

MEMOSAD

Memory loss in Alzheimer disease:
underlying mechanisms and therapeutic targets

A Collaborative Project receiving funds from the European Community's
Seventh Framework Programme (FP7/2007-2013) under Grant Agreement No. 200611



Publications resulting from the project

2008

Tolia A, Horr  K, De Strooper B (July 2008) Transmembrane domain 9 of presenilin determines the dynamic conformation of the catalytic site of gamma-secretase. *J Biol Chem* 283(28): 19793-803. doi: 10.1074/jbc.M802461200 (free article)

Dejaegere T, Serneels L, Sch fer MK, Van Biervliet J, Horr  K, Depboylu C, Alvarez-Fischer D, Herreman A, Willem M, Haass C, H glinger GU, D'Hooge R, **De Strooper B** (July 2008) Deficiency of Aph1B/C-gamma-secretase disturbs Nrg1 cleavage and sensorimotor gating that can be reversed with antipsychotic treatment. *PNAS* 105 (28): 9775-9780. doi: 10.1073.pnas.0800507105 (free article in PubMed Central)

Schraen-Maschke S, Sergeant N, Dhaenens CM, Bombois S, Deramecourt V, Caillet-Boudin ML, Pasquier F, Maurage CA, Sablonni re B, Vanmechelen E, **Bu e L** (August 2008) Tau as biomarker of neurodegenerative diseases. *Biomarkers Med* 2(4): 363-84. doi: 10.2217/17520363.2.4.363 (free article in PubMed)

Wakabayashi T & De Strooper B (August 2008) Presenilins: members of the gamma-secretase quartets, but part-time soloists too. *Physiology* 23(4): 194-204. doi: 10.1152/physiol.00009.2008 (free article)

2009

Bulic B, Pickhardt M, Schmidt B, **Mandelkow EM**, Waldmann H, Mandelkow E (February 2009) Development of tau aggregation inhibitors for Alzheimer's disease. *Angew Chem Int Ed Engl* 48(10): 1740-52. doi: 10.1002/anie.200802621

Bretteville A, Ando K, Ghestem A, Loyens A, B gard S, Beauvillain JC, Sergeant N, Hamdane M, **Bu e L** (March 2009) Two-dimensional electrophoresis of tau mutants reveals specific phosphorylation pattern likely linked to early tau conformational changes. *PLoS ONE* 4(3):e4843. doi:10.1371/journal.pone.0004843 (free article in PubMed Central)

Belarbi K, Schindowski K, Burnouf S, Caillerez R, Grosjean ME, Demeyer D, Hamdane M, Blum D, **Bu e L** (April 2009) Early tau pathology involving the septo-hippocampal pathway in a tau transgenic model: relevance to Alzheimer's disease. *Curr Alzheimer Res* 6(2): 152-7. doi: - (free article in PubMed)

Schraen-Maschke S, Dhaenens CM, Bombois S, Deramecourt V, Van Brussel E, Obriot H, Marzys C, Sergeant N, Maurage CA, Pasquier F, Sablonni re B, **Bu e L** (April 2009) Les marqueurs biologiques de la maladie Alzheimer: quel int r t pour un diagnostic moins tardif? *Revue Neurologique* 165(HS2): 97-103. doi: RN-04-09-165-HS2-0035-3787-101019-200901998

Serneels L, Van Biervliet J, Craessaerts K, Dejaegere T, Horr  K, Van Houtvin T, Esselmann H, Paul S, Sch fer MK, Berezovska O, Hyman BT, Sprangers B, Sciot R, Moons L, Jucker M, Yang Z, May PC, Karran E, Wiltfang J, D'Hooge R, **De Strooper B** (May 2009) gamma-secretase heterogeneity in the Aph1 subunit: relevance for Alzheimer's disease. *Science* 324(5927):639-42. doi: 10.1126/science.1171176 (free article in PubMed)

Paquet D, Bhat R, Sydow A, Mandelkow EM, Berg S, Hellberg S, F lting J, Distel M, K ster RW, Schmid B, **Haass C** (May 2009) A zebrafish model of tauopathy allows in vivo imaging of neuronal cell death and drug evaluation. *J Clin Invest* 119(5): 1382-95. doi: 10.1172/JCI37537 (free article in PubMed Central)

S mann J, Hegermann J, von Gromoff E, Eimer S, **Baumeister R**, Schmidt E (June 2009) Caenorhabditis elegans LRK-1 and PINK-1 act antagonistically in stress response and neurite overgrowth. *J Biol Chem* 284(24):16482-91. doi: 10.1074/jbc.M808255200 (free article)

