Prion protein as a therapeutic target in Alzheimer's disease

Nigel Hooper

University of Manchester
UK

Dementia-2014

OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Alzheimer's Disease & Dementia

September 23-25, 2014 Valencia, Spain

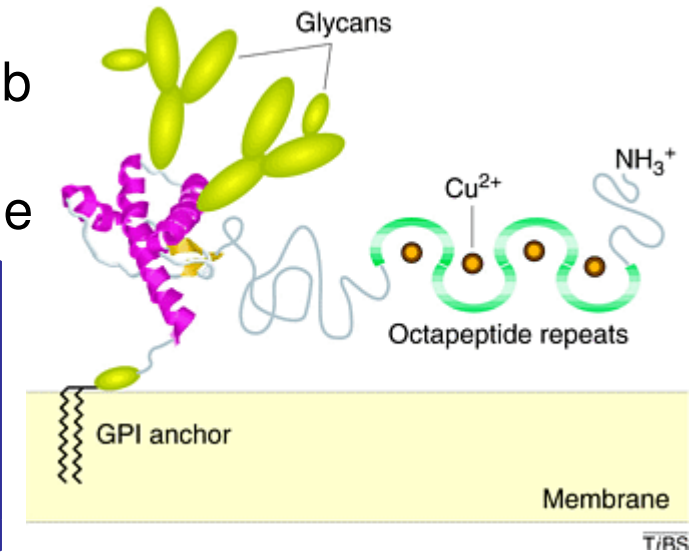


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Prion protein and Alzheimer's – a connection?

- causative agent of transmissible spongiform encephalopathies (TSEs), e.g. Creutzfeldt-Jakob disease (CJD), BSE, scrapie, etc
- cellular PrP^{C} undergoes conformational change to infectious PrP^{Sc}

- Metal homeostasis
- Anti-oxidant response
- Cell signalling
- Ligand/protein binding



- Cases of co-existent Alzheimer's and CJD pathology
(Hainfellner et al. 1998; Voigtlander et al. 2001)
- Met/Val129 polymorphism in *PRNP* a risk factor for Alzheimer's
(Dermaut et al. 2003; Riemenschneider et al. 2004)
- PrP^{C} to PrP^{Sc} conversion & Aβ production occur in cholesterol-rich lipid rafts
(Cordy et al. 2003; Ehehalt et al. 2003; Taraboulos et al. 1995)
- APP & PrP^{C} shed from the cell surface by the zinc metalloprotease ADAM10
(Parvathy et al. 1998; Parkin et al. 2004; Taylor et al. 2009)
- PrP^{C} inhibits the β-secretase cleavage of APP
(Parkin et al. 2007; Griffiths et al. 2011)

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Cellular prion protein (PrP^C): a receptor for Aβ oligomers

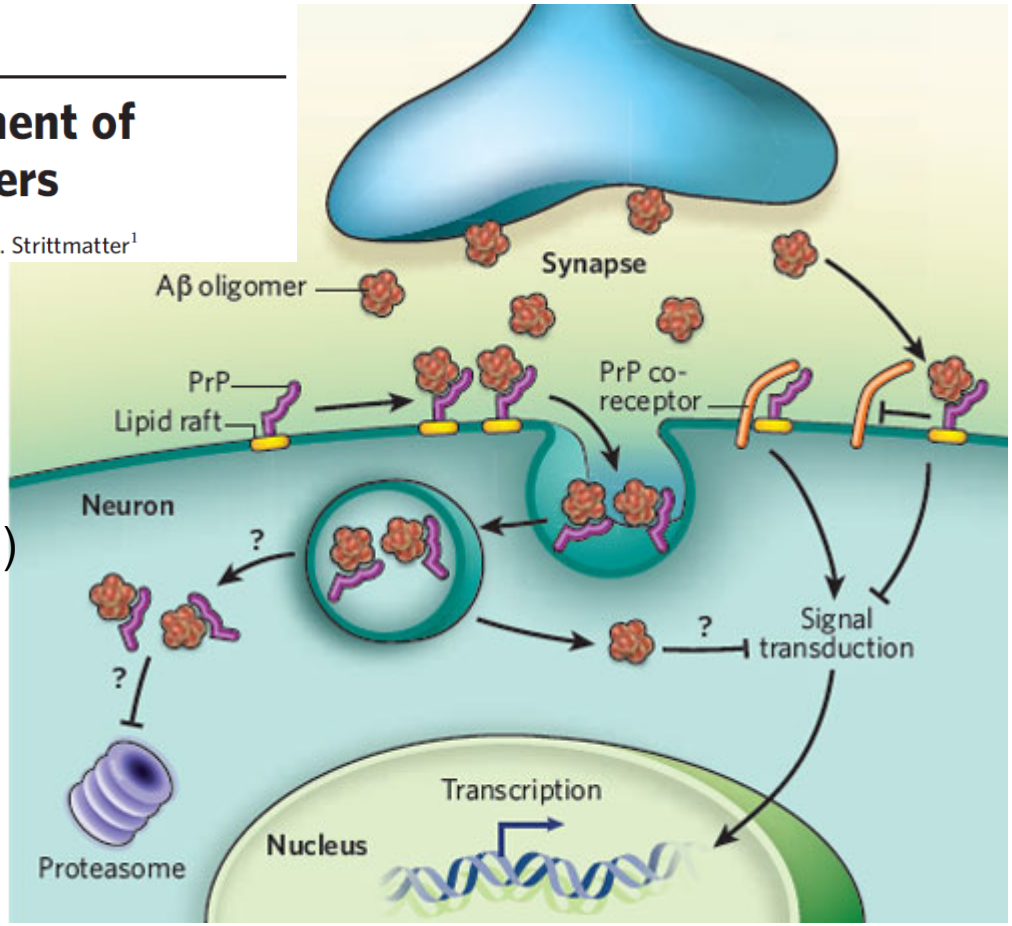
nature Vol 457 | 26 February 2009 | doi:10.1038/nature07761

LETTERS

Cellular prion protein mediates impairment of synaptic plasticity by amyloid-β oligomers

Juha Laurén[1], David A. Gimbel[1], Haakon B. Nygaard[1], John W. Gilbert[1] & Stephen M. Strittmatter[1]

