)** 0.0006

ITT population excluding data collected after March 20, 2019
Negative % means less progression in the treated arm
n: number of randomized and dosed subjects with endpoint assessment at Week 78
www.fda.gov

Donanemab slows clinical decline of Alzheimer's Disease is phase 2 trial

- Donanemab targets aggregated beta amyloid
- 76 week study showed 32 percent slowing in disease progression relative to placebo
- 84 centiloid reduction of amyloid plaque (consistent with target engagement and effect on underlying pathology)

From Eli Lilly press release; Jan 11, 2021

Immunotherapy-Based Trials Will Lead to Successful Disease Modifying Therapy

- Recent results from immunotherapy in Alzheimer's disease support the conceptual framework for this approach in related disorders like Parkinson's disease
- Immunotherapy aimed at removing misfolded proteins addresses the core molecular pathology that causes Parkinson's disease
- The first generation of anti-alpha synuclein monoclonal antibodies already exist and are being tested in multi-center trials
- There is broad industry engagement and additional selective molecules are in the pipeline