Wang Y, Martinez-Vicente M, Kr ger U, Kaushik S, Wong E, **Mandelkow EM**, Cuervo AM, Mandelkow E (November 2009) Tau fragmentation, aggregation and clearance: the dual role of lysosomal processing. *Hum Mol Gen* 18(21): 4153-70. doi: 10.1093/hmg/ddp367 (free article)

Shankar GM & **Walsh DM** (November 2009) Alzheimer's disease: synaptic dysfunction and Abeta. *Mol Neurodeger* (4): 48. doi: 10.1186/1750-1326-4-48 (free article in PubMed Central)

2010

Wang Y, Martinez-Vicente M, Kr ger U, Kaushik S, Wong E, **Mandelkow EM**, Cuervo AM, Mandelkow E (January 2010) Synergy and antagonism of macroautophagy and chaperone-mediated autophagy in a cell model of pathological tau aggregation. *Autophagy* 6(1):182-3. doi: 10.4161/auto.6.1.10815 (free article)

Freir DB, Fedriani R, Scully D, Smith IM, Selkoe DJ, **Walsh DM**, Regan CM (Epub) Abeta oligomers inhibit synapse remodelling necessary for memory consolidation. *Neurobiol Aging* doi: 10.1016/j.neurobiolaging.2010.01.001

Bergmans BA & **De Strooper B** (February 2010) Gamma-secretases: from cell biology to therapeutic strategies. *Lancet Neurol* 9 (2): 215-226. doi:10.1016/S1474-4422(09)70332-1

De Strooper B, Vassar R, Golde T (February 2010) The secretases: enzymes with therapeutic potential in Alzheimer disease. *Nat Rev Neuro* 6(2): 99-107. doi: 10.1038/nrneuro.2009.218 (free article in PubMed Central)

España J, Giménez-Llort L, Valero J, Miñano A, Rábano A, Rodríguez-Alvarez J, Laferla FM, **Saura CA** (March 2010) Intraneuronal beta-amyloid accumulation in the amygdala enhances fear and anxiety in Alzheimer's disease transgenic mice. *Biol Psychiatry* 67(6): 513-21. doi: 10.1016/j.biopsych.2009.06.015

Sydow S, **Mandelkow EM** (April 2010) 'Prion-like' propagation of mouse and human tau aggregates in an inducible mouse model of tauopathy. *Neurodegener Dis* 7(1-3):28-31. doi: 10.1159/000283479

Paquet D, Schmid B, **Haass C** (April 2010) Transgenic zebrafish as a novel model to study tauopathies and other neurodegenerative disorders in vivo. *Neurodegener Dis* 7(1-3):99-102. doi: 10.1159/000285515

Wang Y, Krüger U, Mandelkow E, **Mandelkow EM** (April 2010) Generation of tau aggregates and clearance by autophagy in an inducible cell model of tauopathy. *Neurodegener Dis* 7(1-3):103-7. doi: 10.1159/000285516

Mc Donald JM, Savva GM, Brayne C, Welzel AT, Forster G, Shankar GM, Selkoe DJ, Ince PG, **Walsh DM** (May 2010) The presence of sodium dodecyl sulphate-stable Abeta dimers is strongly associated with Alzheimer-type dementia. *Brain* 133(Pt 5):1328-41. doi: 10.1093/brain/awq065 (free article)

Saura CA (May 2010) Presenilin/gamma-secretase and inflammation. *Front Aging Neurosci* 2:16. doi:10.3389/fnagi.2010.00016 (free article in PubMed Central)

Zhang H, Sun S, Herreman A, De Strooper B, Bezprozvanny I (June 2010) Role of presenilins in neuronal calcium homeostasis. *J Neurosci* 30(25): 8566-80. doi: 10.1523/JNEUROSCI.1554-10.2010 (free article in PubMed)

España J, Valero J, Miñano-Molina AJ, Masgrau R, Martín E, Guardia-Laguarta C, Lleó A, Giménez-Llort L, Rodríguez-Alvarez J, **Saura CA** (July 2010) Beta-amyloid disrupts activity-dependent gene transcription required for memory through the CREB coactivator CRTC1. *J Neurosci* 30(28):9402-10. doi:10.1523/JNEUROSCI.2154-10.2010 (free article)

Buée L, Troquier L, Burnouf S, Belarbi K, Van der Jeugd A, Ahmed T, Fernandez-Gomez F, Caillerez R, Grosjean ME, Begard S, Barbot B, Demeyer D, Obriot H, Brion I, Buée-Scherrer V, Maurage CA, Balschun D, **D'Hooge R**, Hamdane M, Blum D, Sergeant N (August 2010) From tau phosphorylation to tau aggregation: what about neuronal death? *Biochem Soc Trans* 38(4):967-72.