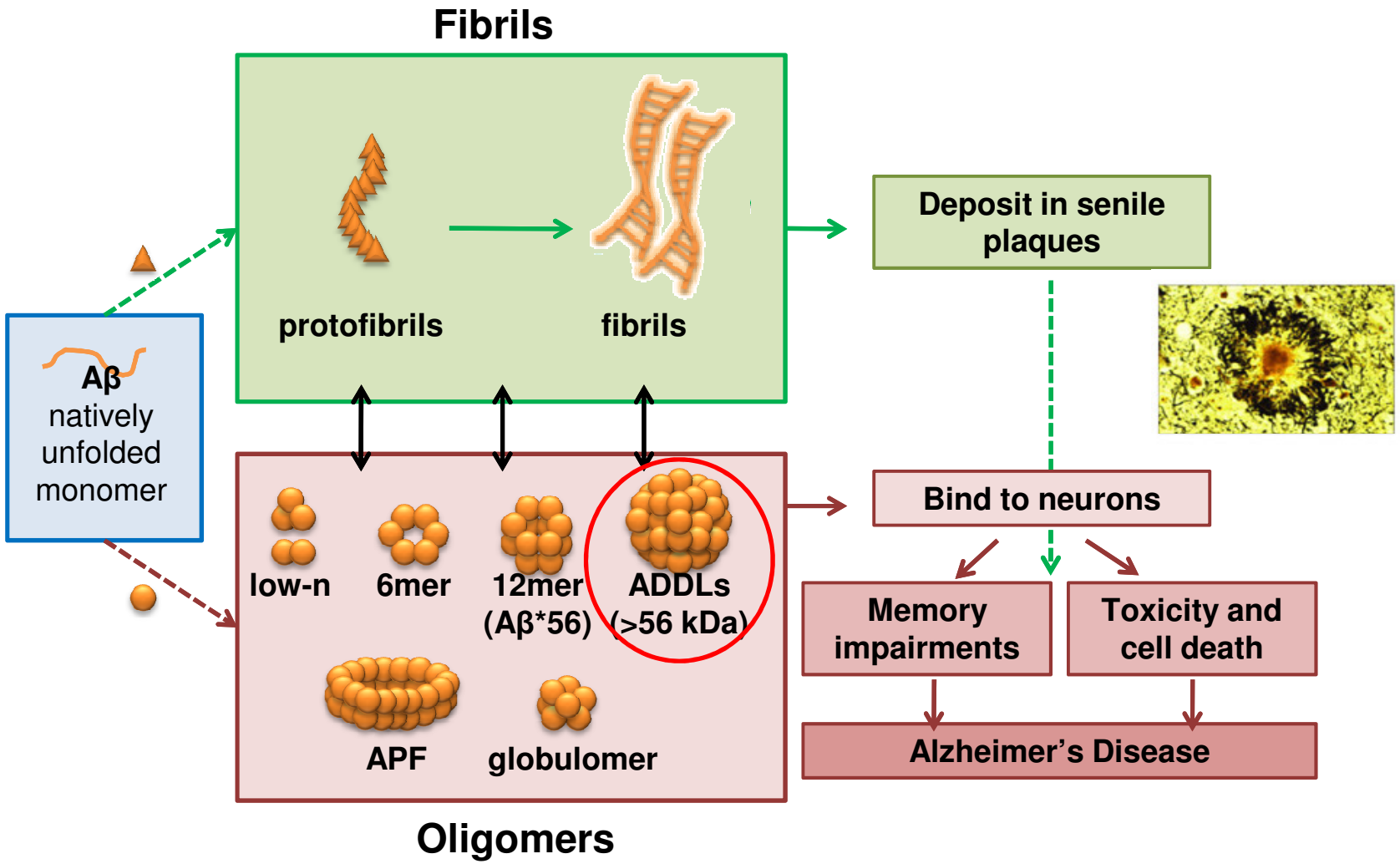
- Screened expression library of 225,000 mouse brain cDNAs
- PrP^C the only specific, high-affinity receptor for Aβ oligomers (k_d ~ 0.4 nM)



Cisse & Mucke (2009) Nature 457, 1090-1

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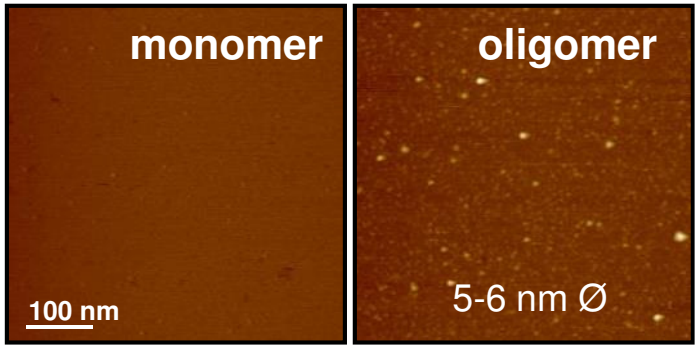
Neurotoxic forms of amyloid-β

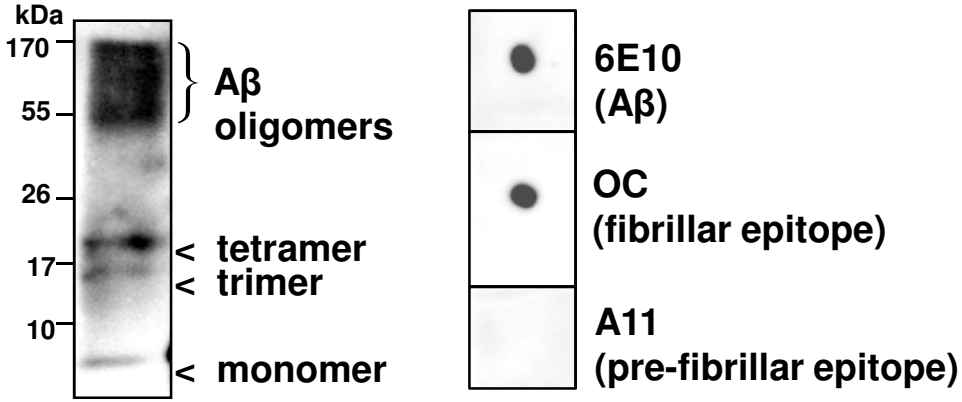


Rushworth & Hooper (2011) Int. J. Alzheimers Dis. Article ID 603052

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Biophysical and immunological characterisation of $A\beta_{1-42}$ oligomers (ADDLs)





Neurobiology of Disease 35 (2009) 352–358

Contents lists available at ScienceDirect

Neurobiology of Disease

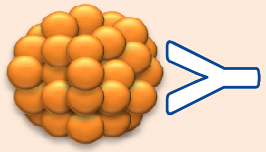
journal homepage: www.elsevier.com/locate/ynbdi

Soluble fibrillar oligomer levels are elevated in Alzheimer's disease brain and correlate with cognitive dysfunction

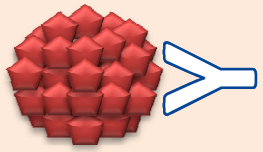
Jennifer L. Tomic [a], Anna Pensalfini [a], Elizabeth Head [b,1], Charles G. Glabe [a,*]

"Levels of soluble fibrillar oligomers detected by OC antibody are significantly elevated in multiple brain regions of AD patients"

Conformation-dependent antibodies
(Charlie Glabe, California)



A11 (pre-fibrillar oligomers)

