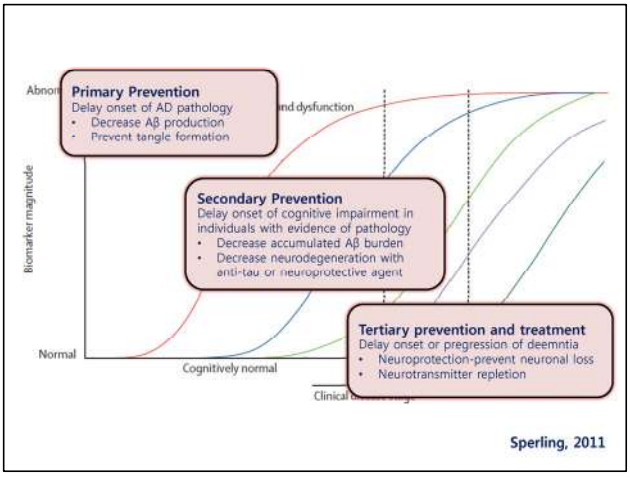
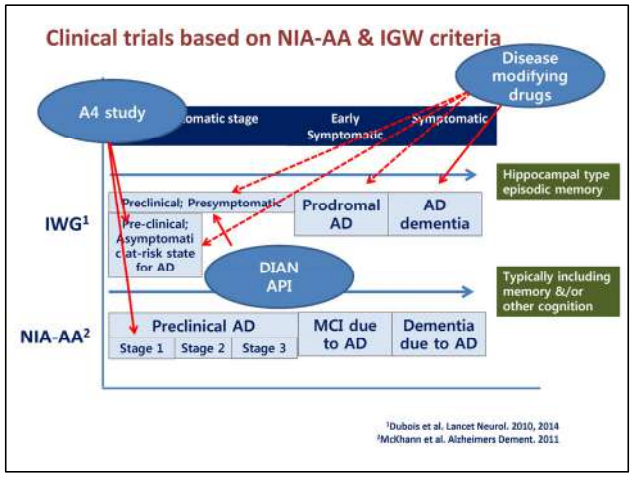
Pharmacological approaches for dementia prevention

박 기 형
가천의대길병원

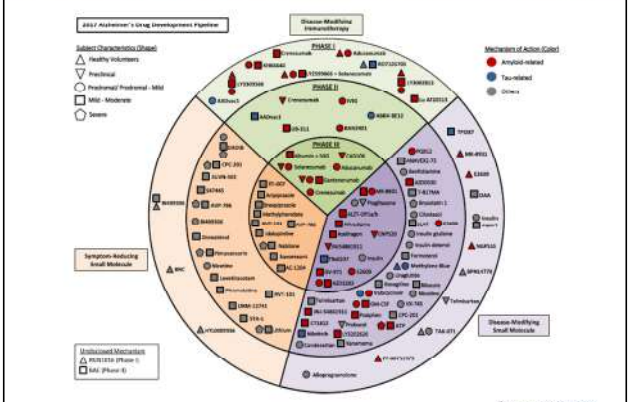




Early investigations of AChEI treatment in MCI

Study title or NCT number	MCI study	InDDEx	00236431/ 00236574	Donepezil401 MCI study	00293176
Compound	Donepezil (and vitamin E)	Rivastigmine	Galantamine	Donepezil	Donepezil
Target population	Mild cognitive impairment	Mild cognitive impairment	Mild cognitive impairment	Mild cognitive impairment	Mild cognitive impairment
Phase	III	III	III	IIIb/IV	IV
Duration	3 years	Up to 4 years	2 years	24 weeks	48 weeks
N number	769	1018	990+1.058	270	821
Clinical inclusion criteria	MMSE 24-30. CDR=0.5 do not Meet criteria for dementia due to AD	CDR=0.5; NYU Paragraph recall test<9. not AD	CDR=0.5	MMSE ≥ 24, CDR=0.5, no AD	MMSE 24-28, CDR=0.5
Biomarker Inclusion criteria	-	-	-	-	-
Clinical primary endpoint	Time to development of probable/possible AD	Progression to AD	Conversion to Dementia (CDR ≥1)	NYU paragraph Recall test, ADCS-CGIC-MCI	ADAS-Cog13, CDR-SB