Wang Y, Garg S, **Mandelkow EM**, Mandelkow E (August 2010) Proteolytic processing of tau. *Biochem Soc Trans* 38(4):955-61. doi: 10.1042/BST0380955

van Bebber F, Paquet D, Hruscha A, Schmid B, **Haass C** (September 2010) Methylene blue fails to inhibit Tau and polyglutamine protein-dependent toxicity in zebrafish. *Neurobiol Dis* 39(3): 265-71. doi: 10.1016/nbd.2010.03.023

Jorissen E, **De Strooper B** (September 2010) Gamma-secretase and the intramembrane proteolysis of Notch. *Curr Top Dev Biol* 92:201-30. doi: 10.1016/S0070-2153(10)92006-1

Zempel H, Thies E, Mandelkow E, **Mandelkow EM** (September 2010) Abeta oligomers cause localized Ca²⁺ elevation, missorting of endogenous Tau into dendrites, Tau phosphorylation, and destruction of microtubules and spines. *J Neurosci* 30(36):11938-50. doi: 10.1523/NEUROSCI.2357-10.2010 (free article)

Bulic B, Pickhardt M, Mandelkow EM, Mandelkow E (September/October 2010) Tau protein and tau aggregation inhibitors. *Neuropharmacology* 59(4-5):276-89. doi: 10.1016/j.neuropharm.2010.01.016

Kuperstein I, Broersen K, Benilova I, Rozenski J, Jonckheere W, Debulpaep M, Vandersteen A, Segers-Nolten I, Van Der Werf K, Subramaniam V, Braeken D, Callewaert G, Bartic C, **D'Hooge R**, Martins IC, Rousseau F, Schymkowitz J, **De Strooper B** (October 2010) Neurotoxicity of Alzheimer's disease Abeta peptides is induced by small changes in the Abeta42 to Abeta 40 ratio. *EMBO J* 29(19):3408-20. doi: 10.1038/emboj.2010.211

Hébert SS, Papadopoulou AS, Smith P, Galas MC, Planel E, Silaharoglu AN, Sergeant N, **Buée L**, **De Strooper B** (October 2010) Genetic ablation of Dicer in adult forebrain neurons results in abnormal tau hyper-phosphorylation and neurodegeneration. *Hum Mol Genet* 19(20):3959-69. doi: 10.1093/hmg/ddq311 (free article)

De Strooper B, Annaert W (November 2010) Novel research horizons for presenilins and gamma-secretase in cell biology and disease. *Annu Rev Cell Dev Biol* 26:235-60. doi:10.1146/annurev-cellbio-100109-104117

2011

Shankar GM, Welzel AT, McDonald JM, Selkoe DJ, **Walsh DM** (January 2011) Isolation of low-n amyloid beta-protein oligomers from cultured cells, CSF, and brain. *Methods Mol Biol* 670:33-44. doi: 10.1007/978-1-60761-744-0_3

Sergeant N, **Buée L** (January 2011) Tau models. *Animal Models of Dementia*:449-68. doi: 10.1007/978-1-60761-898-0_23 (book chapter)

Sergeant N, **Buée L** (January 2011) Tau pathology. *Cytoskeleton of the Nervous System; Advances in Neurobiology* 3:83-132. doi: 10.1007/978-1-4419-6787-9_4 (book chapter)

Garg S, Timm T, **Mandelkow EM**, Mandelkow E, Wang Y (January 2011) Cleavage of Tau by calpain in Alzheimer's disease: the quest for the toxic 17 kD fragment. *Neurobiol Aging* 32(1):1-14. doi: 10.1016/j.neurobiolaging.2010.09.008

Thathiah A & **De Strooper B** (February 2011) The role of G protein-coupled receptors in the pathology of Alzheimer's disease. *Nat Rev Neurosci* 12(2):73-87. doi: 10.1038/nrn2977 (free article)

Valero J, España J, Parra-Damas A, Martín E, Rodríguez-Alvarez J, **Saura CA** (February 2011) Short-term environmental enrichment rescues adult neurogenesis and memory deficits in APP_{Sw,Ind} transgenic mice. *PLoS ONE* 6(2):e16832. doi: 10.1371/journal.pone.0016832 (free article)

