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Supplementary appendix

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Appendix

Table 1. A/T/N biomarkers for AD.

	Amyloid (A)	Tau (T)	Neurodegeneration (N)
Pathology	A β species: monomers; oligomers; protofibrils; plaques	Tau species: monomers; oligomers; neurofibrillary tangles	Neuronal death; synaptic loss
CSF	A β 1-42; A β 1-40	P-tau (181, 217)	Total tau; Mfb;; neurogranin
Blood	A β 42/40	P-tau (181, 217)	Nfl
Imaging	Amyloid PET (fibrillar, insoluble, plaque A'B)	Tau PET (neurofibrillary tangles)	MRI (atrophy); FDG PET (metabolism)

A β - amyloid-beta protein; CSF - cerebrospinal fluid; FDG - fluorodeoxyglucose; MRI - magnetic resonance imaging; Nfl - neurofilament light chain; PET - positron emission tomography; p-tau - hyperphosphorylated tau protein

Table 2. Completed large, long-term multidomain intervention RCT

Study, country	Intervention	Duration	N	Recruitment strategy	Inclusion criteria	Primary Outcome	Primary outcome results	Secondary cognitive outcome results	Other results on cognitive outcomes
FINGER Finland	Multidomain intervention including dietary counselling, exercise and cognitive training, and vascular risk factor monitoring vs. regular health advice (control)	2-year intervention; 7-year follow-up	1260	Participants from previous population-based national surveys; individual randomization	Age: 60-77; Elevated risk for dementia based on CAIDE score ≥ 6 points; and cognitive function at or slightly below average level	Cognition measured with NTB (a composite measure of 14 standard cognitive tasks)	Intervention had beneficial effect on NTB: between-group (intervention vs. control) difference for NTB change was 0.022 (p=0.030) per year	Beneficial effect of intervention on executive functioning (p=0.039), and processing speed (p=0.029), but not on memory (p=0.36)	Beneficial effect of intervention on memory, when including more complex memory tasks (p=0.036). Higher risk of decline in cognition in control group compared to the intervention group
PreDIVA) The Netherlands	Multidomain cardiovascular intervention (advice) vs.	6-year intervention	3526	General practices; cluster-randomization of 116 general practices	Age: 70-78 years	Incidence of dementia	No effect of intervention on dementia: HR 0.92 (p=0.54)	No effect of intervention on MMSE and VAT.	Lower risk of dementia in participants with untreated hypertension at baseline who were adherent to the intervention (p=0.02).

	usual care (control)							No effect of intervention on AD. Lower risk of non-AD dementia in the intervention group (p=0.007)	
MAPT France	Multidomain intervention including integrated cognitive training, physical activity and dietary advice, and preventive consultations plus omega 3 PUFAs vs. multidomain vs. omega 3 PUFAs vs. placebo capsule	3-year intervention	1680	Diverse strategies including patient databases and advertisements; individual randomization	Age: 70+ Presence of memory complaint or IADL limitation or slow gait speed	Cognition measured with a composite z score combining 4 cognitive tests	No significant difference between any of the 3 intervention groups compared to placebo: between group difference was 0.093 (p=0.142) for multidomain + PUFA; 0.079 (p=0.179) for multidomain; and 0.011 (p=0.812) for PUFA compared to placebo.	Multidomain plus PUFA (p=0.036) had less decline in 10 MMSE orientation items compared to placebo group. Other group comparisons and other cognitive outcomes (FCSRT, DSST, Category naming test, COWAT, MMSE, TMT A, TMT B, CDR-	Less cognitive decline in those that received multidomain intervention (2 groups pooled) compared to those that did not (other 2 groups pooled) (p=0.015). Beneficial effect of multidomain plus PUFA vs. placebo among those with CAIDE score >=6. Beneficial effect of multidomain plus PUFA (p<0.001) and multidomain (p=0.003) groups vs. placebo among those with amyloid positivity.

