The Importance of Early Identification of Alzheimer's Disease

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	No, nothing to disclose
X	**Yes, please specify:**

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research	Royalties/ Patent	Stock Options	Ownership/ Equity Position	Employee	Other
Biogen			**X**					
Eli-Lilly		**X**						
Lundbeck		**X**						
Nutricia		**X**						
GE-Health		**X**	**X**					
MSD		**X**						
Roche			**X**					
UCB			**X**					
Lundbeck			**X**					
AVID			**X**					
Boehringer			**X**					
Axovant			**X**					

Disclaimer

- **Aducanumab is an investigational medicine and the benefit/risk profile has not been fully established. It has not received any marketing authorization and there is no guarantee that it will obtain such authorization in the future**
- **The information and any data presented is early interim data from ongoing clinical trials and it is made available for scientific discussion only, in consideration of the general interest of the scientific community with respect to any progress in the research and development of possible treatments for Alzheimer disease**
- **The information and any data presented are developed from scientist research and are not intended to predict the availability of any particular drug or therapy**

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Why we are here today

Alois Alzheimer

“The first person to be cured of Alzheimer's is a person in a Clinical Trial”

AfricanAmericansAgainstAlzheimer's

An assumption

- **We believe that treatment earlier in the disease course may have greater benefit for the patient**

- **With no treatment yet slowing or stopping the course of disease – why do we believe that? Why have we gone in that direction?**

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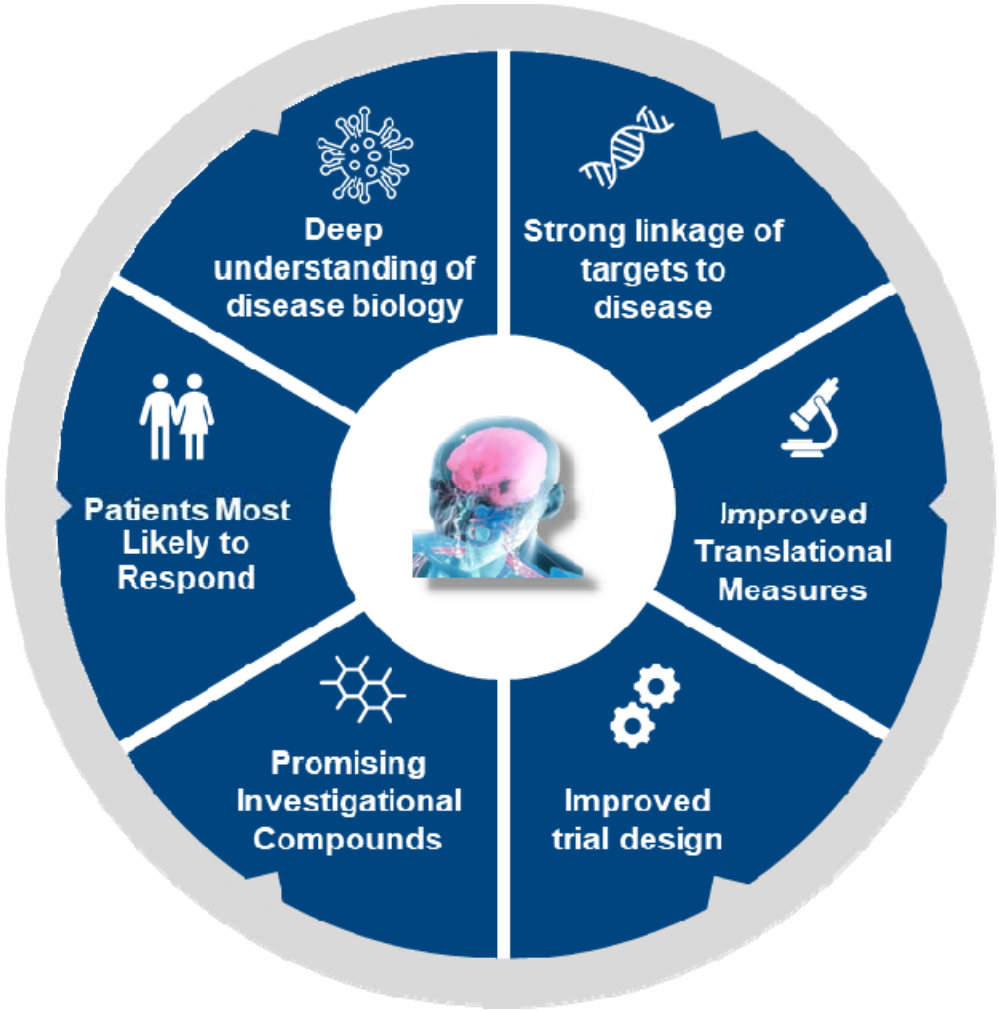
What's important in inventing and developing new therapies?



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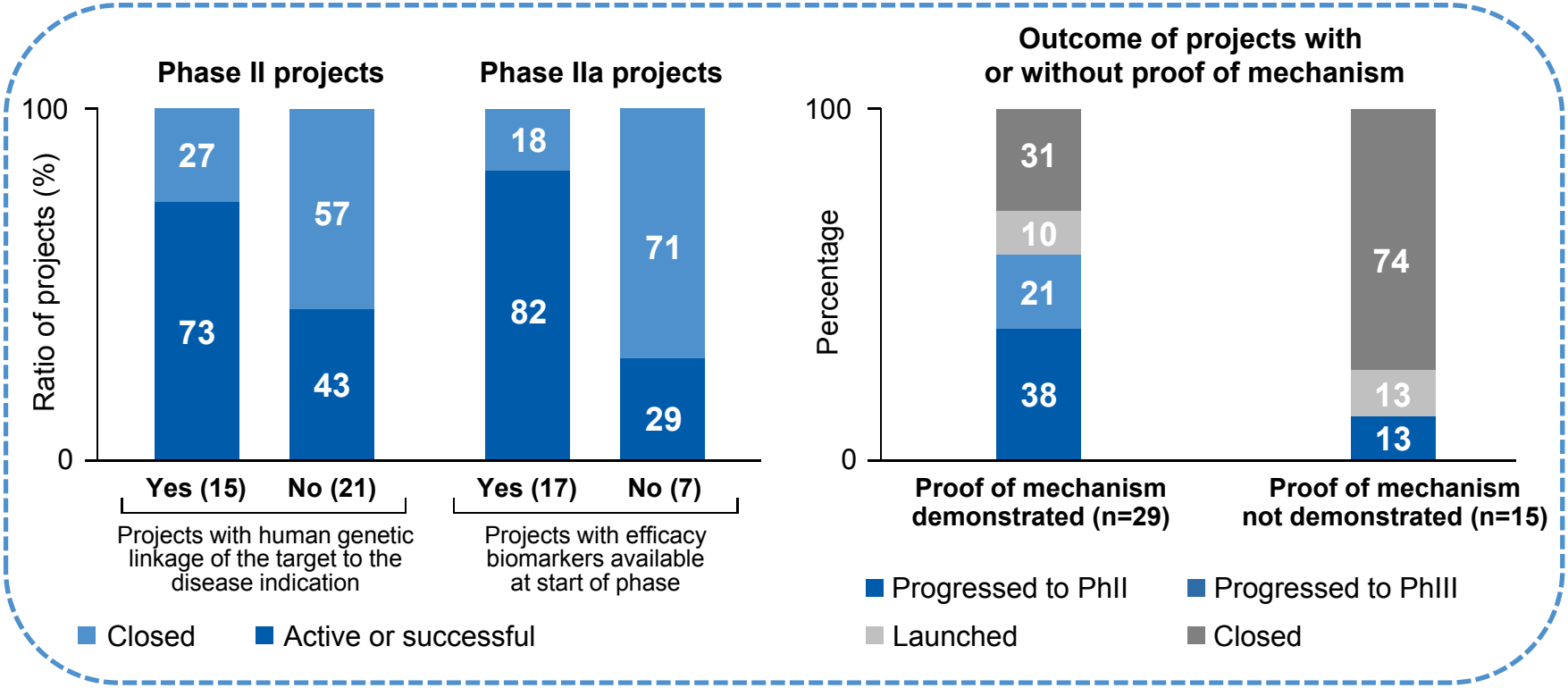
Key factors important to project progression in clinical phase

- Human genetic data is more common in projects that succeed vs fail in PhII
- Successful projects are more likely to have biomarkers (82 vs 30%)[1]
- Proof of Mechanism – quantifiable target engagement has a positive impact on progression to PhII (38%), PhIII (21%) or launch (10%)[2]



1. Cook et al 2014 Nat Rev Drug Disc; 2. Morgan P et al. Nat Rev Drug Disc 2018;17:167–181

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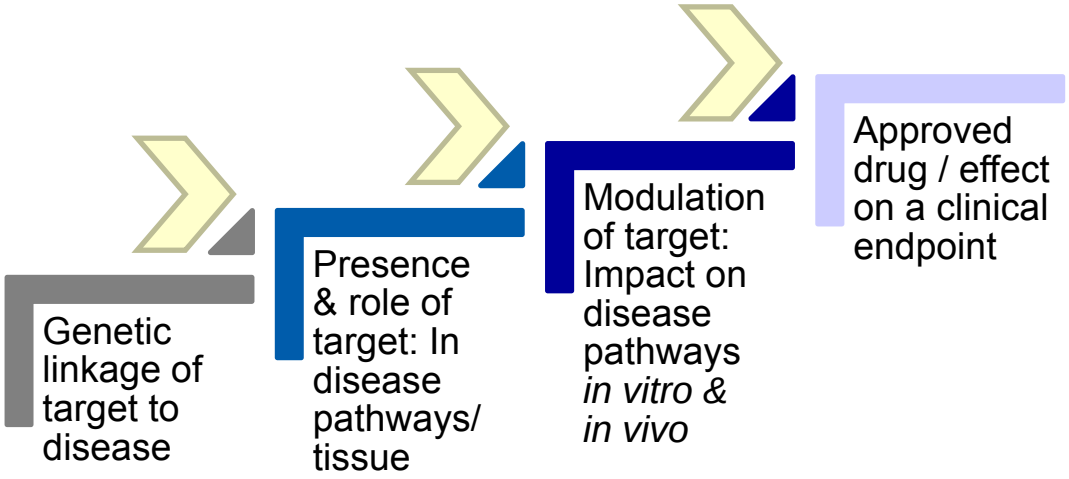
How do we rate the strength of connection to disease?