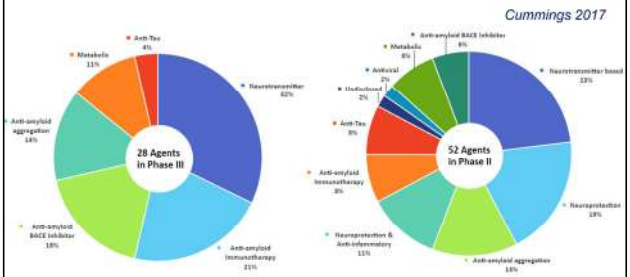
Disease Modifying Strategy for Dementia Prevention



Cummings 2017

Disease Modifying Strategy for Dementia Prevention

Cummings 2017



Phase III trial
- Anti-amyloid therapy : 53%
- Anti-Tau therapy : 4%
- Neurotransmitter : 32%
- Others : 11%

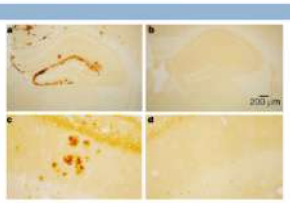
Phase II trial
- Anti-amyloid therapy : 27%
- Anti-Tau therapy : 8%
- Neurotransmitter : 23%
- Others : 42%

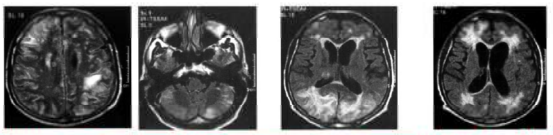
Anti-amyloid approach

Amyloid "vaccine" reduces plaque burden and memory loss in transgenic mouse models

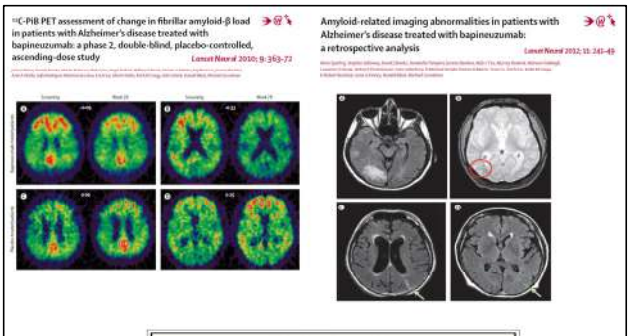
Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse

Schenk et al, Nature 1999





Postvaccination T-cell lymphocitic meningoencephalitis occurred in 18/298 with AN1792



ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease

CONCLUSIONS

Bapineuzumab did not improve clinical outcomes in patients with Alzheimer's disease, despite treatment differences in biomarkers observed in *APOE ε4* carriers.

EXPEDITION 1, 2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease

- May 2009 - April 2012
  - 1012 solanezumab / 1040 placebo
- Inclusion Criteria
  - MMSE 16-26
  - NINCDS-ADRDA
  - GDS less than 6
  - MRI or CT within 2 years
- Clinical outcome
  - ADAS-cog11 (EXPEDITION 1)
  - ADAS-cog 14 (EXPEDITION 2)
  - ADCS-ADL
- Secondary Biomarker
  - Plasma Aβ level
  - Relationship between Plasma solanezumab & Aβ