								SB) showed no effect.	
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Table 3. Principal disease-modifying therapies in the AD drug development pipeline (adapted from Cummings et al, 2020)

Target Class	Drug	Type of Agent	Phase	Population	Diagnostic Biomarker
Amyloid	ABvac40	Active vaccine	II	Prodromal/mild dementia	None
	Aducanumab	Monoclonal antibody	III	Prodromal/mild dementia	Amyloid PET
	APH-1105	Alpha-secretase modulator	II	Mild-moderate dementia	None
	Azeliragon	RAGE inhibitor; anti-inflammatory; glucose modulation	II/III	Mild dementia	None
	BAN-2401	Monoclonal antibody	III	Prodromal/mild dementia	CSF or PET amyloid markers
	Gantenerumab	Monoclonal antibody	III	Prodromal/mild dementia and preclinical ADAD	CSF or PET amyloid markers
	CAD106	Active vaccine	III	Preclinical ADAD	ApoE-4 homozygotes
	Crenezumab	Monoclonal antibody	II	ADAD	PS1 mutation carriers
	Grapeseed extract	Reduces A β oligomerization	II	Mild-moderate dementia	None
	Donanemab	Monoclonal antibody against pyroglutamate A β	II	Prodromal/mild dementia	Amyloid PET/TAU Pet

	PQ912	Small molecule; Glutaminyl cyclase inhibitor to reduce pyroglutamate A β	II	Mild cognitive impairment/ mild dementia	CSF amyloid markers
	Solanezumab	Monoclonal antibody	III	Preclinical AD	Amyloid PET
	Thiethylperazine (TEP)	Activates ABCC1 transporter to remove A β from the brain	II	Mild cognitive impairment/ mild dementia	None
Tau	ABBV-8E12	Monoclonal antibody	II	Prodromal/mild dementia	Amyloid PET
	BIIB080 (IONIS MAPTRx)	Antisense RNA	II	Prodromal/mild dementia	CSF amyloid markers
	BIIB092	Monoclonal antibody	II	Prodromal/mild dementia	CSF or PET amyloid markers
	LY3303560 (zagotenemab)	Monoclonal antibody	II	Prodromal/mild dementia	None
	RO7105705 (semorinemab)	Monoclonal antibody	II	Prodromal/mild dementia and mild- moderate dementia	CSF or PET amyloid markers
	TRx0237	Tau aggregation inhibitor	III	Mild-moderate dementia	Amyloid PET
Proteostasis/ protein opathies	Nilotinib	Tyrosine kinase inhibitor	II	Mild-moderate dementia	CSF amyloid markers

	Posiphen	APP production inhibitor; reduces A β , tau, alpha-synuclein	II	Prodromal/mild dementia	CSF amyloid markers
Epigenetic regulators	GV1001	Mimics extratelomeric function of hTERT	II	Mild to moderate dementia	None
	Nicotinamide	Histone deacetylase inhibitor	II	Prodromal/mild dementia	CSF amyloid markers
	ORY-2001	Regulates HDAC demethylase and MAOB	II	Mild-moderate dementia	CSF amyloid markers
Synaptic plasticity and neuroprotection	ANAVEX-2-73	Sigma-1 receptor agonist; M2 autoreceptor antagonist; ameliorates oxidative stress and protein misfolding	III	Mild cognitive impairment/mild dementia	CSF or PET amyloid markers
	AGB101	SVA2 modulator	III	Prodromal/mild dementia	Amyloid PET
	AMX0035	Mitochondrial and ER stress modulator	II	Prodromal/mild dementia	Amyloid PET, CSF, FDG PET, or vMRI
	AR1001	PDE5 inhibitor	II	Mild-moderate dementia	None
	BPN14770	PDE4 inhibitor	II	Mild cognitive impairment/mild AD dementia	None
	Cilostazol	PDE3 inhibitor	II	Prodromal/mild dementia	None