- Generate evidence that builds confidence in or invalidates the scientific hypothesis
- A target is only truly validated when a drug for that target is successfully approved



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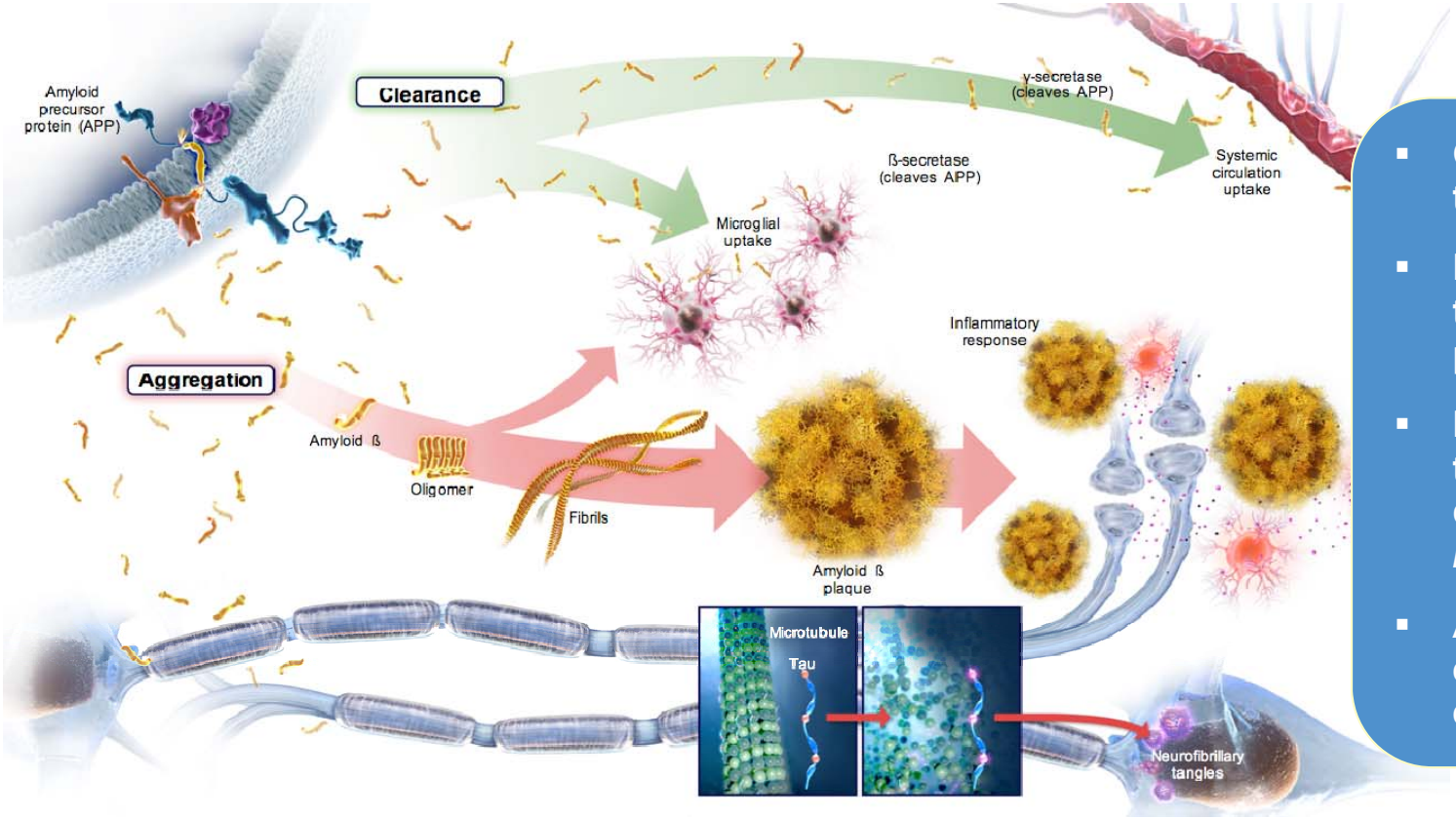
What are the current hypotheses being tested?



- **Genetic linkage of target to disease**
- **Presence & role of target: In disease pathways / tissue**
- **Modulation of target: Impact on disease pathways *in vitro & in vivo***
- **Approved drug / effect on a clinical endpoint**

Alzheimer's Association. 2017 Alzheimer's disease facts and figures. http://www.alz.org/ documents_custom/2017-facts-and-figures.pdf. Accessed March 5, 2018.
Blennow K, et al. Mov Disord. 2016;31:836- 847. Dubois B, et al. Alzheimers Dement. 2016;12:292-323. Hardy J, and Selkoe DJ. Science. 2002;297:353-356.
Cummings, J. et al. Alzheimer's Research & Therapy 2016; 8:39. Hampel, H. et al. Pharmacol Res. 2018; S1043-6618(17)31330-0.

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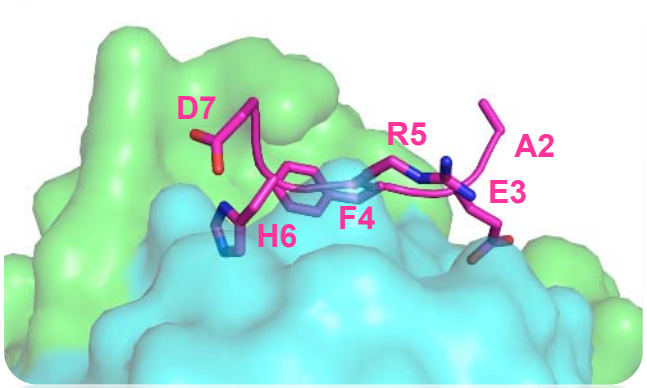

Investigational Compounds – Aducanumab

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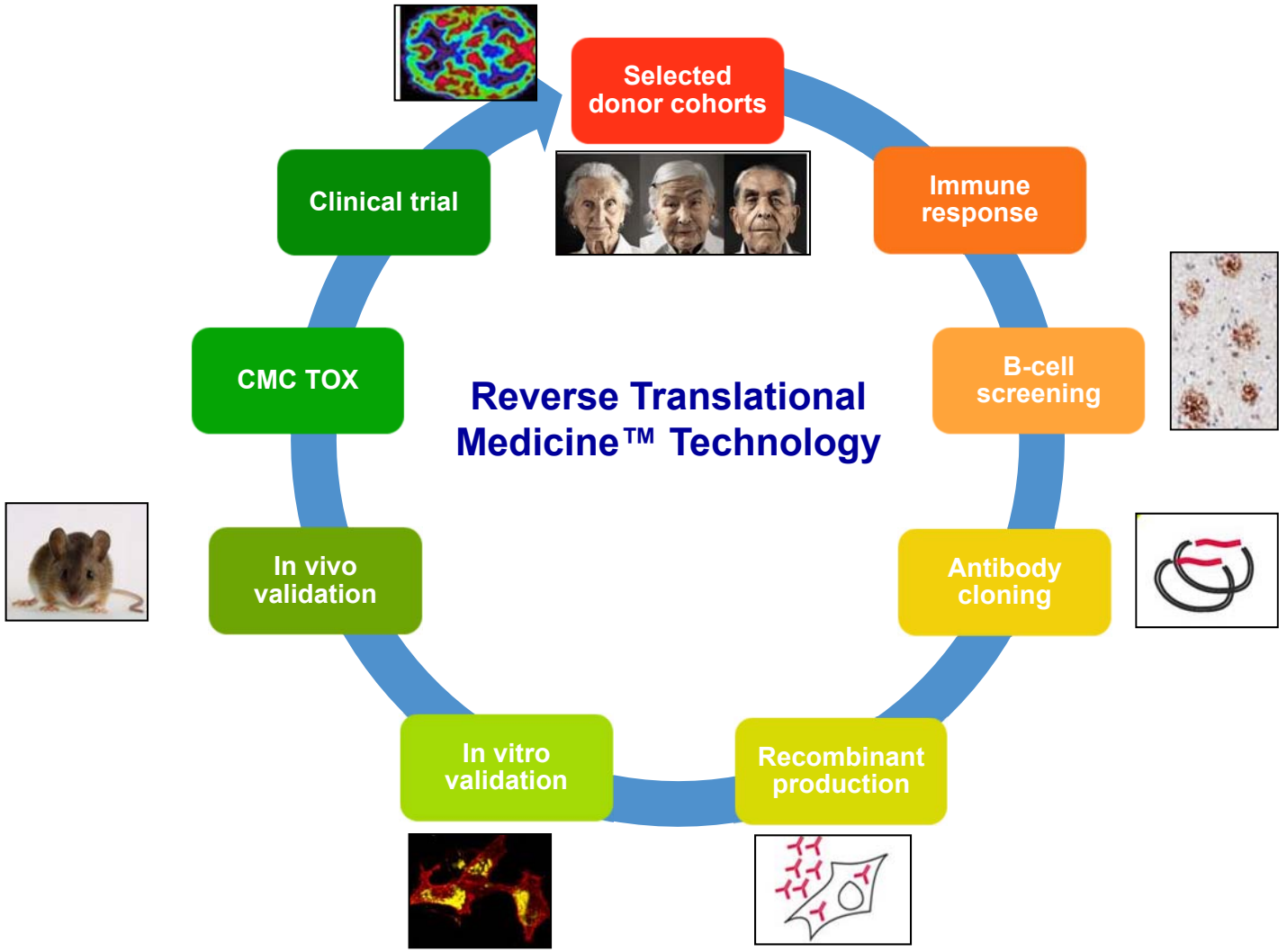
Aducanumab is a human IgG1 anti-Aβ monoclonal antibody developed by Biogen and Neurimmune



Dunstan R et al. Alzheimer's and Dementia 2011;7:S457. Data presented at AAIC 2011; Sevigny J et al. Nature. 2016;537:50–56.