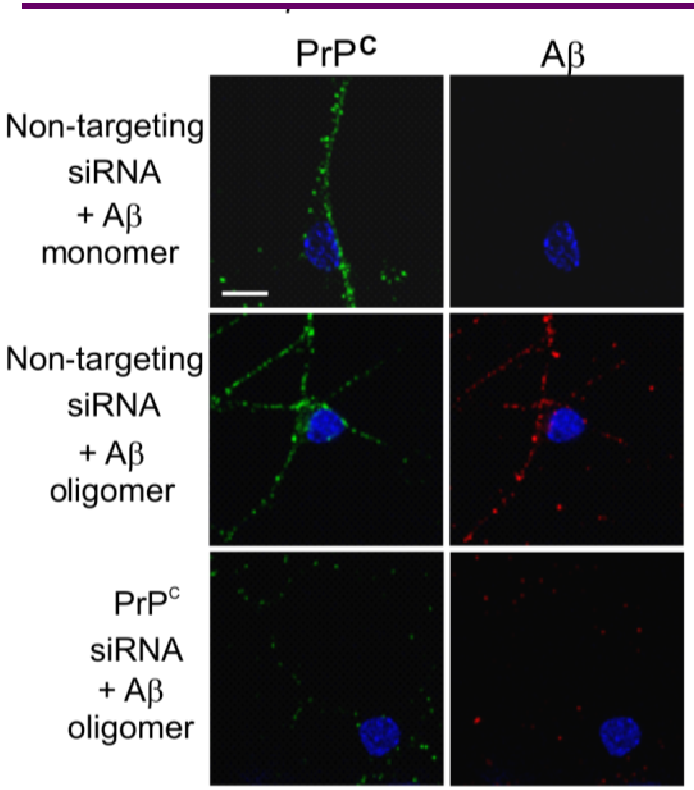


OC (fibrillar oligomers)

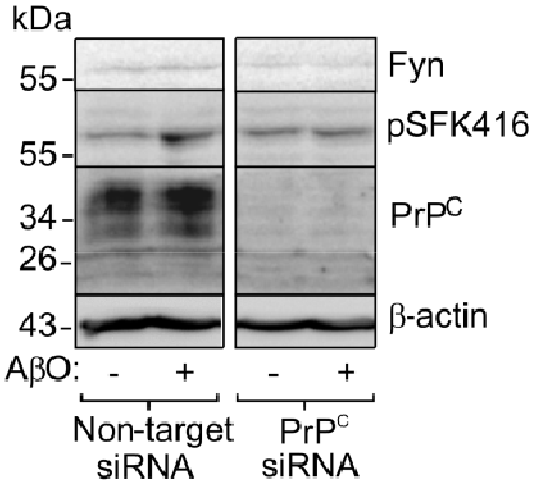
Rushworth et al. (2013) J. Biol. Chem. 288, 8935

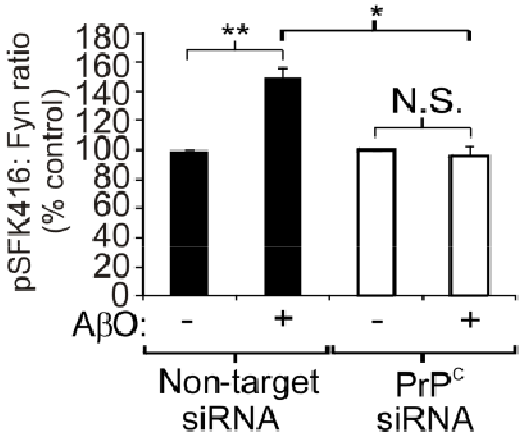
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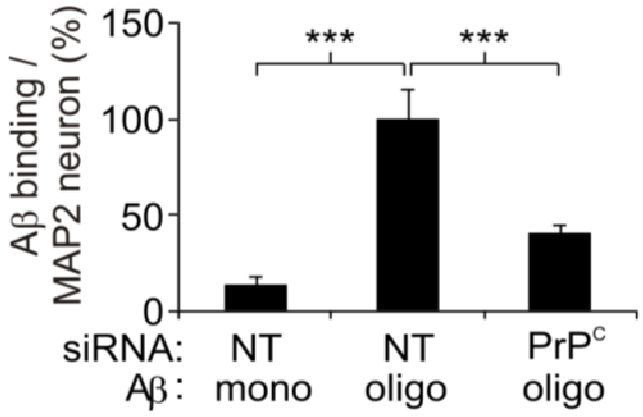
PrP^C is required for the cellular binding of fibrillar Aβ oligomers and activation of Fyn kinase



