The β-secretase BACE1 in Alzheimer's Disease

SUPPLEMENTAL INFORMATION

Supplemental Tables

Supplemental Table S1. Studies on BACE1 candidate biomarkers in body fluids

BACE1 parameter(s)	Study population	Matrix	Outcome/interpretation	Reference
Activity (comm)	31 AD	CSF	BACE1 correlates with brain amyloid load	(1)
Activity (Wu G)	99 HC, 87 MCI, 79 AD	CSF	No significant differences	(2)
Activity (Wu G)	48 HC, 39 sMCI, 76 MCI-AD, 56 AD	CSF	Increase BACE1 in MCI due to AD	(3)
Activity (Wu G)	33 HC, 45 MCI-AD, 52 sMCI, 16 cMCI, 87 AD	CSF	Increased BACE1 in incipient AD	(4)
Activity (Wu G)	65 HC, 75 AD	CSF	AD patients in advanced clinical stage had decreased BACE1 levels	(5)
Activity (Wu G)	106 HC, 183 MCI, 92 AD	CSF	No difference	(6)
Activity and concentration	59 HC, 59 MCI, 80 AD	CSF	BACE1 is a predictor of MCI	(7)
Activity and concentration	37 HC, 51 MCI, 60 AD	CSF	Increased BACE1 activity in APOE ε4 carriers	(8)
Activity and concentration	19 HC, 28 AD	CSF	BACE1 associated with decreased HV	(9)
Activity	12 HC, 18 MCI, 17 AD	CSF	Subjects with an AD-like biomarker profile had higher BACE1 level	(10)
Concentration	31HC, 6 MCI, 53 AD	CSF	Increased BACE1 levels are correlated with tau	(11)
Concentration	20 HC, 38 MCI, 50 AD	CSF	BACE1 correlates with neurogranin and neurogranin /BACE has prognostic value	(12)
Concentration	38 HC	CSF	Chronic BACE1 inhibition did not influence BACE1 levels	(13)
Concentration	38 HC	CSF	BACE1 correlates with neurogranin, α-synuclein and precuneus pathology	(14)
Activity and concentration	28 HC, 34 MCI, 45 AD	platelets	Increased BACE1 in AD platelets not in MCI	(15)

BACE1 parameter(s)	Study population	Matrix	Outcome/interpretation	Reference
Concentration	12 HC, 15 AD	plasma and platelets	Reduced platelet BACE1 levels in AD no difference in plasma	(16)
Concentration	44 HC, 19 MCI, 68 AD	platelets	Increased BACE1 levels only in AD patients	(17)
Activity	115 HC, 86 AD	platelets	Increased BACE1 activity in AD patients	(18)
Activity	85 HC, 97 MCI	plasma	No change in BACE1 activity in MCI	(19)
Activity and concentration (WB)	53 HC, 96 MCI, 75 AD	plasma	Increased BACE1 in plasma from MCI and AD patients	(20)
Concentration	32 non-AD, 47 AD	plasma	Increased BACE1 in plasma of AD patients	(21)

Abbreviations: Comm: commercial; WB: Western-blot; CSF: cerebral spinal fluid; MCI: Mild Cognitive Impairment; AD: Alzheimer's disease; HC: healthy controls; sMCI: stable MCI; cMCI: converters MCI. **Notes:** Wu G refers to the description of the BACE1 activity assay: Wu G et al, Clin Biochem 2008; 41: 986.

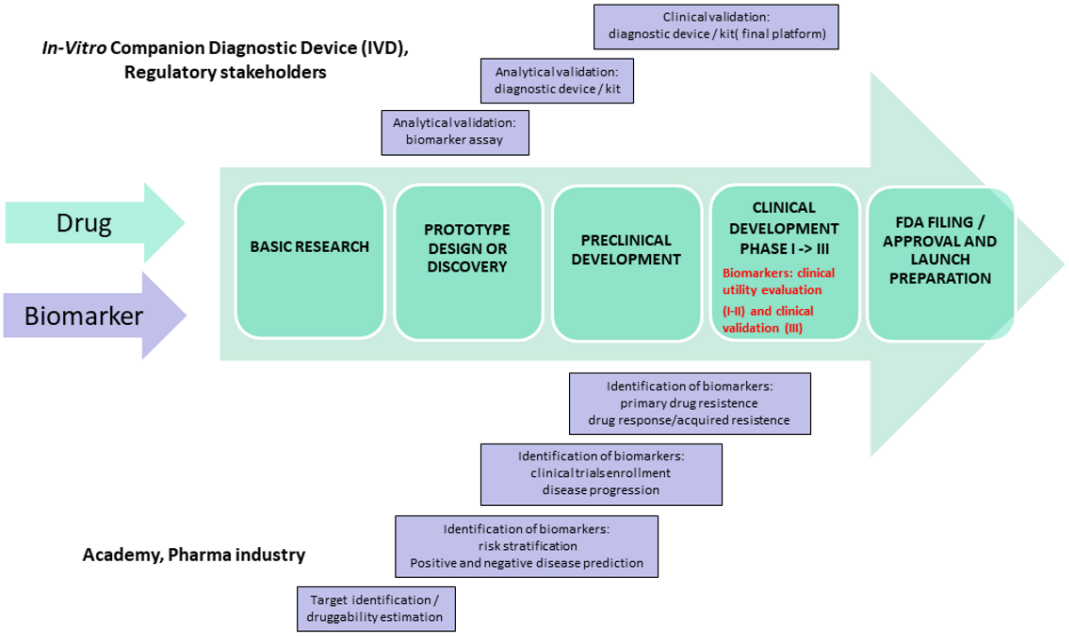
Supplemental Table S2. BACE1 null phenotypes in the Central Nervous System