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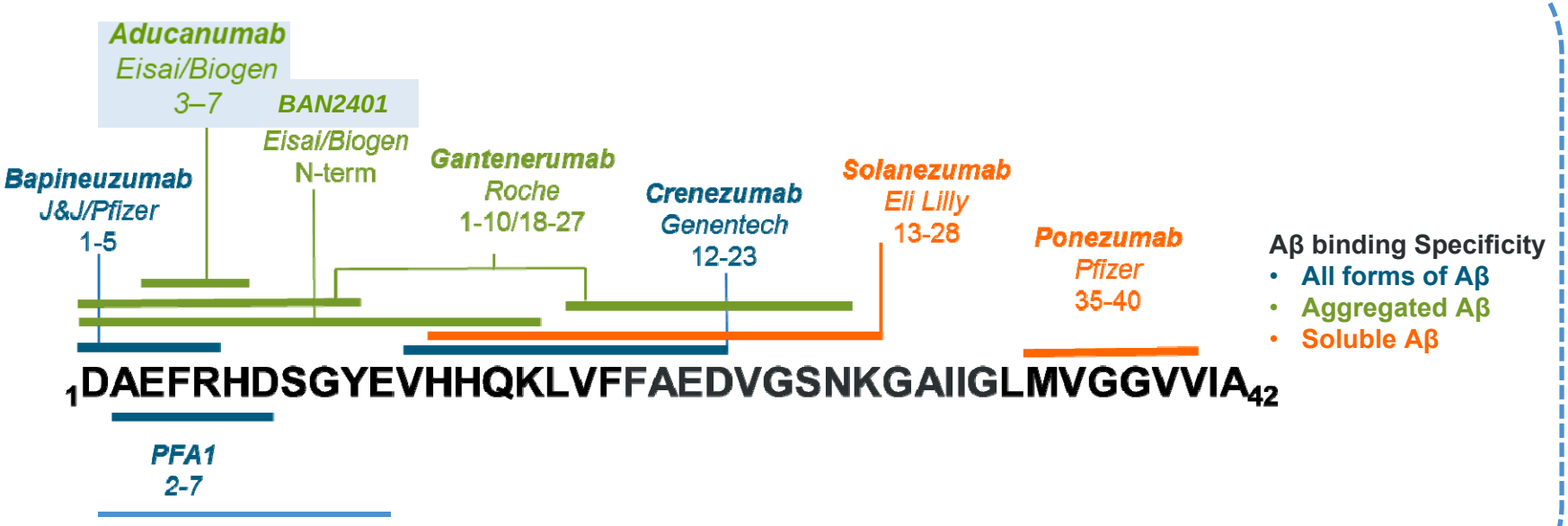
Multiple Aβ antibodies target the N-terminus



Adolfsson O, et al. J Neurosci. 2012;32:9677-9689; Bohrmann B, et al. J Alzheimers Dis. 2012;28:49-69; Crespi G, et al. Sci Rep. 2015;5:9649; Feinberg H, et al. Alzheimers Res Ther. 2014;6:31; Lannfelt L, et al. Alzheimers Res Ther. 2014;6:16; LaPorte SL, et al. J Mol Biol. 2012;421:525-536

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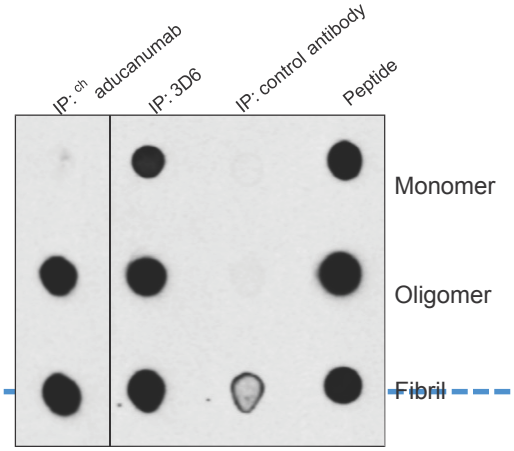
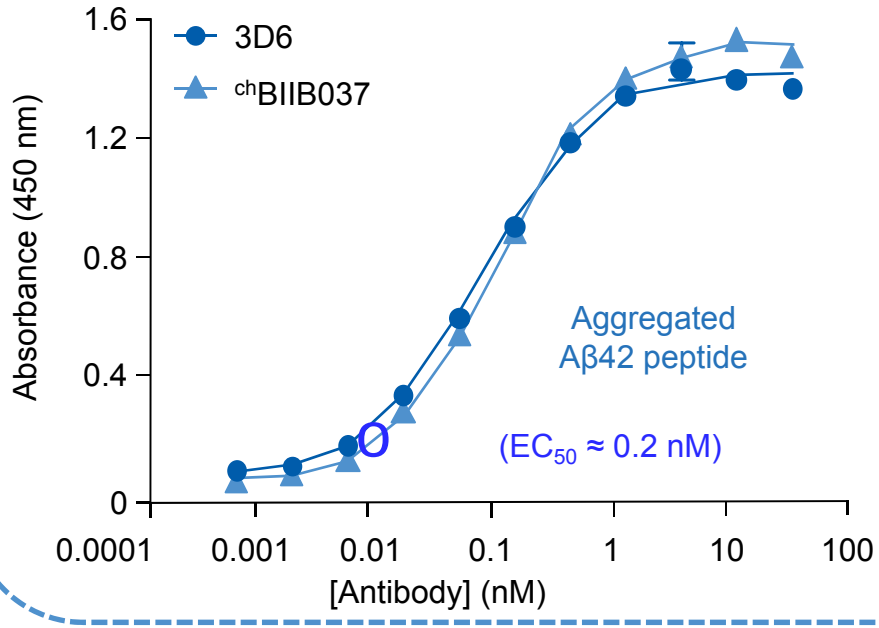
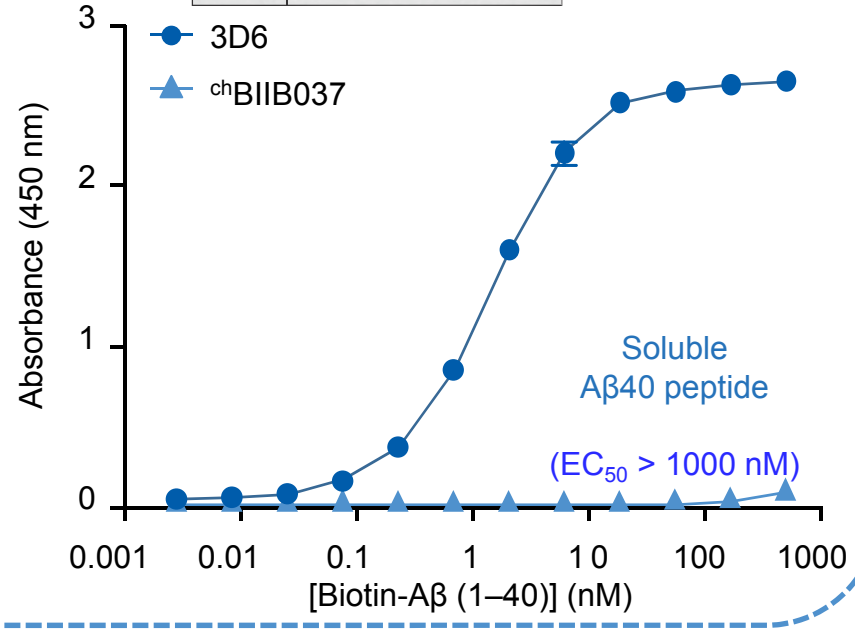
Aducanumab is highly selective for aggregated Aβ