EXPEDITION 3

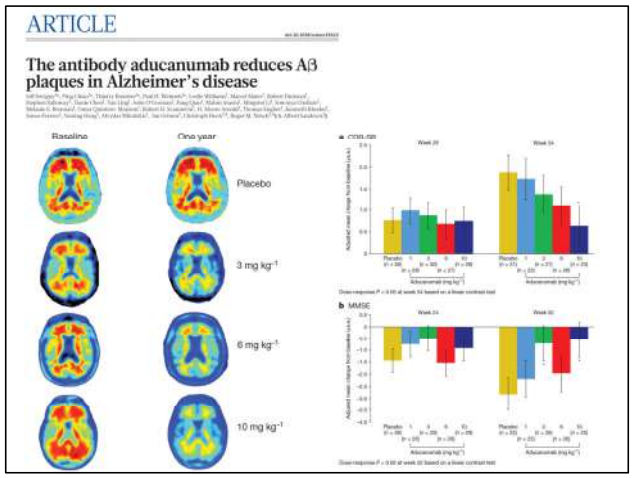
The NEW ENGLAND JOURNAL of MEDICINE

Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease

- July 2013 – Feb 2017
  - 1057 solanezumab / 1072 placebo
- Inclusion Criteria
  - NINCDS-ADRDA
  - MMSE 20-26
  - GDS less than 6
  - MRI or CT within 2 years
  - **Presence of amyloid pathology**
- Clinical outcome
  - ADAS-cog 14
  - Plasma Aβ
  - Change of Florbetapir Aβ image
  - Change of CSF Aβ level

Antibody	Manufacturer	Origin	Subclass	Epitope	Conformations Recognized			
					Monomer	Oligomer	Fibril	ARIA-E
Bapineuzumab	Pfizer Inc./Janssen Pharmaceuticals, Inc.	Humanized	IgG1	AA 1–5	Yes	Yes	Yes	High
Solanezumab	Eli Lilly and Company	Humanized	IgG1	AA 16–26	Yes	No	No	Low
Gantenerumab	Hoffman-La Roche	Human	IgG1	AA 3–12, 18–27	Weak	Yes	Yes	High (?)
Crenezumab	Genentech, Inc.	Humanized	IgG4	AA 13–24	Yes	Yes	Yes	Low
Ponezumab	Pfizer Inc.	Humanized	IgG2	AA 30–40	Yes	No	No	None
BAN2401	BioArctic Neuroscience, AB/Eisai Co., Ltd.	Humanized	IgG1	Protofibrils	–	–	–	–
Aducanumab	Biogen, Inc.	Human	IgG1	AA 3–6	No	Yes	Yes	High