	CT1812	Sigma-2 receptor antagonist	II	Mild-moderate dementia	CSF or PET amyloid markers
	Deferiprone	Iron chelating agent	II	Prodromal/mild dementia	Amyloid PET
	GV1001	Telomerase reverse transcriptase vaccine reduces A β related neurotoxicity	II	Moderate-severe dementia	None
	GRF6019	Human plasma protein fractions	II	Moderate-severe dementia	None
	Icosapent ethyl (IPE)	Improves synaptic function; neuroprotective; reduces inflammation	III	Cognitively normal	None
	Levetiracetam	SV2A modulator	II	Mild-moderate dementia	None
	LM11A-31-BHS	P75 neurotrophin receptor ligand	II	Mild-moderate dementia	CSF amyloid markers
	Neflamapimod (VX-745)	Enhances endolysosomal function to reduce synaptic dysfunction	II	Prodromal AD	CSF or PET amyloid markers
	PTI-125	FLNA inhibitor	II	Mild-moderate dementia	None
	NA-831 (traneurocin)	Endogenous small molecule that exhibits neuroprotection, neurogenesis, and	II	Mild cognitive impairment	None

		cognitive protective properties			
	Riluzole	Glutamate receptor antagonist	II	Prodromal/mild dementia	None
	RPh201	Neuroprotective	II	Mild-moderate dementia	None
	Troriluzole (BHV4157)	Reduces synaptic levels of glutamate; improves synaptic functioning	III	Probable AD dementia	None
Inflammation and infection	ALZT-OP1 (cromolyn + ibuprophen)	Mast cell stabilizer (cromolyn), anti-inflammatory (ibuprofen)	III	Prodromal AD	CSF amyloid markers
	COR388	Bacterial protease inhibitor	III	Mild-moderate dementia	None
	Curcumin + aerobic yoga	Decrease inflammation and reduce oxidation-related neuronal injury	II	Mild cognitive impairment	None
	Daratumumab	Monoclonal antibody targeting CD38	II	Mild-moderate dementia	Amyloid PET
	Dasatinib + quercetin	Tyrosine kinase inhibitor + flavinoid	II	Mild-moderate dementia	None
	Elderberry juice	Antioxidant, anti-inflammatory, mitochondrial effects	II	Mild cognitive impairment	None
	GB301	Regulates T cells and reduced inflammation	II	Mild-moderate AD dementia	Amyloid PET

	Lenalidomide	Immunomodulator	II	Mild cognitive impairment	None
	L-serine	Amino acid	II	Prodromal/mild dementia	None
	Masitinib	Modulation of mast cell-related inflammatory processes	III	Mild-moderate dementia	None
	Montelukast	Leukotriene receptor antagonist	II	Mild cognitive impairment/ mild dementia	None
	Rifaximin	Anti-inflammatory; reduces cytokines derived from gut bacteria	II	Mild-moderate dementia	None
	Sargamostim	Immune system stimulation	II	Mild cognitive impairment/ mild dementia	Amyloid PET
	Valacyclovir	Antiviral agent to reduce impact of herpes viral influence in AD	II	Prodromal/mild dementia	None
Metabolism and bioenergetics	Banfotiamine	Improve glucose utilization and neuronal metabolism	II	Mild cognitive impairment/mild AD dementia	Amyloid PET
	Dapagliflozin	SGLT2 inhibitor	II	Mild-moderate dementia	None
	Elderberry juice	Antioxidant; anti-inflammatory	II	Mild cognitive impairment	None

