Tau Blue Revolution

Tau neurofibrillary pathology represents the main hallmark of AD and human neurodegenerative tauopathies. In the last decade, therapeutic strategies targeting misfolded tau protein have been gain- ing momentum. An increasing body of evidence shows that modulation of tau cascade has a benefi- cial effect in the animal models in preclinical studies. Tau therapy is becoming the leading therapeutic approach in AD.

10 reasons why Axon Neuroscience believes that tau is the proper target for AD-modifying therapy

1. Tau neurofibrillary pathology is the major correlate of clinical symptoms in Alzheimer's disease[1,2,3]
2. Distribution of neurofibrillary pathology defines subtypes of Alzheimer's disease with distinct clinical characteristics[4]
3. Decline in memory that occurs around 12 years before clinically diagnosed Alzheimer's disease may correlate with the presence of neurofibrillary pathology in the temporal areas[5]
4. Neurofibrillary tangles precede amyloid beta pathology[6,7,8]
5. Cortical atrophy measured by MRI is associated with neurofibrillary pathology[9]
6. Neurofibrillary lesions and neuroinflammation display the same regional distribution in Alzheimer's disease and other human tauopathies[10-19]
7. There is strong regional, inversely proportional relationship between the number of neurons and the number of neurofibrillary tangles[20-22]
8. Tau pathology in the absence of amyloid pathology strongly correlates with clinical features in human tauopathies such as progressive supranuclear palsy, corticobasal degeneration, tangle-only dementia and argyrophilic grain disease[23-29]
9. Tau gene mutations are pathogenic for frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17)[30-32]
10. Tau animal models reproduce neuronal and glial tau pathology leading to the progressive cognitive and/or motor impairment[33-35]

Selected Scientific Papers

1. Duyckaerts C. Disentangling Alzheimer's disease. Lancet Neurol 2011; 10(9):774-5.

2. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991; 82(4):239-59.

3. Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ, Castellani RJ, Crain BJ, Davies P, Del Tredici K, Duyckaerts C, Frosch MP, Haroutunian V, Hof PR, Hulette CM, Hyman BT, Iwatsubo T, Jellinger KA, Jicha GA, Kövari E, Kukull WA, Leverenz JB, Love S, Mackenzie IR, Mann DM, Masliah E, McKee AC, Montine TJ, Morris JC, Schneider JA, Sonnen JA, Thal DR, Trojanowski JQ, Troncoso JC, Wisniewski T, Woltjer RL, Beach TG. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. J Neuropathol Exp Neurol 2012, 71(5):362-81.

4. Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. Lancet Neurol 2011;10(9):785-96.

5. Amieva H, Le Goff M, Millet X, Orgogozo JM, Pérès K, Barberger- Gateau P, Jacqmin-Gadda H, Dartigues JF. Prodromal Alzheimer's disease: successive emergence of the clinical symptoms.Ann Neurol 2008; 64(5):492-8.

6. Duyckaerts C. Tau pathology in children and young adults: can you still be unconditionally baptist? Acta Neuropathol 2011;121(2):145-7.

7. Braak H, Del Tredici K. The pathological process underlying Alzheimer's disease in individuals under thirty. Acta Neuropathol 2011; 121(2):171-81.

8. Schönheit B, Zarski R, Ohm TG. Spatial and temporal relationships between plaques and tangles in Alzheimer-pathology. Neurobiol Aging 2004; 25(6):697-711.

9. Whitwell JL, Josephs KA, Murray ME, Kantarci K, Przybelski SA, Weigand SD, Vemuri P, Senjem ML, Parisi JE, Knopman DS, Boeve BF, Petersen RC, Dickson DW, Jack CR Jr. MRI correlates of neurofibrillary tangle pathology at autopsy: a voxel-based morphometry study. Neurology 2008; 71(10):743-9.

10. Grundke-Iqbal I, Fleming J, Tung YC, Lassmann H, Iqbal K, Joshi JG. Ferritin is a component of the neuritic (senile) plaque in Alzheimer dementia. Acta Neuropathol 1990, 81:105–110.

11. Sheffield LG, Marquis JG, Berman NE. Regional distribution of cortical microgliaparallels that of neurofibrillary tangles in Alzheimer's disease. Neurosci Lett 2000; 285:165–168.

12. Serrano-Pozo A, Mielke ML, Gómez-Isla T, Betensky RA, Growdon JH, Frosch MP, Hyman BT. Reactive glia not only associates with plaques but also parallels tangles in Alzheimer's disease. Am J Pathol 2011; 179(3):1373-84.

13. Overmyer M, Helisalmi S, Soininen H, Laakso M, Riekkinen P, Alafuzoff I. Reactive microglia in aging and dementia: an immunohistochemical study of postmortem humanbrain tissue. Acta Neuropathol 1999; 97:383–392.

14. Schwab C, Steele JC, McGeer PL. Neurofibrillary tangles of Guam Parkinson dementiaare associated with reactive microglia and complement proteins. Brain Res 1996; 707:196–205.

15. Ishizawa K, Dickson DW. Microglial activation parallels system degeneration in progressive supranuclear palsy and corticobasal degeneration. J Neuropathol Exp Neurol 2001; 60:647–657.