Sultan A, Nesslany F, Violet M, Bégard S, Loyens A, Talahari S, Mansuroglu Z, Marzin D, Sergeant N, Humez S, Colin M, Bonnefoy E, **Buée L**, Galas MC (February 2011) Nuclear tau, a key player in neuronal DNA protection. *J Biol Chem* 286(6):4566-75. doi: 10.1074/jbc.M110.199976

Schirmer H, Adler H, Pickhardt M, **Mandelkow E** (Epub ahead of print) "Lest we forget you – methylene blue ..." . *Neurobiol Aging* xxx. doi: 10.1016/j.neurobiolaging.2010.12.012

Sydow A, Van der Jeugd A, Zhen F, Ahmed T, Balschun D, Petrova O, Drexler D, Zhou L, Rune G, Mandelkow E, **D'Hooge R**, Alzheimer C, **Mandelkow EM** (February 2011) Tau-induced defects in synaptic plasticity, learning and memory are reversible in transgenic mice after switching off the toxic Tau mutant. *J Neurosci* 31(7):2511-25. doi: 10.1523/JNEUROSCI.5245-10.2011

Welzel AT, **Walsh DM** (March 2011) Aberrant protein structure and diseases of the brain. *Ir J Med Sci* 180(1):15-22. doi: 10.1007/s11845-010-0606-2

Saura CA & Valero J (March 2011) The role of CREB signaling in Alzheimer's disease and other cognitive disorders. *Rev Neurosci* 22(2):153-69. doi: 10.1515/RNS.2011.018

Van der Jeugd A, Ahmed T, Burnouf S, Belarbi K, Hamdane M, Grosjean ME, Humez S, Balschun D, Blum D, **Buée L**, **D'Hooge R** (March 2011) Hippocampal tauopathy in tau transgenic mice coincides with impaired hippocampus-dependent learning and memory, and attenuated late-phase long-term depression of synaptic transmission. *Neurobiol Learn Mem* 95(3):296-304. doi: 10.1016/nlm.2010.12.005

Zhou L, Chavez-Gutierrez L, Bockstael K, Sannerud R, Annaert W, May PC, Karran E, **De Strooper B** (March 2011) Inhibition of {beta}-secretase in vivo via antibody binding to unique loops (D and F) of BACE1. *J Biol Chem* 286(10):8677-87. doi: 10.1074/jbc.M110.194860 (free article)

Bammens L, Chavez-Gutierrez L, Tolia A, Zwijsen A, **De Strooper B** (April 2011) Functional and topological analysis of Pen-2, the fourth subunit of the gamma-secretase complex. *J Biol Chem* 286(14):12271-82. doi: 10.1074/jbc.M110.216978 (free article)

Lléo A, **Saura CA** (Epub) gamma-secretase substrates and their implications for drug development in Alzheimer's disease. *Curr Top Med Chem*

Barry AE, Klyubin I, McDonald JM, Mably AJ, Farrell MA, Scott M, **Walsh DM**, Rowan MJ (May 2011) Alzheimer's disease brain-derived Abeta-mediated inhibition of LTP in vivo is prevented by immunotargeting cellular prion protein. *J Neurosci* 31(20):7259-63. doi: 10.1523/JNEUROSCI.6500-10.2011

Belarbi K, Burnouf S, Fernandez-Gomez F, Desmercieries J, Troquier L, Brouillette J, Tsambou L, Grosjean ME, Caillierez R, Demeyer D, Hamdane M, Schindowski K, Blum D, **Buée L** (Epub) Loss of medial septum cholinergic neurons in THY-Tau22 mouse model: what links with Tau pathology? *Curr Alzheimer Res*

Belarbi K, Burnouf S, Fernandez-Gomez FJ, Laurent C, Lestavel L, Figeac M, Sultan A, Troquier L, Leboucher A, Caillierez R, Grosjean ME, Demeyer D, Obriot H, Brion I, Barbot B, Galas MC, Staels B, Humez S, Segeant N, Schraen-Maschke S, Muhr-Tailleux A, Hamdane M, **Buée L**, Blum D (August 2011) Beneficial effects of exercise in a transgenic mouse model of Alzheimer's disease-like Tau pathology. *Neurobiol Dis* 43(2):486-94. doi: 10.1016/j.nbd.2011.04.022