Phenotype	Substrate
Astrogenesis increase, neurogenesis decrease	Jag1
Axon guidance defects	CHL1
Hyperactivity	NRG1
Hypomyelination	NRG1
Memory deficits	–
Neurochemical deficits	–
Neurodegeneration w/ age	$Na_V\beta 2$
Post-natal lethality, growth retardation	–
Retinal pathology	VEGFR1
Schizophrenia endophenotypes	NRG1
Seizures	$Na_V\beta 2$
Spine density reduction	NRG1

Abbreviations: Jag1: Jagged-1; NRG1: neuregulin-1, SEZ6: seizure-related protein 6, CHL1: neural cell adhesion molecule L1, VEGFR1: Vascular endothelial growth factor receptor 1, Naβ2: Voltage-gated sodium channels beta 2.

Supplemental Figures

Supplemental Figure S1. Schematic representation of a biomarker-drug co-development program



Ideally, biomarkers should be carried through all phases of drug development and validated and qualified in agreement with regulators.

The picture shows one possible model for biomarker-drug co-development program: a regulatory scenario for a single test that would be used in conjunction with a single drug in the clinical management of a patient. The figure highlights key events for both the diagnostic test and drug regulation with overall coordination of the regulatory processes governing them so that the products launch together [Adapted from Hampel H et al. Biomarker-Drug and Liquid Biopsy Co-development for Disease Staging and Targeted Therapy: Cornerstones for Alzheimer's Precision Medicine and Pharmacology. Front Pharmacol. 2019 Mar 29;10:310].

Supplemental Description Of Previous Clinical Trials With Bace1 Inhibitors

HUMAN CLINICAL TRIALS WITH BACE1 INHIBITORS: a brief overview

All BACE inhibitors, investigated in RCT, were discontinued for either futility or safety reasons.

A Phase 3, trial of verubecestat (12 or 40 mg/day) conducted in mild-to-moderate AD patients (EPOCH) was terminated due to futility(22). The Phase 3 study of the same compound and dose regimens, investigated in prodromal AD, reported cognitive and functional worsening as well as higher rats of anxiety and depressive symptoms(22) in 40-mg verubecestat group compared with the placebo group. The former group also showed faster reduction of brain volumes compared with the placebo(22).

A Phase 2/3, trial of atabecestat (5 or 25 mg/day) investigated in asymptomatic Aβ-positive individuals at risk of AD (EARLY),was discontinued at the enrolment phase out of liver toxicity(23). Analysis of data gathered showed that the high-dose group was associated with cognitive worsening(23).

The Phase 3 trials of lanabecestat investigated in prodromal AD and mild AD (AMARANTH and DAYBREAK-ALZ respectively) were stopped due to futility(24). Prodromal individuals treated with the highest dose of lanabecestat significantly dropped out due to mood disorders and weight loss(24).

A Phase 2 trial of LY3202626 (3 or 12 mg/day) involving mild AD patients (NAVIGATE-AD) was discontinued according to the interim futility analysis(25).

The phase 2/3 umibecestat (CNP520) was investigated in asymptomatic at risk for AD, i.e. APOE ε4 allele carriers (GENERATION trial) (177). The study was conducted in either Aβ positive or Aβ negative individuals. However, it was discontinued due to higher rates of cognitive decline in the treatment group compared with the placebo(26).

The Phase 2 of elenbecestat (E2609), conducted in MCI-to-moderate AD participants showed significantly reduced Aβ burden in the highest dose group compared with placebo.

On September 13, Eisai and Biogen announced the discontinuation of the Phase III clinical trials, MISSION AD 1 and 2, evaluating the efficacy and safety of 50 mg of elenbecestat in patients with early AD. The decision to end the trials was based on the results of a safety review conducted by the Data Safety Monitoring Board (DSMB), which recommended discontinuation of these trials due to an unfavourable risk-benefit ratio although the study did not achieve prespecified statistical criteria for significant cognitive worsening on elenbecestat (https://www.alzforum.org/therapeutics/elenbecestat).

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