Rat hippocampal neurons



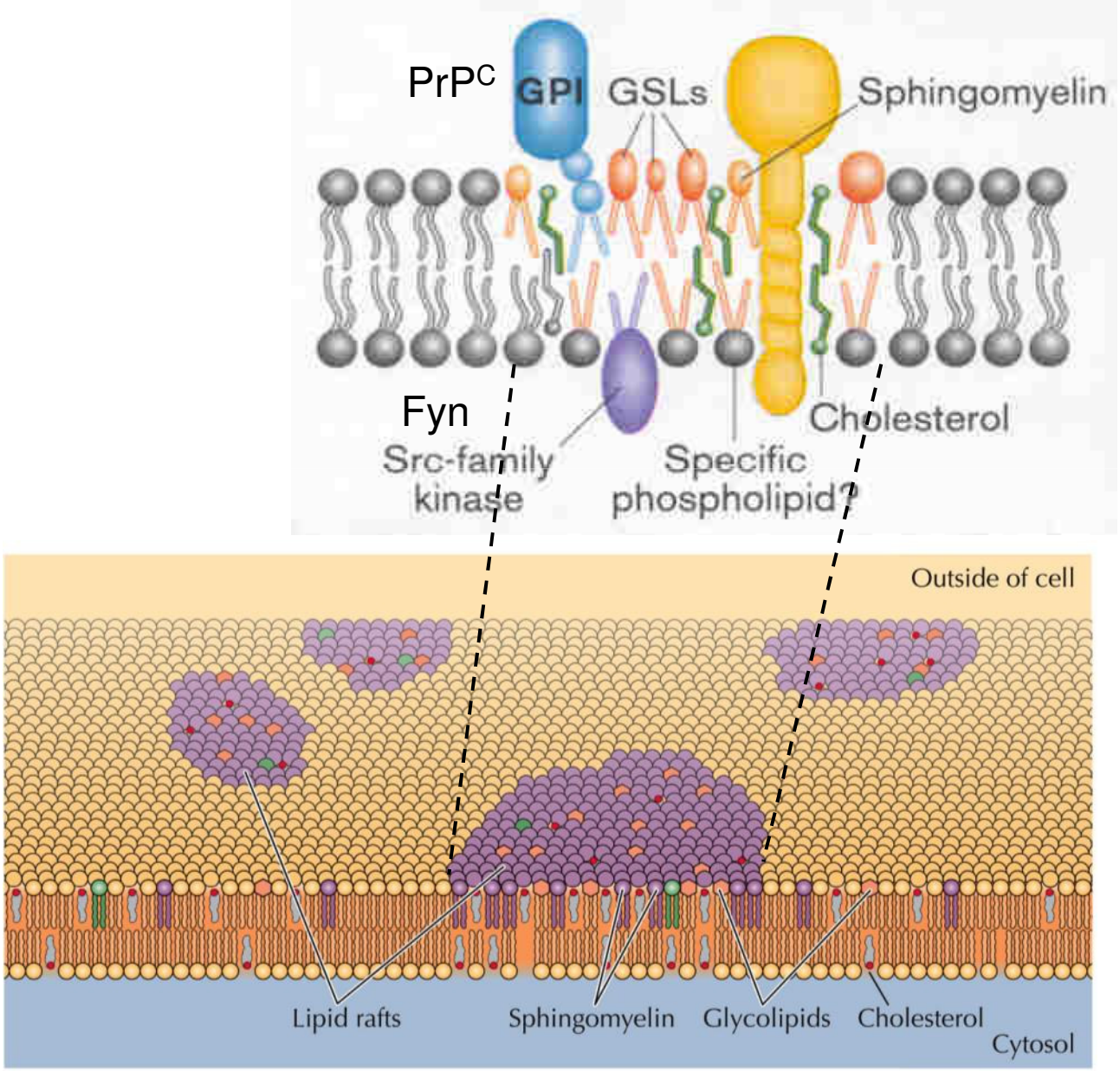




Rushworth et al. (2013) J Biol Chem 288, 8935

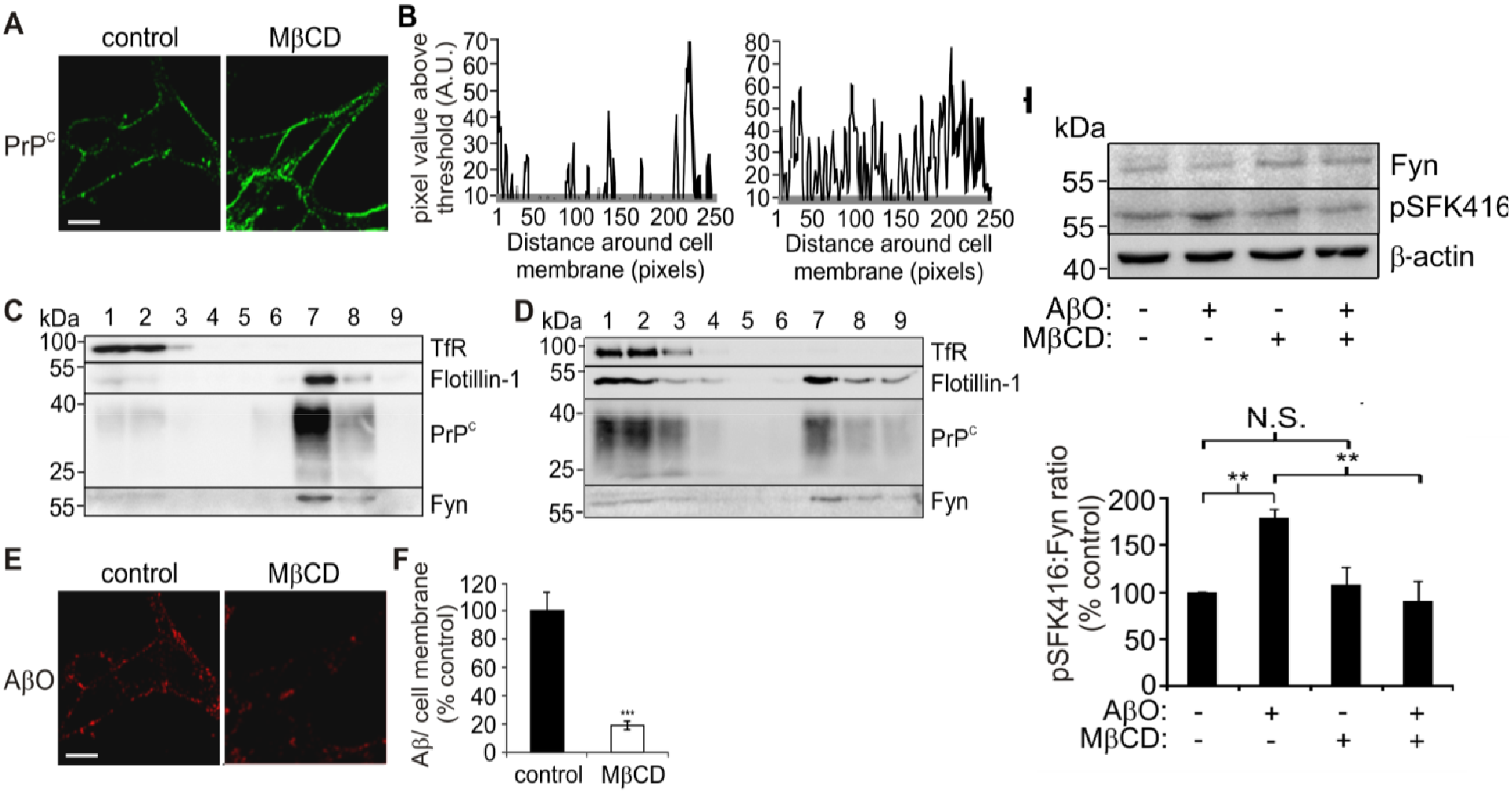
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PrP^C is GPI anchored and localised in cholesterol-rich, detergent-resistant lipid rafts



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Disruption of lipid rafts prevents Aβ oligomer binding and activation of Fyn kinase

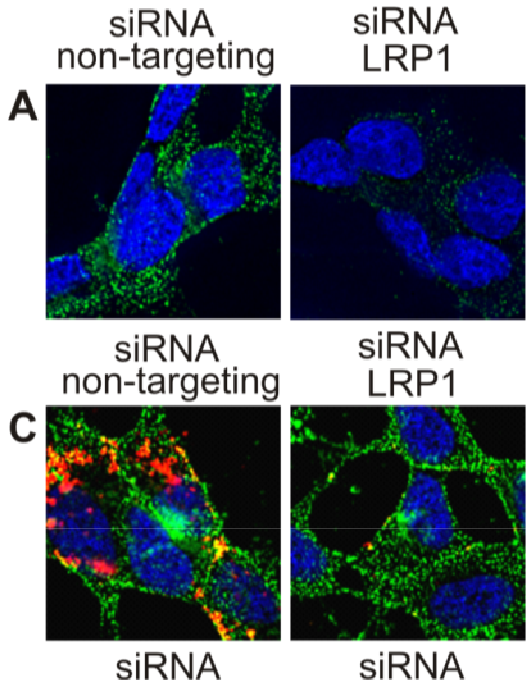


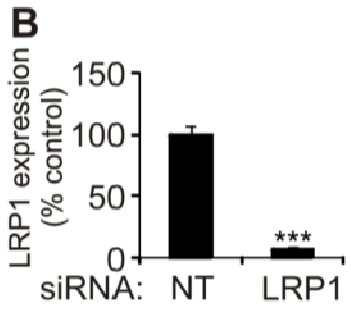
MβCD = methyl β-cyclodextrin, sequesters cholesterol

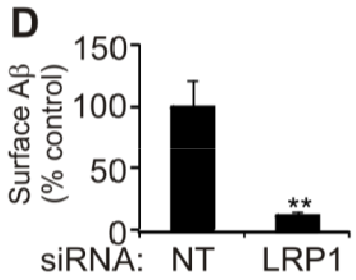
Rushworth et al. (2013) J. Biol. Chem. 288, 8935