Aducanumab binds to:
- **Soluble oligomers**
- **Insoluble fibrils**







Sevigny J et al. Nature. 2016;537:50–56

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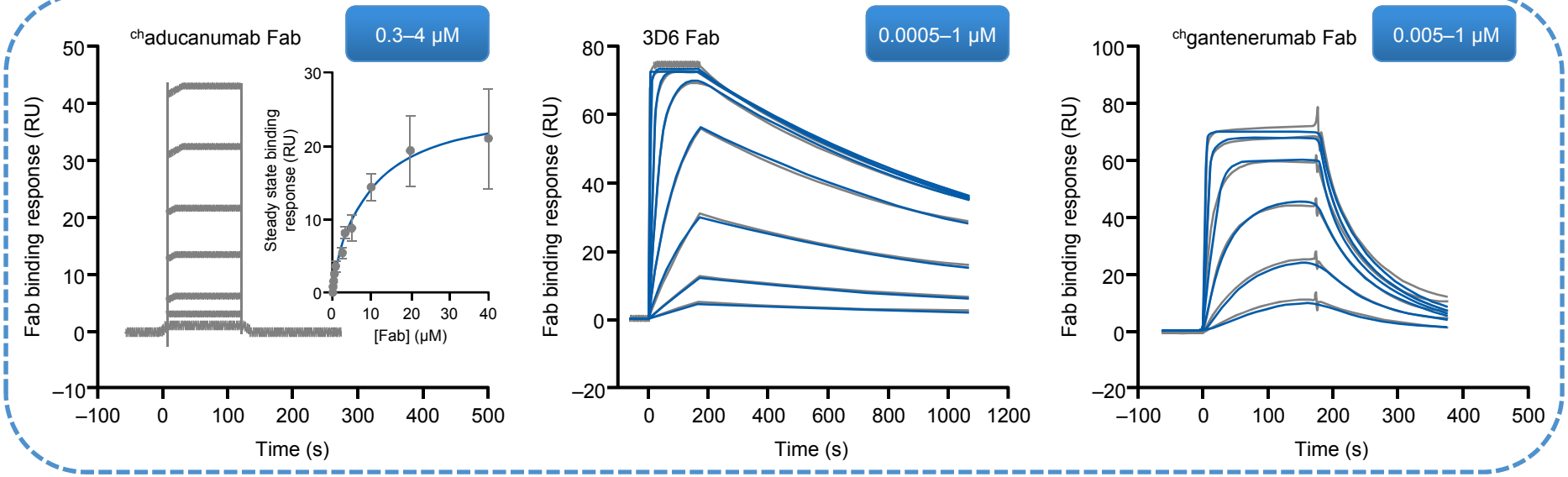
Selectivity of aducanumab for aβ aggregates is driven by valency, low affinity for soluble monomer, and rapid kinetics

Binding studies using SPR



	Dissociation rate	Equilibrium affinity
Fab Fragment	$K_d(s^{-1})$	$K_D(nM)$
Aducanumab (mIgG chimer)	>1	~9,000
Gantenerumab (mIgG chimer)	$1.5x10^{-2}$	23
Bapineuzumab (mouse 3D6)	$7.9x10^{-4}$	1.1

Arndt JW et al. Structural basis of unique selectivity of aducanumab for aggregated forms of amyloid-beta. Platform Presented at: Antibody Engineering & Therapeutics; December 11-15, 2017.

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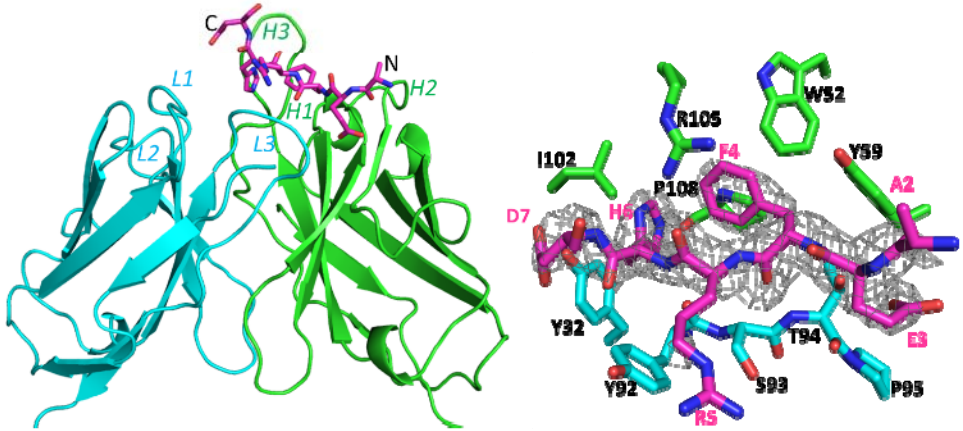
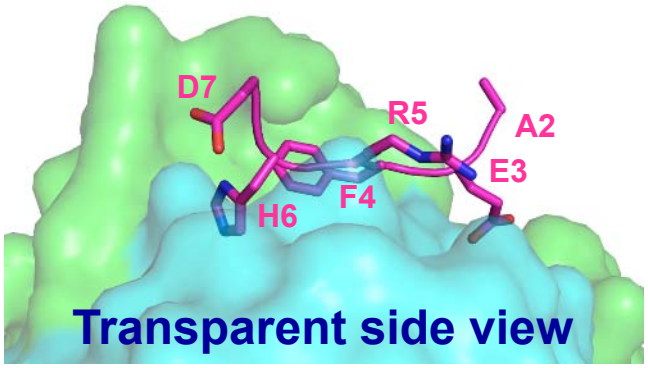
What structural features drive the selectivity of antibodies for Aβ aggregates?

Crystal structure (2.1 Å) of aducanumab Fab with Aβ 1-11





Aducanumab binds to Aβ peptide with a "light touch"

A shallow and compact epitope may contribute to the selectivity for high molecular weight Aβ forms, without targeting Aβ monomers

	BSA (Å²)	CDR contacts
Aducanumab	530	12
Bapineuzumab	537	23
Gantenerumab	903	24

Arndt JW et al. Structural basis of unique selectivity of aducanumab for aggregated forms of amyloid-beta. Poster Presented at: AAIC July 24-28, 2016; Toronto, Canada.
BSA, buried surface area; CDRs, complementary-determining regions

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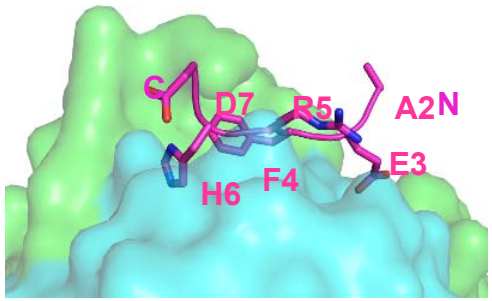
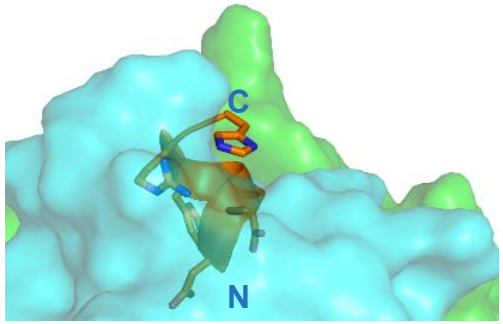
Interaction between aducanumab and Aβ is shallow, with a subtle interface in comparison with those of other anti-Aβ antibodies

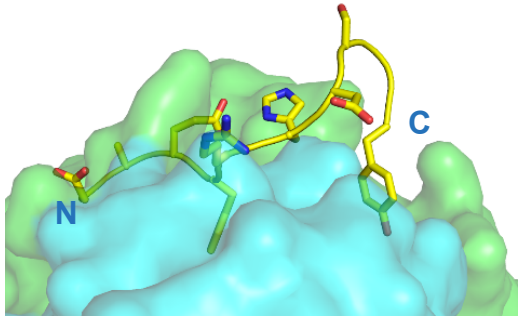
Side view comparison of N-terminal Aβ antibodies



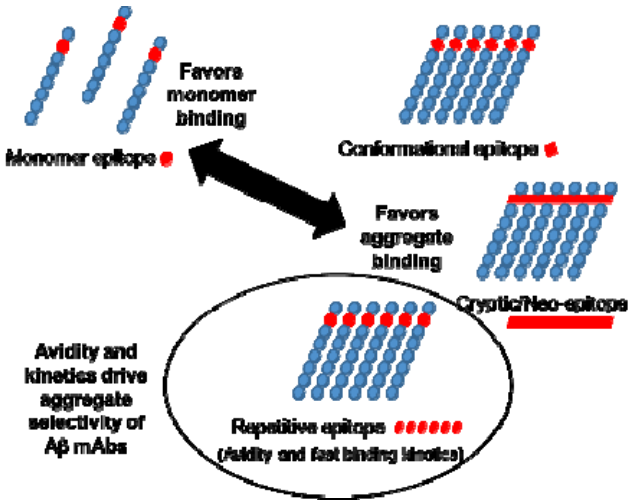
Aducanumab



Bapineuzumab



Gantenerumab



Aducanumab discriminates between Aβ monomers and aggregates based on its strong avidity for epitope-rich aggregates

Protein data bank (PDB): http://www.rcsb.org/pdb/home/home.do; Bapineuzumab structure: PDB ID 4ONF; Gantenerumab structure: PDB ID 5CSZ

Arndt JW et al. Structural basis of unique selectivity of aducanumab for aggregated forms of amyloid-beta.
Poster Presented at: AAIC July 24-28, 2016; Toronto, Canada.