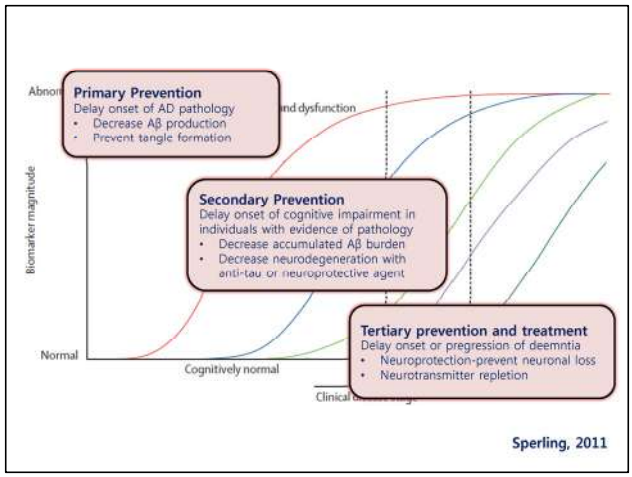
Christopher H.van Dyck 2017



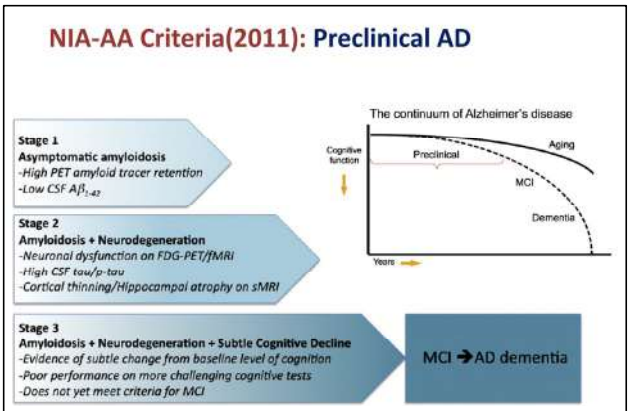
BACE-I

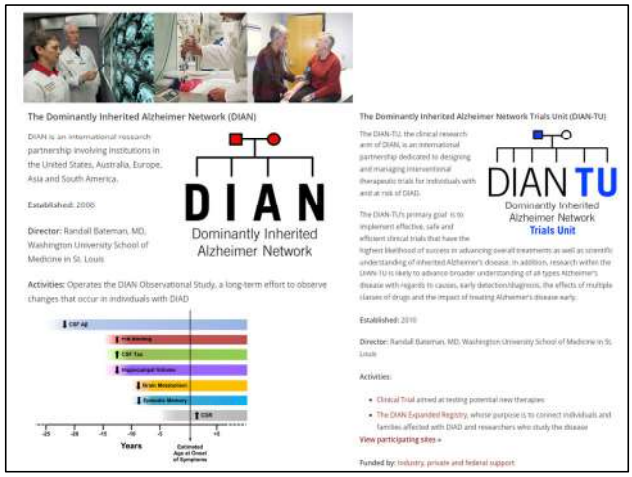
Drug Name	Company	Status	Patient population	Start to Estimated end date
Verubecestat	Merk®	Phase III	Prodromal to mild AD	11/2012-06/2017
Elenbecestat	Biogen/Eisai®	Phase III	Prodromal to mild AD	10/2016-06/2020
LY3314814	Eli Lilly®	Phase III	Prodromal to mild AD	09/2014-08/2019
JNJ-54867977	Johonson & Johonson®	Phase II/III	Asymptomatic at-risk	11/2015-05/2023
CNP520	Norvatis	Phase II/III	Asymptomatic at-risk (ApoE4)	11/2015-08/2023

2017 Nature Reviewed Drug Discovery 2017, Cummings



NIA-AA Criteria(2011): Preclinical AD

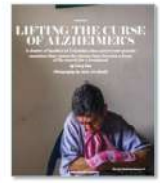




Alzheimer's Prevention Initiative (API) study

Autosomal Dominant Alzheimer's Disease (ADAD)

- Collaboration between Banner Alzheimer's Institute, National Institute on Aging (NIA) and Genentech.
- Largest ADAD cohort in the world with near 100% certainty of development of Alzheimer's disease due to a single genetic mutation in PSEN1 (E280A)
- Crenezumab 720 mg q2w SC for 5 years
- Development of a sensitive cognitive endpoint: "API Composite Cognitive Test"
- Study assessments performed at one clinical site reduced variability



Primary Endpoint: Efficacy in pre-symptomatic participants who carry the PSEN-1 E280A autosomal dominant mutation (MMSE >26, 30-60 years old) but do not meet criteria for AD or MCI

Colombian Study (300 patients)	60 Month Treatment Period Interim Analysis at 24 Months
N=100	ADAD carriers active drug repeating
N=100	ADAD carriers placebo repeating
N=100	ADAD non-carriers placebo repeating

Primary endpoints:
- API Cognitive Test Battery

Secondary endpoints:
- AV-45 PET
- FDG-PET
- vMRI
- CSF analysis

U.S. National Library of Medicine

ClinicalTrials.gov

A Study of CAD106 and CNP520 Versus Placebo in Participants at Risk for the Onset of Clinical Symptoms of Alzheimer's Disease (Generation S1)

A Study of CNP520 Versus Placebo in Participants at Risk for the Onset of Clinical Symptoms of Alzheimer's Disease (Generation S2)

Study	Generation I	Generation II
Estimated enrollment	1340	2000
Durgs	CAD106 /Placebo CNP520 / Placebo	CNP520 / Placebo
Inclusion Criteria	• Age 60 to 75 years • MMSE ≥ 24 and cognitively unimpaired • Homozygous APOE4 genotype	• Age 60 to 75 years • Cognitively unimpaired • At least one APOE4 gene
Primary outcome	Time to MCI due to AD APCC test score	Time to MCI due to AD APCC test score
Estimated study duration	11/2015 – 05/2024	08/2017 – 07/2024