	Ginkgo biloba	Mitochondrial modulator; cerebral blood flow enhancer	II/III	Dementia	None
	Insulin glulisine	Insulin sensitivity enhancer	II	Prodromal/mild dementia	None
	Liraglutide	Glucagon-like peptide I receptor agonist	II	Prodromal/mild dementia	None
	Metabolic cofactors	Enhances mitochondrial activity	II	Mild-moderate dementia	None
	Metformin	Insulin sensitizer to improve neuronal glucose utilization	III	Mild cognitive impairment + obesity	None
	S-equol (AUS-131)	Nonhormonal estrogen receptor B agonist; mitochondrial protectant	II	Mild-moderate dementia	None
	Tricaprin	Induces ketosis as alternative neuronal energy source	III	Mild-moderate dementia	FDG PET
	T3D-959	PPAR agonist			
Vascular	Losartan + amlodipine + atorvastatin + exercise	Vascular risk reduction	III	Cognitively normal at elevated risk for AD	None
	Candesartan	Angiotensin receptor blocker	II	Prodromal/mild dementia	CSF or PET amyloid markers

	Omega-3 PUFA	Long chain fatty acid with anti-inflammatory properties	II	Cognitively normal or mild cognitive impairment with white matter hyperintensities	None
	Telmisartan plus perindopril	Angiotensin converting enzyme inhibitor	II	Mild-moderate dementia	None
Growth factors	Lupron	Growth factor; neuroprotection	II	Mild-moderate AD dementia	Amyloid PET

A β - amyloid beta-protein; ADAD – autosomal dominant Alzheimer’s disease; ApoE-4 – apolipoprotein E 4; APP – amyloid precursor protein; CSF – cerebrospinal fluid findings indicative of AD; ER – endoplasmic reticulum; FDG PET – fluorodeoxyglucose positron emission tomography; FLNA – filamin A; HDAC – histone deacetylase; hTERT – human telomerase reverse transcriptase; MAOB – monoamine oxidase B; MAPK – microtubule associate protein kinase; PET – positron emission tomography; PDE - phosphodiesterase; PPAR – peroxisome proliferator-activated receptor; PS1 – presenilin 1; RNA – ribonucleic acid; SGLT – sodium glucose transporter; SVA2 – synaptic vesicle glycoprotein 2A

Our Reference	First filing date	Filing date priority Year	Patent Management	Description	Inventor(s)	Status	Number
BaDS/GSSC/577	12/01/2017	2017	K.U.Leuven (Applicant) VIB (Applicant) VIB (Prosecution)	Gamma-secretase stabilizing compound screening assay	Bart De Strooper Lucía Chávez Gutiérrez Maria Szaruga	Pending non-licensed	WO 2018/130555 US Patent App. 16/477,391, 2019
JoDW/APPbinding/557	20/07/2016	2016	K.U.Leuven (Applicant) VIB (Applicant) VIB (Prosecution)	Therapeutic agents for neurological and psychiatric disorders	Bart De Strooper Heather Rice Joris de Wit	Pending non-licensed	WO 2018/015296
BaDS/MIR27/442	25/01/2013	2013	K.U.Leuven (Applicant) VIB (Applicant) VIB (Prosecution)	MicroRNA markers for the prognosis and diagnosis of Alzheimer's disease	Bart De Strooper Carlo Sala Frigerio	Abandoned	US 61/756,611
BaDS/PINKSUB/435	07/11/2012	2012	K.U.Leuven (Applicant) VIB (Applicant) VIB (Prosecution)	Restoring phosphorylation of a novel PINK1 substrate to treat Parkinson's disease	Bart De Strooper Patrik Verstreken Vanessa Morais Epifânio	Pending non-licensed	WO 2014/072412
BaDS/TSPAN6/405	30/01/2012	2012	K.U.Leuven (Applicant) VIB (Applicant) VIB (Prosecution)	Means and method for diagnosis and treatment of Alzheimer's disease	Bart De Strooper Francesc Guix	Abandoned	WO 2013/113696
WiAn/ARF6/330	04/12/2009	2009	K.U.Leuven (Applicant) VIB (Applicant) VIB (Prosecution)	ARF6 as a new target for treating Alzheimer's disease	Bart De Strooper Katrijn Coen Ragna Sannerud Willem Annaert	Abandoned	WO 2011/067420
BaDS/ABBACE/312	15/06/2009	2009	ADx NeuroSciences (Licensee) Denali Therapeutics (Licensee) Denali Therapeutics (Prosecution) K.U.Leuven (Applicant) VIB (Applicant) VIB (Prosecution)	BACE1 Inhibitory Antibodies	Bart De Strooper Lujia Zhou Willem Annaert	Non Exclusive Licensed	WO2010/146058
BaDS/ARR/311	08/06/2009	2009	K.U.Leuven (Applicant) VIB (Applicant) VIB (Prosecution)	Screening for compounds that modulate GPR3-mediated β -arrestin signaling and amyloid beta peptide generation	Amantha Thathiah Bart De Strooper	Abandoned	WO 2010/142603
BDS/NANOBACE/281	03/04/2008	2008	Denali Therapeutics (Licensee) Denali Therapeutics (Prosecution) K.U.Leuven (Applicant) VIB (Applicant) VIB (Prosecution) Vrije Universiteit Brussel (Applicant)	Single domain antibodies capable of modulating BACE activity	Bart De Strooper Els Marjaux Lujia Zhou Serge Muyldermans	Non Exclusive Licensed	WO 2009/121948
BDS/TETRA/269	04/10/2007	2007	K.U.Leuven (Applicant) VIB (Applicant) VIB (Prosecution)	Extracellular targets for Alzheimer's disease	Bart De Strooper Tomoko Wakabayashi	Abandoned	WO 2009/043922