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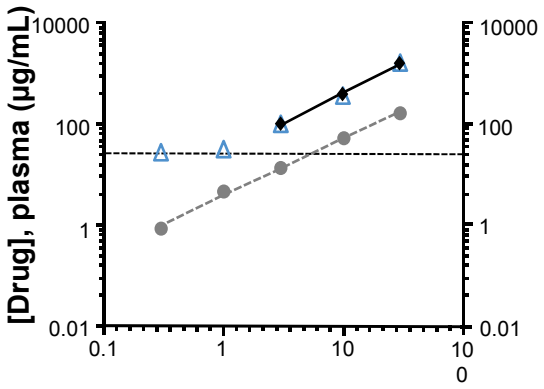
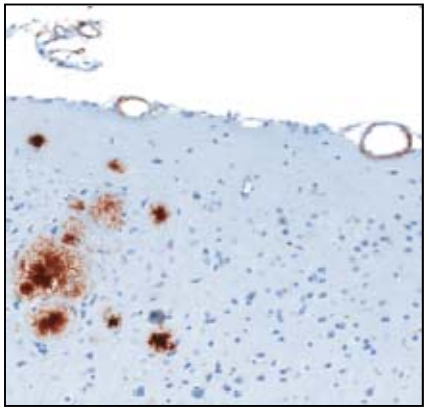
Dose-dependent reduction of amyloid burden upon chronic treatment in Tg2576 mice

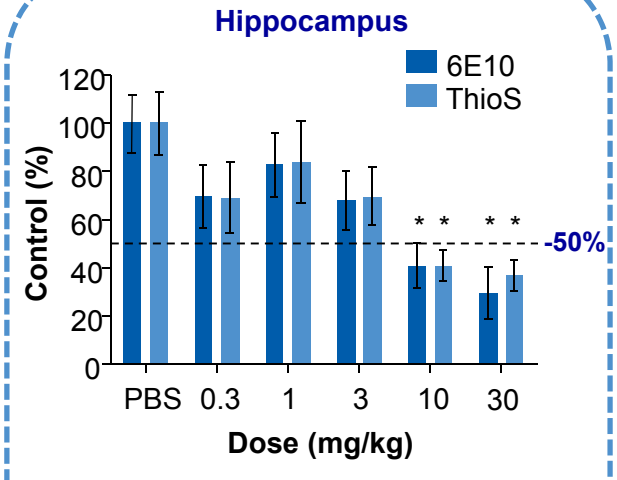


Brain exposure proportional to dose and plasma

Range of brain-to-plasma ratio 0.1–1%



In vivo binding to amyloid deposits (anti-hu IHC)



Dose-dependent reduction of amyloid

(chronic treatment in Tg2576 mice)

Sevigny J et al. Nature. 2016;537:50–56.

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Patients Most Likely to Respond / Improved Translational Measures from Preclinical to the Clinic

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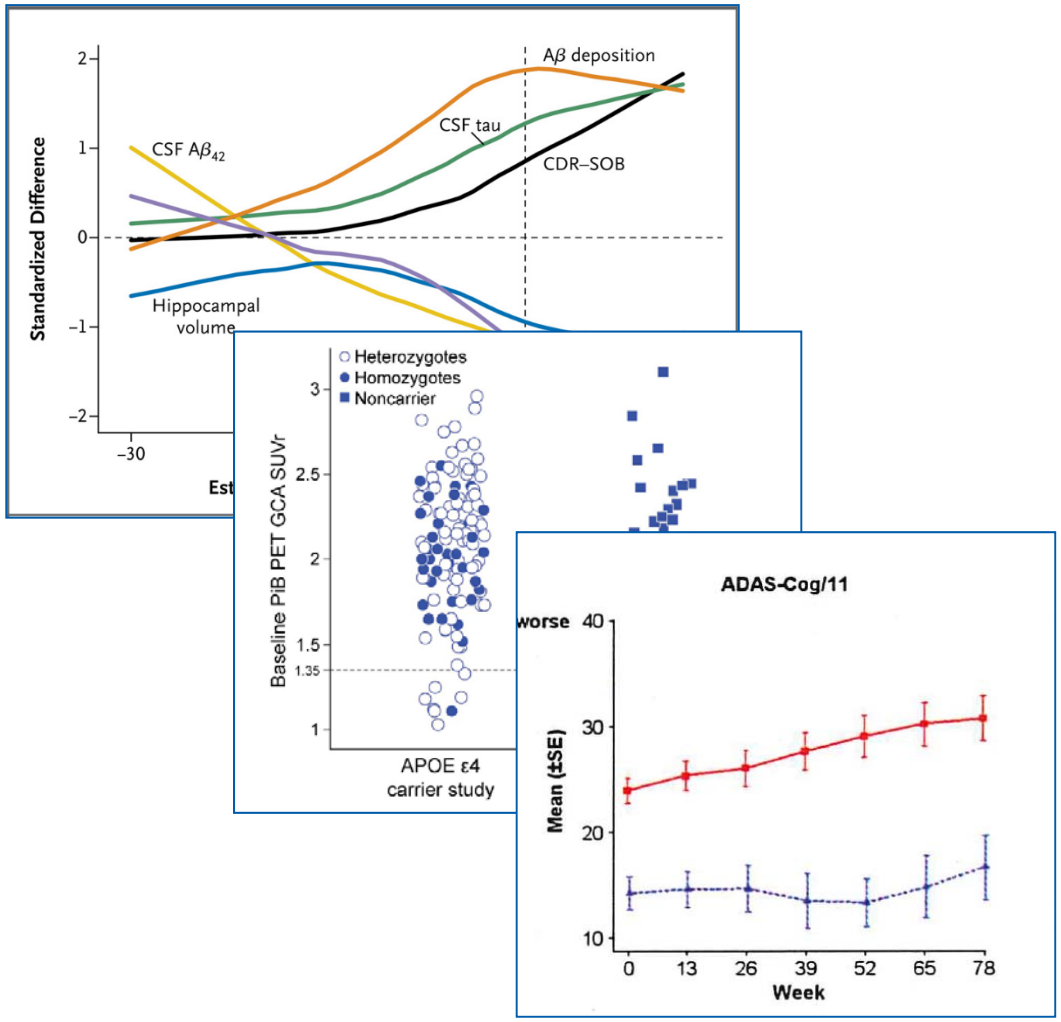
What have we learnt about disease progression?



- **Biomarkers tell us that Alzheimer's starts many years prior to the appearance of symptoms**
- **In previous Phase 3 studies, patients were enrolled without evidence of amyloid pathology (Alzheimer's pathogenesis)**
- **The presence of pathology defines different baseline scores and trajectories for cognitive and functional decline in Ab+ and Ab- subjects**

Bateman B et al NEJM 2012;367(9):795–804, Liu E et al Neurology 2015;85(8):692–700; Salloway S et al. Alzheimers Dement 2013;9(4):P888–P889

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Identifying patients most likely to respond to an anti-amyloid mechanism of action – amyloid PET screening

	Prodromal (n=139)	Mild (n=133)	Overall (n=278)[a]
Amyloid PET findings by binary visual readings, n (%)			
Amyloid-positive Amyloid-negative	69 (50) 70 (50)	100 (75) 33 (25)	170 (61) 108 (39)
Amyloid PET findings via quantitative analysis, n (%)			
Amyloid-positive Amyloid-negative	79 (57) 60 (43)	104 (78) 29 (22)	185 (67) 93 (33)

[a]Includes 6 patients with unknown AD stage.

Sevigny J, et al. Alzheimer Dis Assoc Disord. 2016
AD, Alzheimer disease; PET, positron-emission tomography; SD, standard deviation

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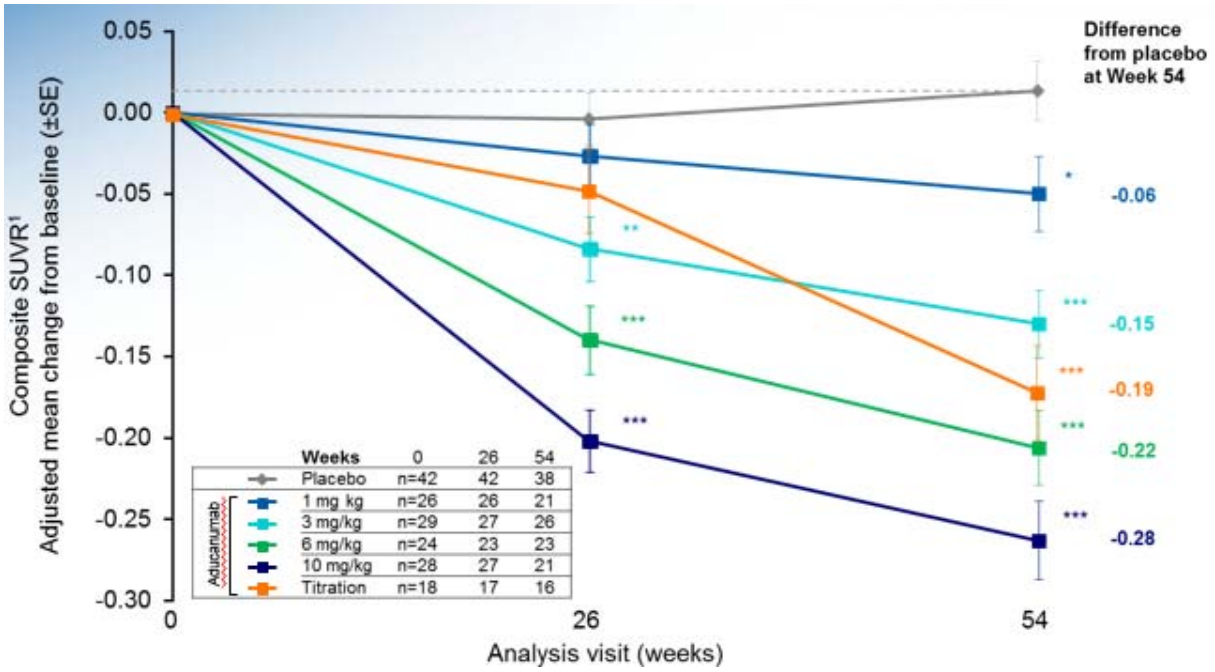
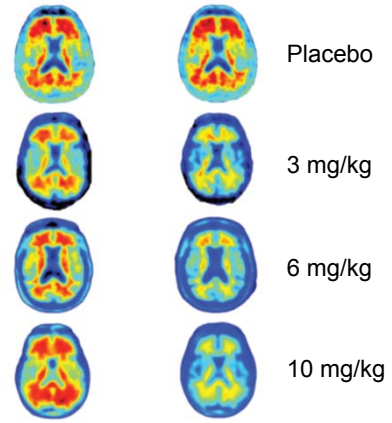
Clinical proof of mechanism for aducanumab – dose and time-dependent reduction in amyloid plaque as measured by PET

Dose and time dependent reduction in composite SUVR (PET)[1]



Amyloid-β (Aβ) plaque reduction: example amyloid PET images[2]



Nominal p values: * P<0.05; **P<0.01; ***P<0.001 vs placebo.