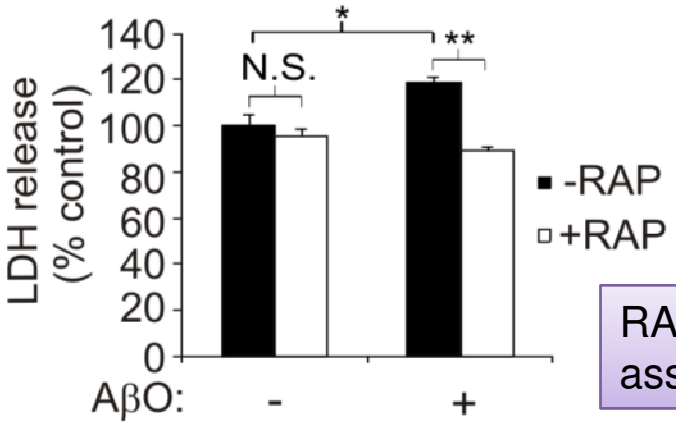
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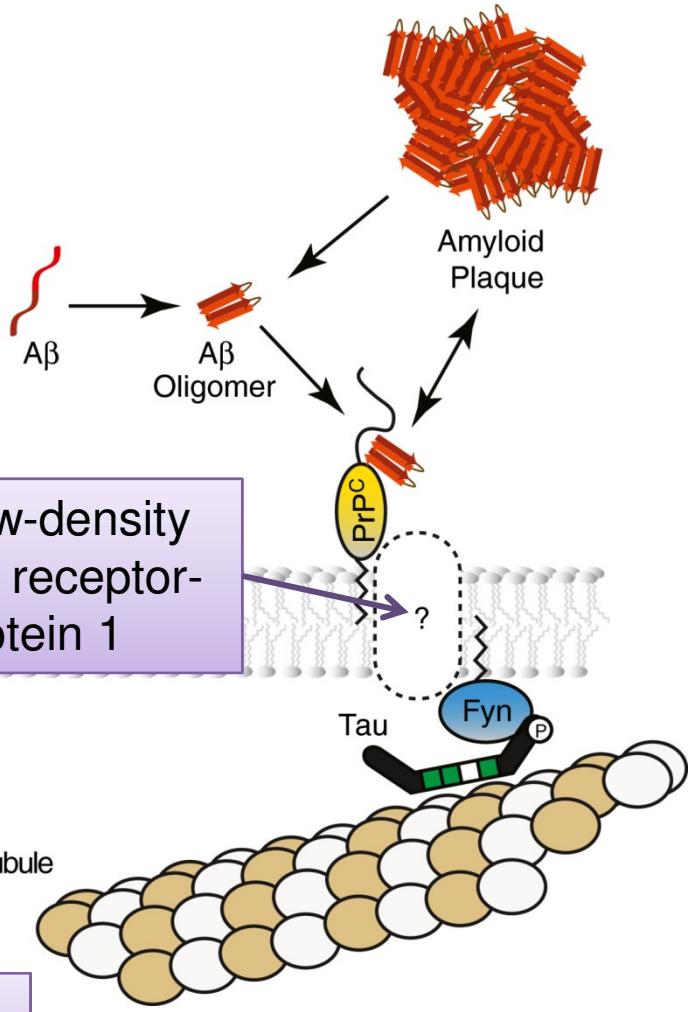
The transmembrane LRP1 is required for the binding and cytotoxicity of Aβ oligomers











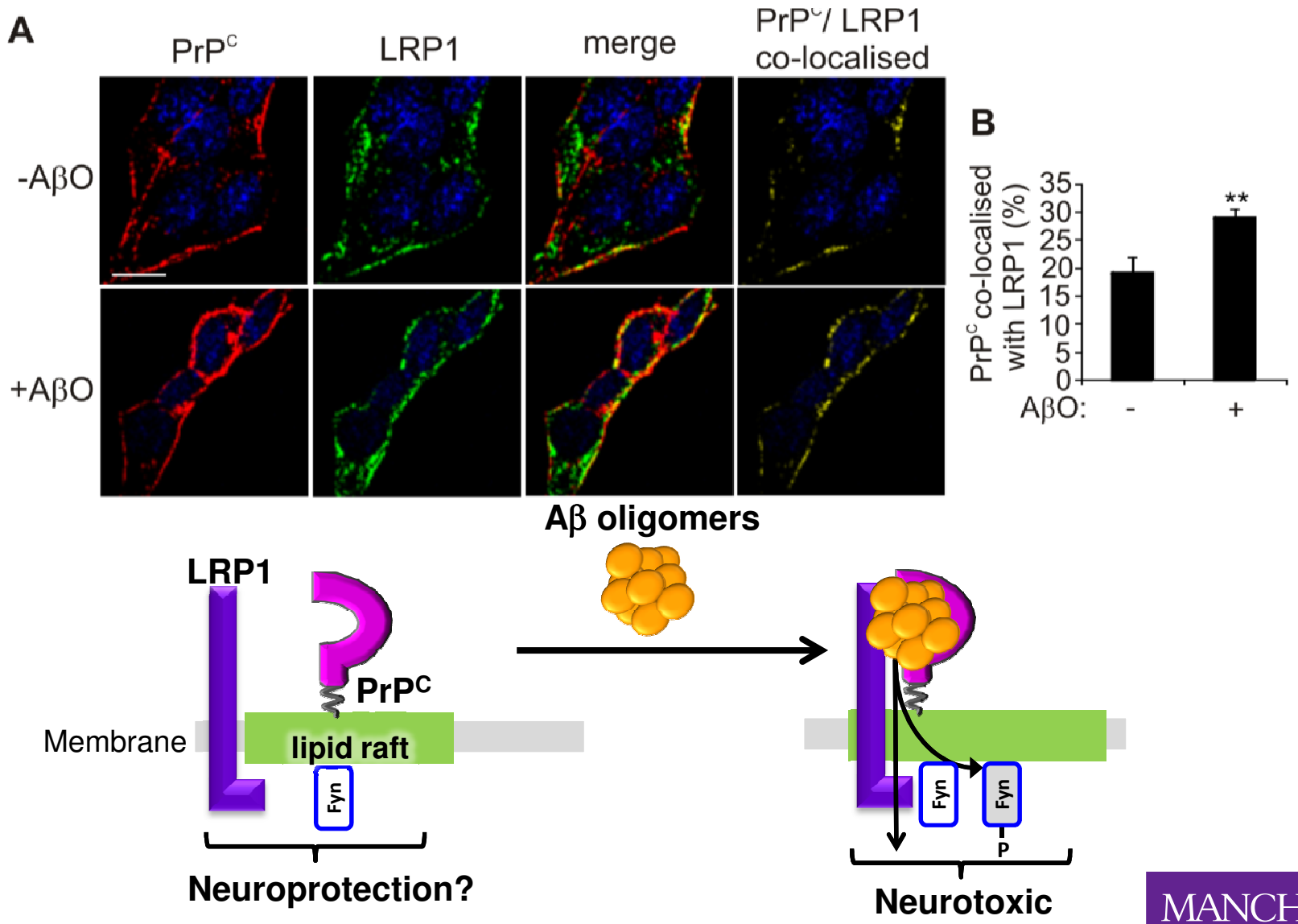
LRP1 = low-density lipoprotein receptor-related protein 1