16. Gerhard A, Trender-Gerhard I, Turkheimer F, Quinn NP, Bhatia KP, Brooks DJ. In vivoimaging of microglial activation with [11C](R)-PK11195 PET in progressive supranuclear palsy. Mov Disord 2006; 21:89–93.

17. Gerhard A, Watts J, Trender-Gerhard I, Turkheimer F, Banati RB, Bhatia K, Brooks DJ. In vivo imaging of microglial activation with [11C] (R)-PK11195 PET in corticobasal degeneration. Mov Disord 2004; 19:1221–1226.

18. Henkel K, Karitzky J, Schmid M, Mader I, Glatting G, Unger JW, Neumaier B, Ludolph AC, Reske SN, Landwehrmeyer GB. Imaging of activated microglia with PET and[11C]PK11195 in corticobasal degeneration. Mov Disord 2004; 19:817–821.

19. Paulus W, Bancher C, Jellinger K. Microglial reaction in Pick's disease. Neurosci Lett 1993; 161:89–92.

20. Gomez-Isla T, Price JL, McKeel DW Jr, Morris JC, Growdon JH, Hyman BT. Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. J Neurosci 1996; 16(14): 4491-500.

21. Gomez-Isla T, Hollister R, West H, Mui S, Growdon JH, Petersen RC, Parisi JE, Hyman BT. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. Ann Neurol 1997; 41(1): 17-24.

22. Bobinski M, Wegiel J, Wisniewski HM, Tarnawski M, Bobinski M, Reisberg B, De Leon MJ, Miller DC. Neurofibrillary pathology--correlation with hippocampal formation atrophy in Alzheimer disease. Neurobiol Aging 1996; 17: 909-19.

23. Josephs KA, Petersen RC, Knopman DS, Boeve BF, Whitwell JL, Duffy JR, Parisi JE, Dickson DW. Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. Neurology 2006; 66(1):41-8.

24. Cairns NJ, Bigio EH, Mackenzie IR, Neumann M, Lee VM, Hatanpaa KJ, White CL 3rd, Schneider JA, Grinberg LT, Halliday G, Duyckaerts C, Lowe JS, Holm IE, Tolnay M, Okamoto K, Yokoo H, Murayama S, Woulfe J, Munoz DG, Dickson DW, Ince PG, Trojanowski JQ, Mann DM. Consortium for Frontotemporal Lobar Degeneration. Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. Acta Neuropathol 2007; 114(1):5-22.

25. Yamada M. Senile dementia of the neurofibrillary tangle type (tangle- only dementia): neuropathological criteria and clinical guidelines for diagnosis. Neuropathology 2003; 23(4):311-7.

26. Bancher C, Jellinger KA. Neurofibrillary tangle predominant form of senile dementia of Alzheimer type: a rare subtype in very old subjects. Acta Neuropathol 1994; 88(6):565-70.

27. Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. Lancet Neurol 2009; 8(3):270-9.

28. Kouri N, Murray ME, Hassan A, Rademakers R, Uitti RJ, Boeve BF, Graff-Radford NR, Wszolek ZK, Litvan I, Josephs KA, Dickson DW. Neuropathological features of corticobasal degeneration presenting as corticobasal syndrome or Richardson syndrome. Brain 2011; 134 (Pt 11):3264-75.

29. Tolnay M, Sergeant N, Ghestem A, Chalbot S, De Vos RA, Jansen Steur EN, Probst A, Delacourte A. Argyrophilic grain disease and Alzheimer's disease are distinguished by their different distribution of tau protein isoforms. Acta Neuropathol 2002; 104(4):425-34.

30. Lee VM, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. Annu Rev Neurosci 2001; 24:1121-59.

31. Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, Pickering-Brown S, Chakraverty S, Isaacs A, Grover A, Hackett J, Adamson J, Lincoln S, Dickson D, Davies P, Petersen RC, Stevens M, de Graaff E, Wauters E, van Baren J, Hillebrand M, Joosse M, Kwon JM, Nowotny P, Che LK, Norton J, Morris JC, Reed LA, Trojanowski J, Basun H, Lannfelt L, Neystat M, Fahn S, Dark F, Tannenberg T, Dodd PR, Hayward N, Kwok JB, Schofield PR, Andreadis A, Snowden J, Craufurd D, Neary D, Owen F, Oostra BA, Hardy J, Goate A, van Swieten J, Mann D, Lynch T, Heutink P. Association of missense and 5'-splice- site mutations in tau with the inherited dementia FTDP-17. Nature 1998; 393(6686):702-5.

32. Goedert M, Crowther RA, Spillantini MG. Tau mutations cause frontotemporal dementias. Neuron 1998; 21(5):955-8.

33. Filipcik P, Zilka N, Bugos O, Kucerak J, Koson P, Novak P, Novak M. First transgenic rat model developing progressive cortical neurofibrillary tangles. Neurobiol Aging 2012; 33(7):1448-56.

34. Zilka N, Korenova M, Novak M. Misfolded tau protein and disease modifying pathways in transgenic rodent models of human tauopathies. Acta Neuropathol 2009; 118(1):71-86.

35. Zilka N, Filipcik P, Koson P, Fialova L, Skrabana R, Zilkova M, Rolkova G, Kontsekova E, Novak M. Truncated tau from sporadic Alzheimer's disease suffices to drive neurofibrillary degeneration in vivo. FEBS Lett 2006; 580(15):3582-8.