[1]Viglietta et al. Aducanumab titration dosing regimen: 12-month interim analysis from PRIME, a randomized, double-blind, placebo-controlled Phase 1b study in patients with prodromal or mild Alzheimer's disease. Platform Presentation at CTAD 2016; [2]Sevigny J et al. Nature. 2016;537:50–56
ANCOVA, analysis of covariance; SE, standard error; SUVR, Standardized uptake value ratio

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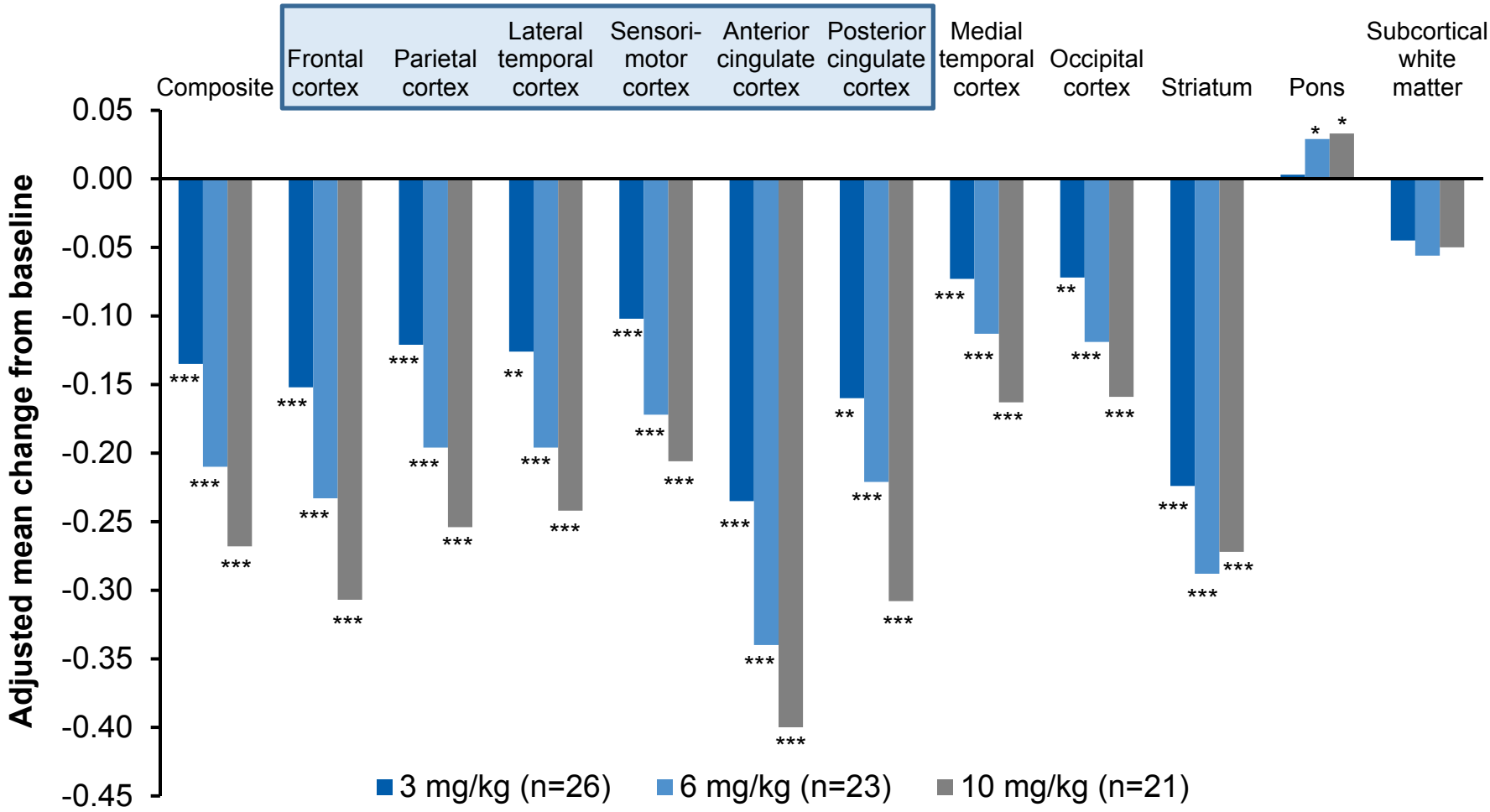
Amyloid plaque reduction with aducanumab regional analysis SUVR at Week 54



*P<0.05; **P<0.01; ***P<0.001 vs placebo

Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline composite SUVR. PD analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter;

Sevigny et al. Randomized, Placebo-Controlled, Phase 1b Study of the Anti–Amyloid Beta Antibody Aducanumab (BIIB037) in Patients with Prodromal or Mild Alzheimer's Disease: Interim Results. Platform Presentation at CTAD 2015.

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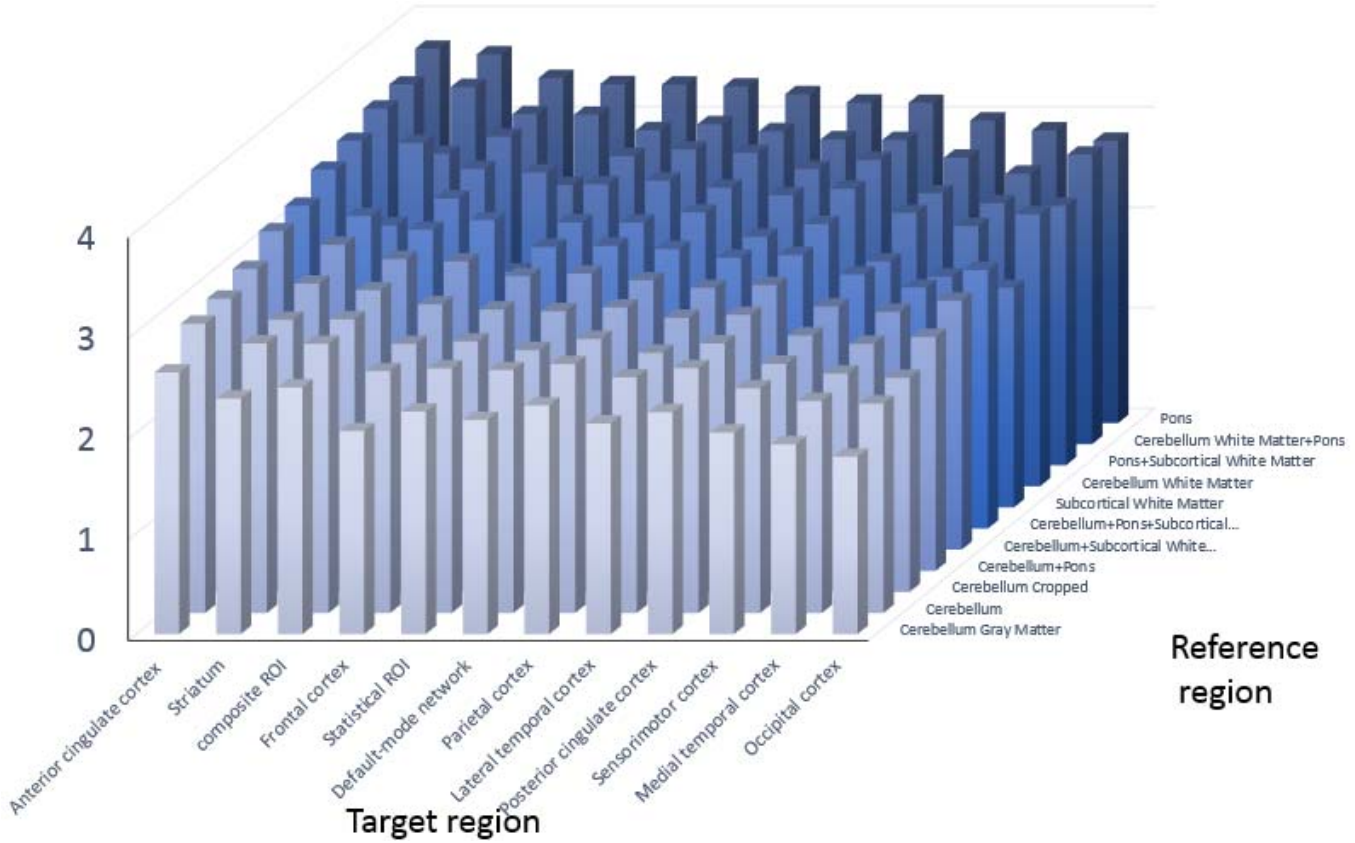
Dose- and time-dependent reductions in SUVR observed with aducanumab regardless of reference/target regions



Effect size for each brain target region in 10 mg/kg aducanumab group by reference region at week 54

Chiao P et al. Optimization of standard uptake value ratio quantification through investigation of different brain target and reference regions for the detection of change in amyloid beta PET in the ongoing Phase 1b PRIME study of aducanumab. Poster Presented at HAI 2016.