RAP = receptor-associated protein

Rushworth et al. (2013) J. Biol. Chem. 288, 8935

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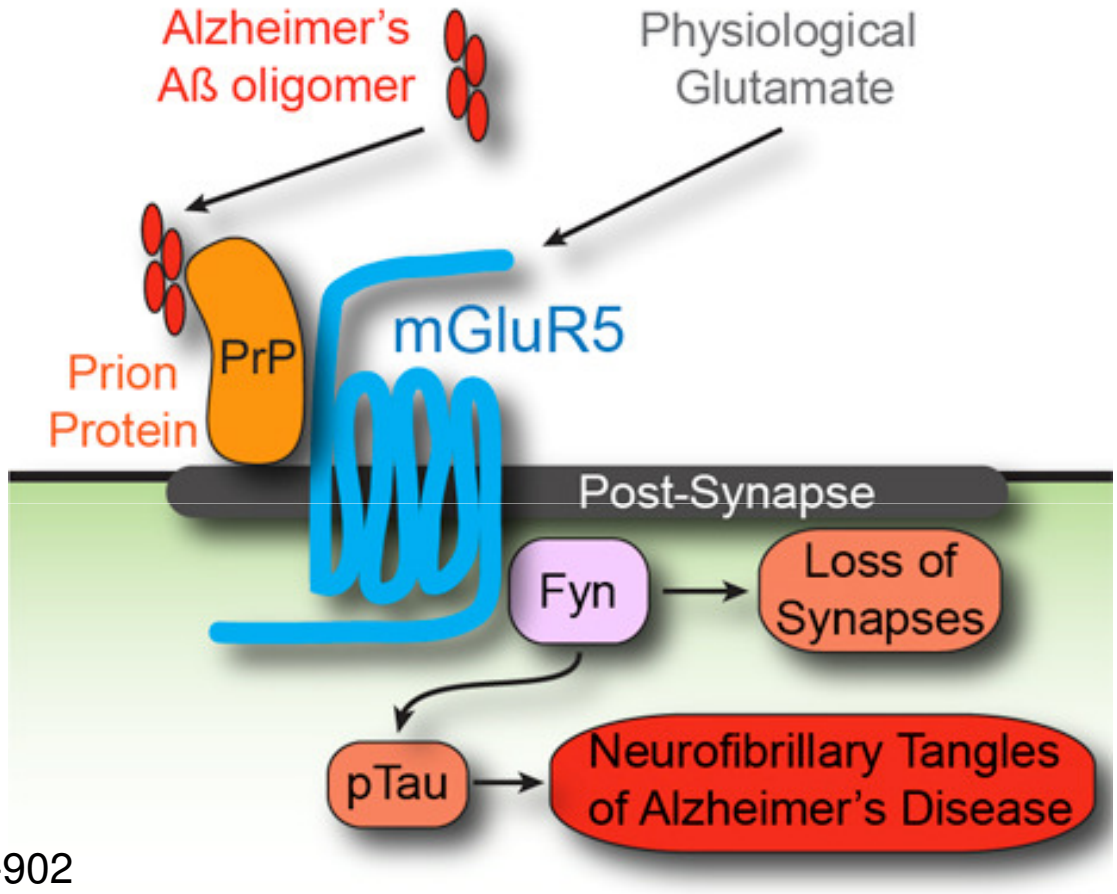
Aβ oligomers promote the clustering of PrP^C and LRP1



Rushworth et al. (2013) J. Biol. Chem. 288, 8935

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Metabotropic glutamate receptor 5 (mGluR5) is a coreceptor with PrP^C for Aβ oligomers



Neuron
Article

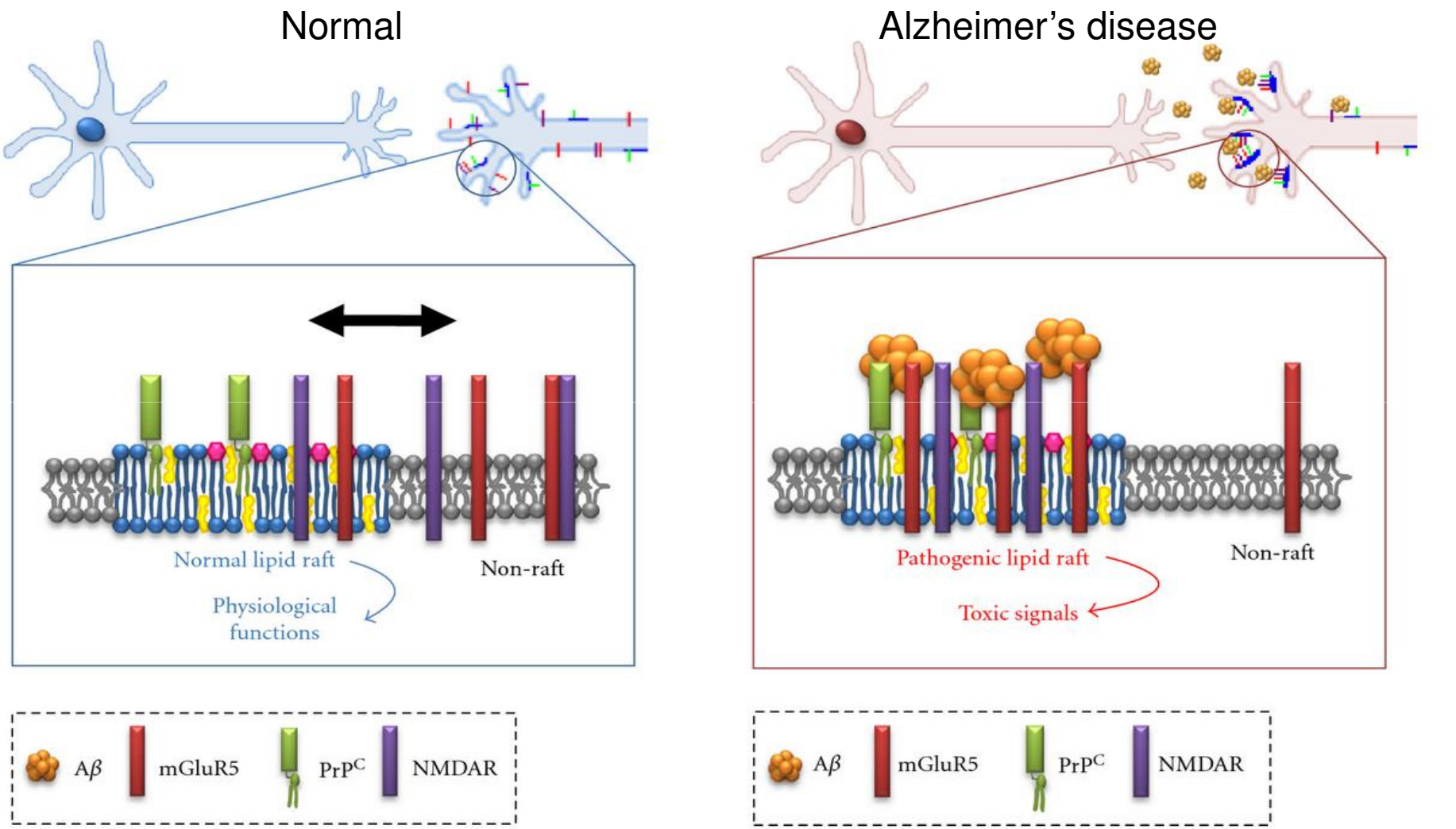
Neuron 79, 887-902

Metabotropic Glutamate Receptor 5 Is a Coreceptor for Alzheimer Aβ Oligomer Bound to Cellular Prion Protein