SHE/MIR29/261	19/04/2007	2007	K.U.Leuven (Applicant) VIB (Applicant) VIB (Prosecution)	Oligonucleotide compositions for the treatment of Alzheimer's disease	Bart De Strooper Sébastien Hébert	Abandoned	WO 2008/129023
JSC/OLI/248	08/09/2006	2006	K.U.Leuven (Applicant) VIB (Applicant) VIB (Prosecution) Vrije Universiteit Brussel (Applicant)	Means and methods for the production of amyloid oligomers	Bart De Strooper Frederic Rousseau Ivo da Rocha Martins Joost Schymkowitz	Abandoned	WO 2008/028939
BDS/PARL/213	12/08/2005	2005	K.U.Leuven (Applicant) VIB (Applicant) VIB (Prosecution)	A mitochondrial rhomboid protease as a target for lymphoma	Bart De Strooper L. Scorrano Sara Cipolat Tomasz Rudka	Abandoned	WO 2007/020244
BDS/APH/198	13/12/2004	2004	K.U.Leuven (Applicant) VIB (Applicant) VIB (Prosecution)	Transgenic animal models for neurodevelopmental disorders	Bart De Strooper Dieter Hartmann Lutgarde Serneels Tim Dejaegere	Abandoned	WO 2006/064007
WAN/APPpep/128	17/09/2002	2002	K.U.Leuven (Applicant) Pepscan Therapeutics (Applicant) VIB (Applicant) VIB (Prosecution)	Peptides inhibiting specific cleaving activities of presenilins	Bart De Strooper H Langedijk Willem Annaert	Abandoned	WO 2004/026331
BDS/BACE/089	12/06/2001	2001	VIB (Applicant) VIB (Prosecution)	BACE interacting proteins	Bart De Strooper Diana Dominguez Els Marjaux Willem Annaert	Abandoned	WO 02/101232
BDS/PST/080	16/03/2001	2001	VIB (Applicant) VIB (Prosecution)	Binding domains between presenilins and their substrates as targets for drug screening	Bart De Strooper Willem Annaert	Abandoned	WO 02/074804
BDS/PSKO/052	25/02/2000	2000	VIB (Applicant) VIB (Prosecution)	Presenilin deficient multipotent cell lines and screening methods for g-secretase activities and modulators of g-secretase activities using these lines	An Herreman Bart De Strooper Luc Schoonjans Lutgarde Serneels Willem Annaert	Abandoned	WO 01/62897