Centiloid conversion

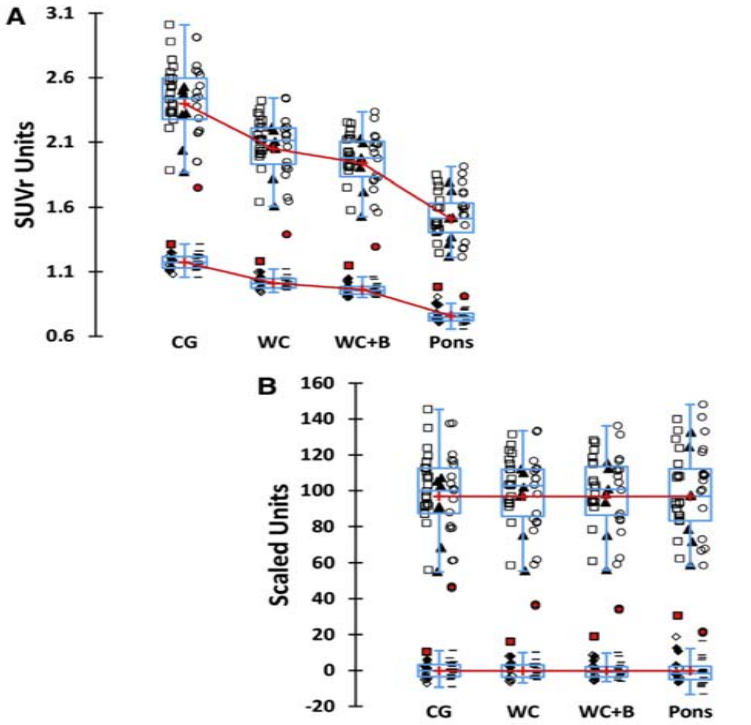
Centiloid: a 0 to 100 scale, anchored by young controls (45 years) and typical AD patients

Objective: to standardize quantitative amyloid imaging measures by converting the outcome of each particular analysis method or tracer to the centiloid scale

Methods:

- **A centiloid conversion equation established using a public database from Global Alzheimer's Association Information Network (GAAIN; http://www.gaain.org) and an amyloid PET data set from Avid Radiopharmaceuticals (46 subjects, each underwent a PiB and a florbetapir scan)**
- **PRIME amyloid PET SUVR measures converted to centiloid units using the centiloid conversion equation**
- **Percent change in amyloid PET measures calculated using the following:**

$$\frac{\text{Follow up } Centiloid - Baseline}{\text{Baseline Centiloid}} \times 100$$



Klunk WE et al. Alzheimers Dement 2015;11(1):1–15

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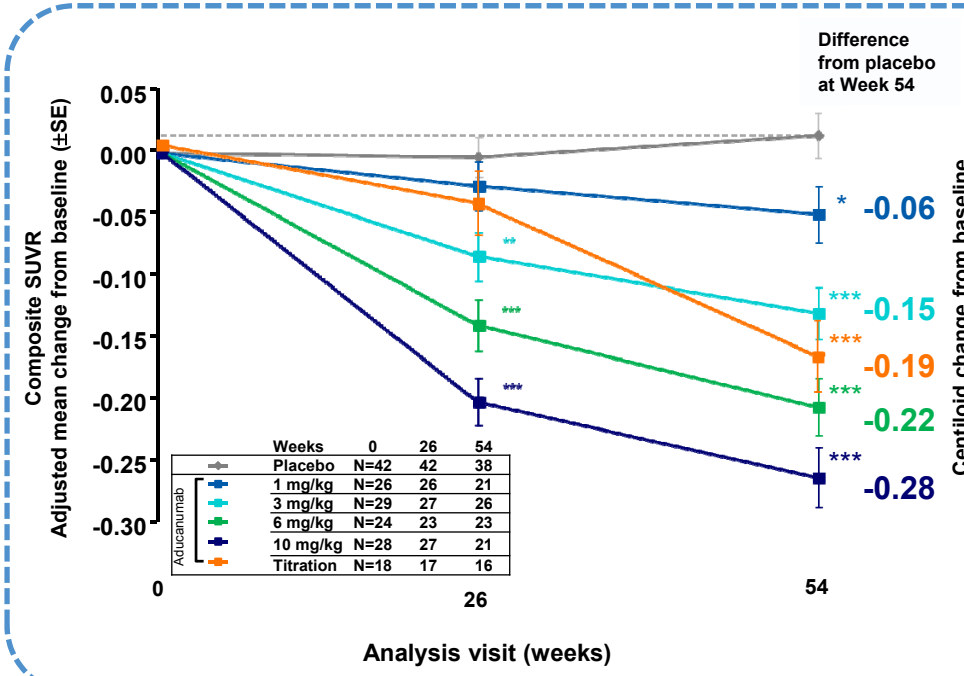
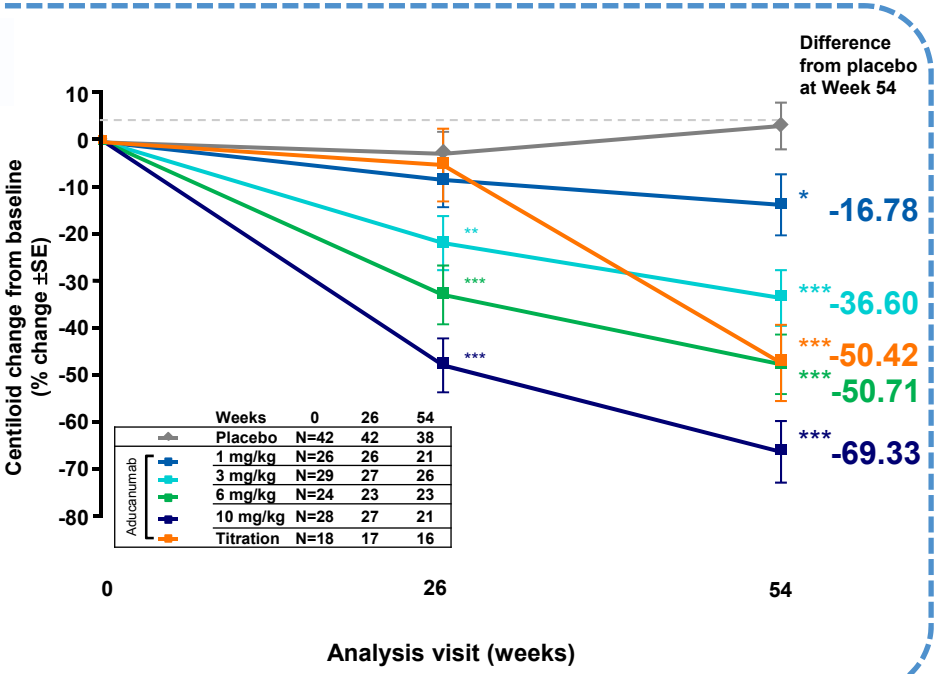
Aducanumab Ph1b amyloid results in SUVR and centiloid: 69% reduction in amyloid plaque load

Change in SUVR



Percentage change in centiloid



Viglietta et al. Aducanumab titration dosing regimen: 12-month interim analysis from PRIME, a randomized, double-blind, placebo-controlled Phase 1b study in patients with prodromal or mild Alzheimer's disease. Platform Presentation at CTAD 2016. Data on file.
Nominal p values: * P<0.05; **P<0.01; ***P<0.001 vs placebo.
Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline composite SUVR. PD analysis population is defined as all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter. ANCOVA, analysis of covariance; SE, standard error

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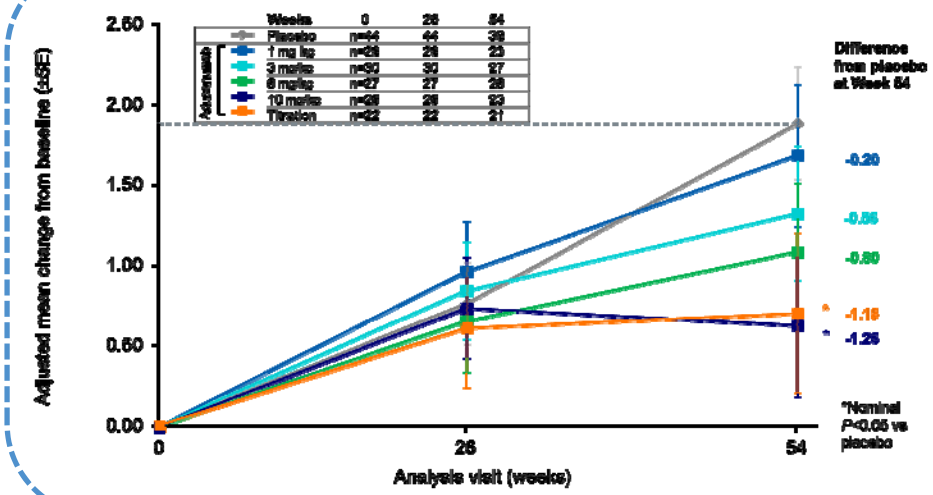
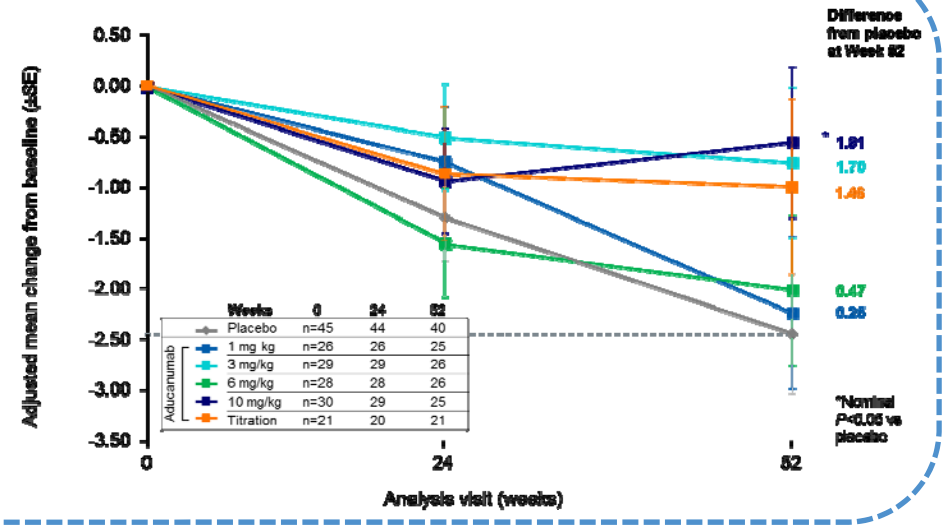
Clinical proof of concept: effect of aducanumab on clinical decline as measured by CDR-SB & MMSE (exploratory endpoints)

Change in CDR-SB



Change in MMSE



CDR-SB is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-SB. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment

MMSE is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline MMSE. Efficacy analysis population is defined as all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment

Viglietta et al. Aducanumab titration dosing regimen: 12-month interim analysis from PRIME, a randomized, double-blind, placebo-controlled Phase 1b study in patients with prodromal or mild Alzheimer's disease. Platform Presentation at CTAD 2016. Data on file.