Ji Won Um,[1] Adam C. Kaufman,[1] Mikhail Kostylev,[1] Jacqueline K. Heiss,[1] Massimiliano Stagi,[1] Hideyuki Takahashi,[1] Meghan E. Kerrisk,[2] Alexander Vortmeyer,[3] Thomas Wisniewski,[4] Anthony J. Koleske,[2] Erik C. Gunther,[1] Haakon B. Nygaard,[1] and Stephen M. Strittmatter[1,*]

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Aβ oligomer binding stimulates the clustering of specific neuronal receptors into aberrant signalling platforms at the synapse



Rushworth & Hooper (2011) Int. J. Alzheimers Dis. Article ID 603052

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PrP^C as a therapeutic target in Alzheimer's disease?

Chung et al. BMC Neuroscience 2010, 11:130
http://www.biomedcentral.com/1471-2202/11/130

BMC Neuroscience

RESEARCH ARTICLE Open Access

Anti-PrP^C monoclonal antibody infusion as a novel treatment for cognitive deficits in an alzheimer's disease model mouse

Erika Chung[1], Yong Ji[1], Yanjie Sun[1], Richard J Kascsak[2], Regina B Kascsak[2], Pankaj D Mehta[2], Stephen M Strittmatter[3], Thomas Wisniewski[1,4,5*]

nature COMMUNICATIONS OPEN

ARTICLE

Received 1 Mar 2011 | Accepted 5 May 2011 | Published 7 Jun 2011 DOI: 10.1038/ncomms1341

Interaction between prion protein and toxic amyloid β assemblies can be therapeutically targeted at multiple sites

Darragh B. Freir[1,*], Andrew J. Nicoll[2,*], Igor Klyubin[3], Silvia Panico[4], Jessica M. Mc Donald[1], Emmanuel Risse[2], Emmanuel A. Asante[2], Mark A. Farrow[2], Richard B. Sessions[5], Helen R. Saibil[4], Anthony R. Clarke[2,5], Michael J. Rowan[3], Dominic M. Walsh[1] & John Collinge[2]

The Journal of Neuroscience, May 18, 2011 • 31(20):7259–7263 • 7259

Brief Communications

Alzheimer's Disease Brain-Derived Amyloid-β-Mediated Inhibition of LTP *In Vivo* Is Prevented by Immunotargeting Cellular Prion Protein

Andrew E. Barry,[1] Igor Klyubin,[1] Jessica M. Mc Donald,[2] Alexandra J. Mably,[2] Michael A. Farrell,[3] Michael Scott,[2] Dominic M. Walsh,[2] and Michael J. Rowan[1]

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But… PrP^C has several physiological roles

Physiol Rev 88: 673–728, 2008;
doi:10.1152/physrev.00007.2007.

Physiology of the Prion Protein

RAFAEL LINDEN, VILMA R. MARTINS, MARCO A. M. PRADO, MARTÍN CAMMAROTA, IVÁN IZQUIERDO, AND RICARDO R. BRENTANI

Published April 28, 2008

JCB: ARTICLE

Prion protein attenuates excitotoxicity by inhibiting NMDA receptors

Houman Khosravani,[1] Yunfeng Zhang,[1] Shigeki Tsutsui,[2] Shahid Hameed,[1] Christophe Altier,[1] Jawed Hamid,[1] Lina Chen,[1] Michelle Villemaire,[2] Zenobia Ali,[2] Frank R. Jirik,[2] and Gerald W. Zamponi[1]

[1]Department of Physiology and Biophysics, Hotchkiss Brain Institute, and [2]Department of Biochemistry and Molecular Biology, McCaig Institute for Bone and Joint Health, University of Calgary, Calgary T2N4N1, Canada

nature COMMUNICATIONS

ARTICLE

Received 4 May 2011 | Accepted 14 Sep 2012 | Published 16 Oct 2012

DOI: 10.1038/ncomms2135

Prion protein facilitates uptake of zinc into neuronal cells

Nicole T. Watt[1], David R. Taylor[1], Talitha L. Kerrigan[2,†], Heledd H. Griffiths[1], Jo V. Rushworth[1], Isobel J. Whitehouse[1] & Nigel M. Hooper[1]

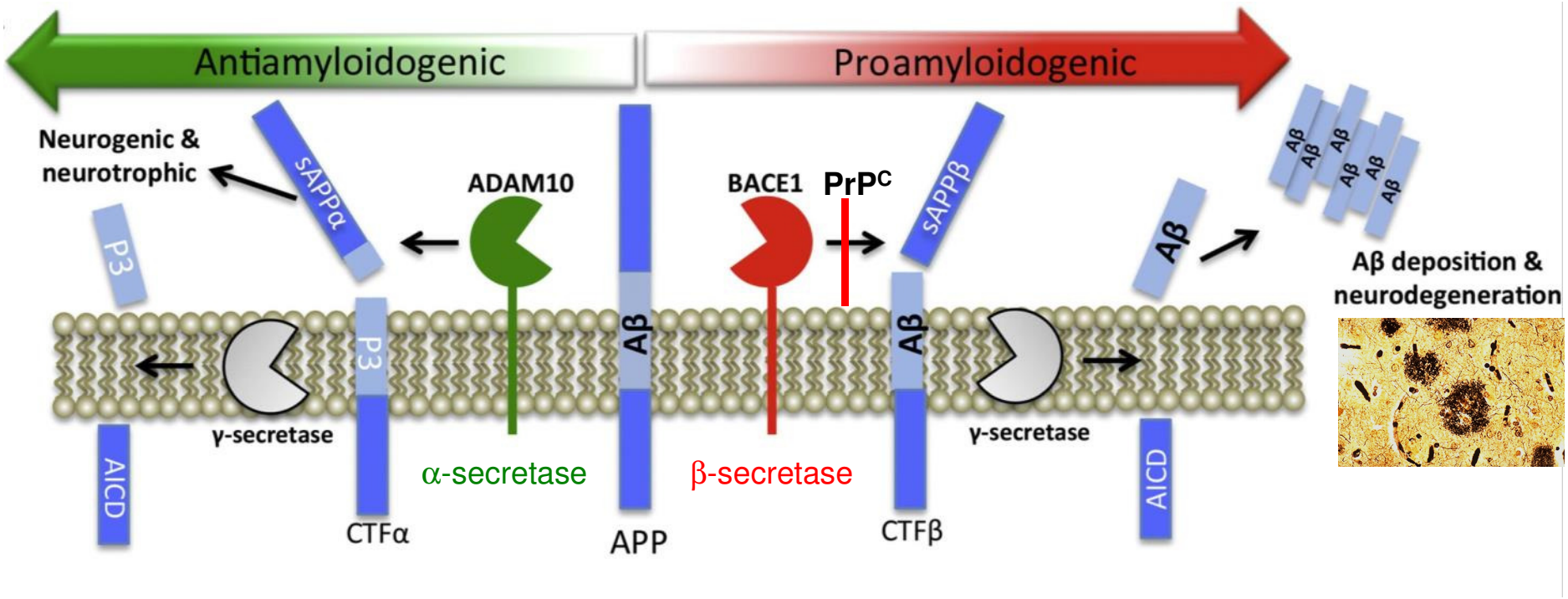
Cellular prion protein regulates β-secretase cleavage of the Alzheimer's amyloid precursor protein

