Additional Table 1 Summary of the effect of epidermal growth factor receptor (EGFR) modulation in different in vivo and in vitro models of Alzheimer's disease

EGFR modulation	Subjects	Main outcomes	References
Overexpression of EGFR	5-month-old female fruit flies	Mild impact on memory performance.	Chiang et al., 2010
Co-overexpression of EGFR and Aβ42	5-month-old female fruit flies	Synergetic effect on Memory loss as proved by behavioral tests accompanied by hyperactivation of PI3K/Akt pahway.	Chiang et al., 2010
Oral administration of 0.01mg/kg/day Gefitinib (EGFR inhibitor) for 7 days	8-month old Tg(APPswe.PSEN1dE9) double transgenic mice	Memory loss was rescued as indicated by better performance in the Morris water maze test.	Wang et al., 2012
Oral administration of 10 mg/kg/day Gefitinib (EGFR inhibitor) for 18 days	8-month old Tg(APPswe.PSEN1dE9) double transgenic mice	Decreased hippocampal expression of p-EGFR^{Tyr1068}, the domain for binding with Grb2 that results in activation of MAPK.	Wang et al., 2012
10^{-5} mg of gefitinib or erlotinib	COS-7 cells transfected with human wild-type EGFR.	Decreased levels of Aβ42 oligomers-activated EGFR as indicated by the western blotting technique.	Wang et al., 2012
Treatment with anti-EGFR for 48 hours using co-immunoprecipitation.	COS-7 cultured cells were co-transfected with genes encoding a human EGFRwt and Aβ42.	Aβ42 were drawn down with EGFR, proving the binding of EGFR with amyloid proteins	Wang et al., 2012
0.01, 0.1, 1, and 10 μg/mL of erlotinib or gefitinib for one week	10-day-old male fruit flies	All dose regimens significantly improved memory. This neuroprotective effect was dose-dependent for gefitinib while it was not dose-dependent for erlotinib.	Wang et al., 2012
100 μg/mL of *JKF-006 *JKF-011 *JKF-027	Human EGFR expressing COS-7 cell	Reversed a 10 μg/mL Aβ42-mediated activation of human EGFR expressing COS-7 cell.	Wang et al., 2012
*58 mg/kg JKF-006 *14.4 mg/kg JKF-011 *55 mg/kg JKF-027 * 40 mg/kg JKF-01	6–8-month-old double transgenic rats	Amelioration of memory loss conformed by Morris water maze test.	Wang et al., 2012
----------	10-day-old Pan-neuronal expressing human Aβ42 fruit fly (exemplifying early stage of AD)	EGFR expression is elevated, and Aβ42 stimulates EGFR/PI3K, distorts the synaptic	Wang et al., 2013

		plasticity, and eventually results in memory impairment.	
----------	35-day-old Pan-neuronal expressing human Aβ42 fruit fly (exemplifying late stage of AD)	Aβ42 leads to a pronounced decrease in EGFR which ultimately causes neuronal degeneration.	Wang et al., 2013
----------	APP/PS1 8-month-old double transgenic mice	The ratio of (p-EGFR/EGFR) is increased relative to wild-type mice	Wang et al., 2013
*CL-387,785 (HER1/2 dual inhibitor) *AG825 (HER-2-selective inhibitor) *Gefitinib (EGFR-selective inhibitor) * Lapatinib (HER1/2 dual)	*HEK293-derived cell line (CG) *HEK293-derived cell line (NG)	Only CL-387,785 but not AG825, gefitinib, or lapatinib blocked the processing of APP in CG cells but not in NG cells.	Wang et al., 2017
CL-387,785 (HER1/2 dual inhibitor)	*HEK293 cells that overexpressed C99-YFP *double transgenic mice	Reduction in p62 accompanied by an increase in the LC3-II/LC3-I ratio suggestive of autophagy induction.	Wang et al., 2017
Afatinib (selective EGFR inhibitor)	*Primary cultured astrocytes *CTX-TNA2 cells subjected to oxygen and glucose deprivation (OGD).	Afatinib blocked Akt and ERK pathways. Furthermore, afatinib amended the OGD-induced increase in GFAP, NO, cyclooxygenase II, inducible nitric oxide synthase authenticating anti-inflammatory effects of EGFR inhibition.	Chen et al., 2019
C56 (selective EGFR inhibitor)	Neuronal cells treated with H_2O_2 or 6-hydroxydopamine	Selective EGFR inhibitor C56 inhibited 6 OHDA-mediated neuronal apoptosis and axonal degeneration.	Cao and Fang, 2015
Lapatinib ditosylate (dual EGFR/HER2 inhibitor)	D-galactose/ovarctomized rats	Lapatinib ameliorated behavioral performance as indicated by Morris water maze, novel object recognition test. It suppressed EGFR, HER-2, Aβ1-42, p-tau, GFAP, TNF-α, P38 MAPK, GluR-II, and mTOR. While activating the prosuvival pathway; PI3K/AKT/GSK-3β and neuroprotective nitrite content.	Mansour et al., 2021
Ibrutinib (an EGFR inhibitor)	*5xFAD mice * PS19 mice	Ibrutinib inhibited Aβ, p-tau, p-CDK-5, neuroinflammation, along with induction of dendritic spinogenesis via activation of PI3K.	Lee et al., 2021

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