CDR-SB is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-SB. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment

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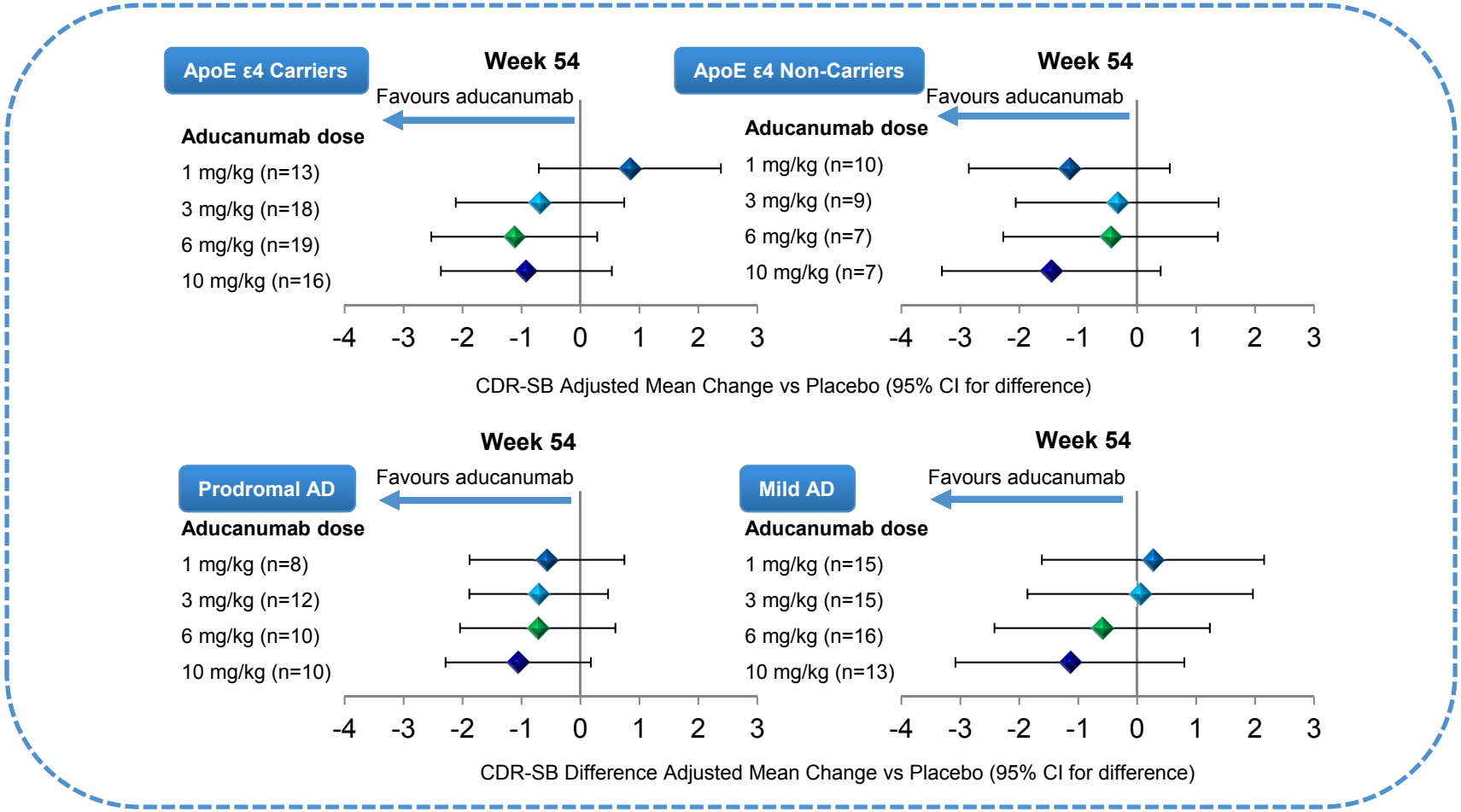
Ph1b Aducanumab CDR-SB by patient subgroup



Viglietta et al. 12-Month Interim Analysis of APOE4 Carriers for Fixed and Titration Dosing Regimens in PRIME, a Phase 1b study of Aducanumab. Platform presentation at ADPD 2017, Vienna, Austria.

CDR-SB was an exploratory endpoint. Analyses based on observed data. Difference from placebo and 95% CI based on ANCOVA model. ANCOVA for change from baseline with factors of treatment, laboratory Apo ε4 status (carrier and non-carrier) [for clinical stage subgroup analysis only], and baseline CDR-SB. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.

ApoE ε4, apolipoprotein E; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, confidence interval; SUVR, standardized uptake value ratio

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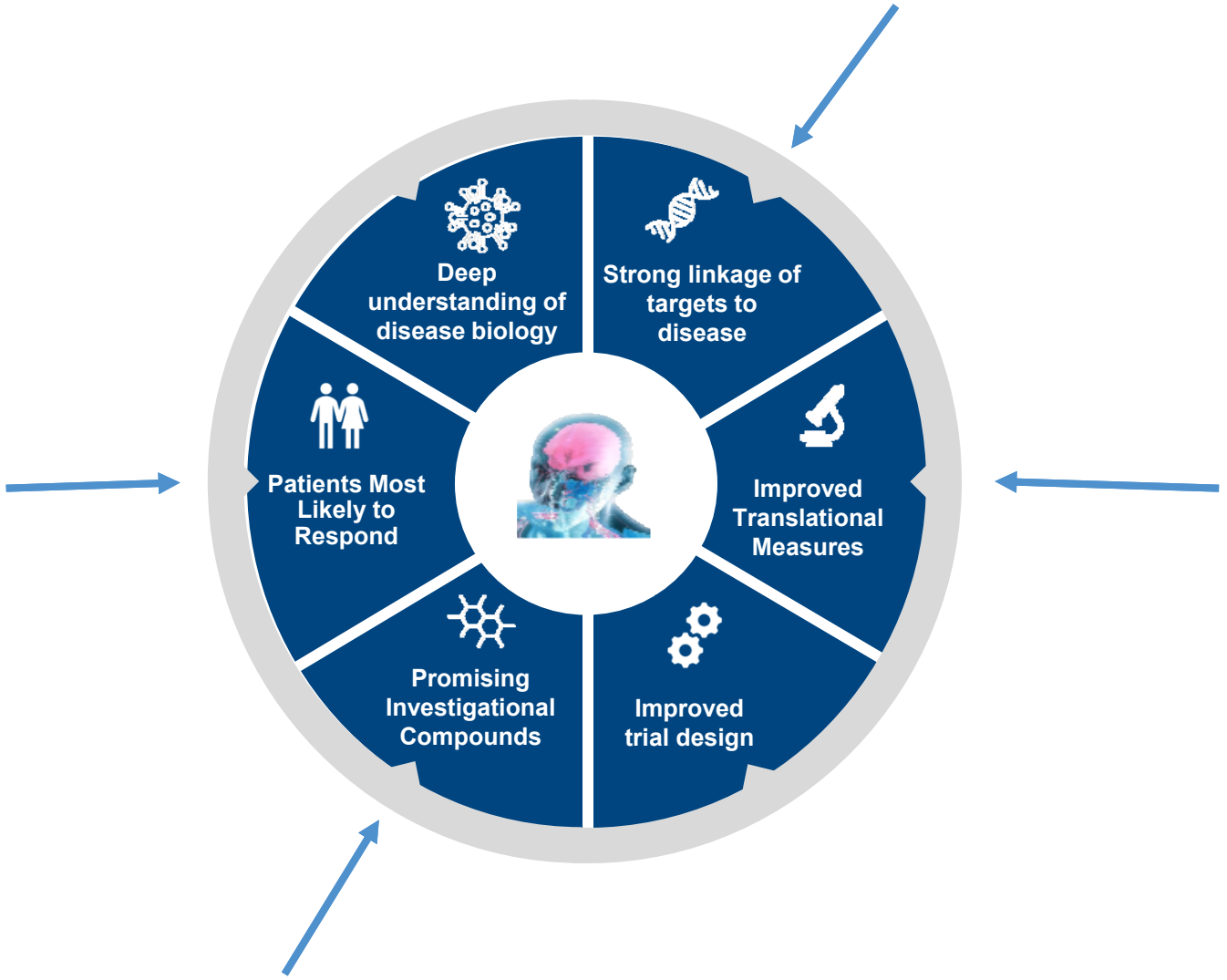
What's important in inventing and developing new therapies?



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