Edward T. Parkin*†‡, Nicole T. Watt*†, Ishrut Hussain§, Elizabeth A. Eckman¶, Christopher B. Eckman¶, Jean C. Manson‖, Herbert N. Baybutt‖, Anthony J. Turner*, and Nigel M. Hooper*†**

11062–11067 | PNAS | June 26, 2007 | vol. 104 | no. 26

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PrP^C inhibits the amyloidogenic processing of the amyloid precursor protein (APP)



11062–11067 | PNAS | June 26, 2007 | vol. 104 | no. 26

Cellular prion protein regulates β-secretase cleavage of the Alzheimer's amyloid precursor protein

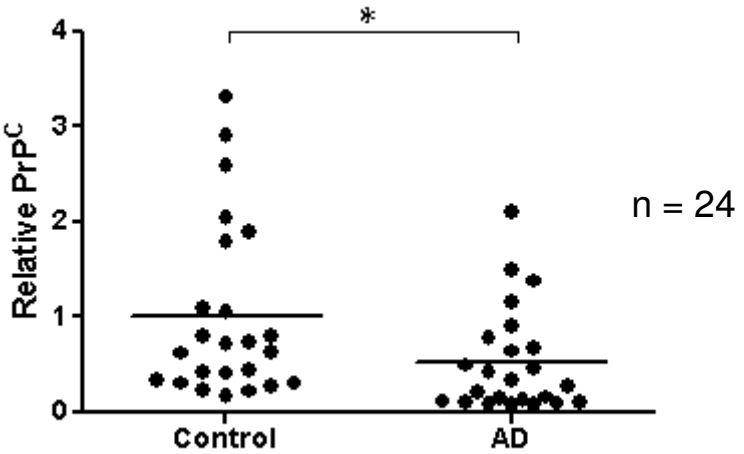
Edward T. Parkin*†‡, Nicole T. Watt*†, Ishrut Hussain§, Elizabeth A. Eckman¶, Christopher B. Eckman¶, Jean C. Manson‖, Herbert N. Baybutt‖, Anthony J. Turner*, and Nigel M. Hooper*†**

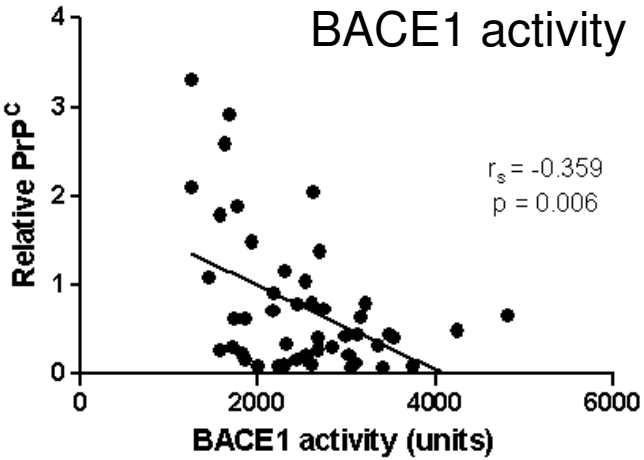
*Proteolysis Research Group, Institute of Molecular and Cellular Biology, Faculty of Biological Sciences, and †Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds LS2 9JT, United Kingdom; §Neurodegeneration Research, Neurology and Gastrointestinal Centre of Excellence for Drug Discovery, GlaxoSmithKline Research and Development Limited, Third Avenue, Harlow, Essex CM19 5AW, United Kingdom; ¶Mayo Clinic, Jacksonville, FL 32224; and ‖Roslin Institute, Neuropathogenesis Unit, Edinburgh EH9 3JF, United Kingdom

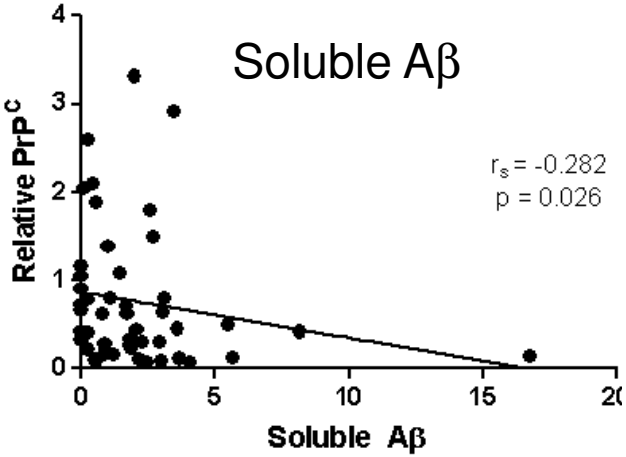
Edited by Stanley B. Prusiner, University of California, San Francisco, CA, and approved May 10, 2007 (received for review October 30, 2006)

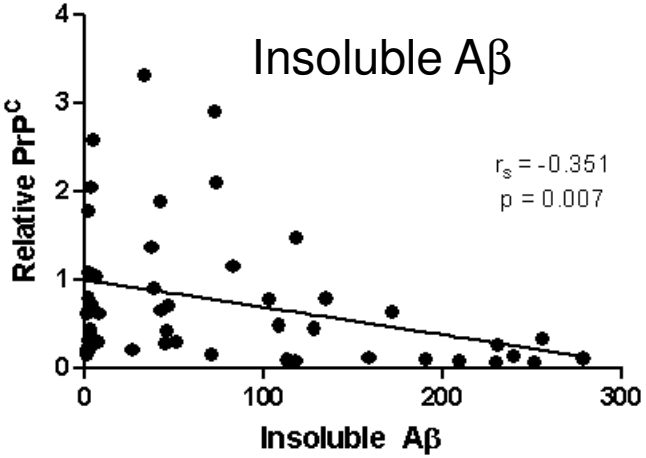
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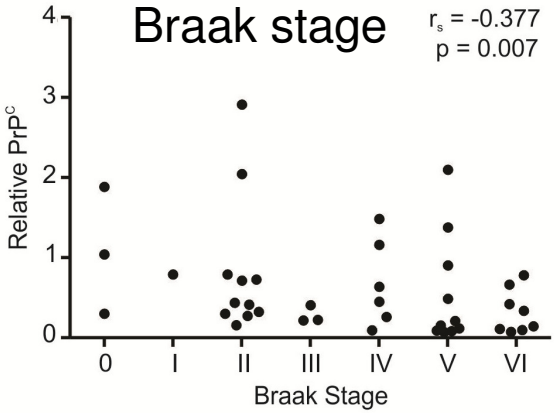
PrP^C is reduced in sporadic Alzheimer's brain and inversely correlates with BACE1 activity, Aβ and Braak stage







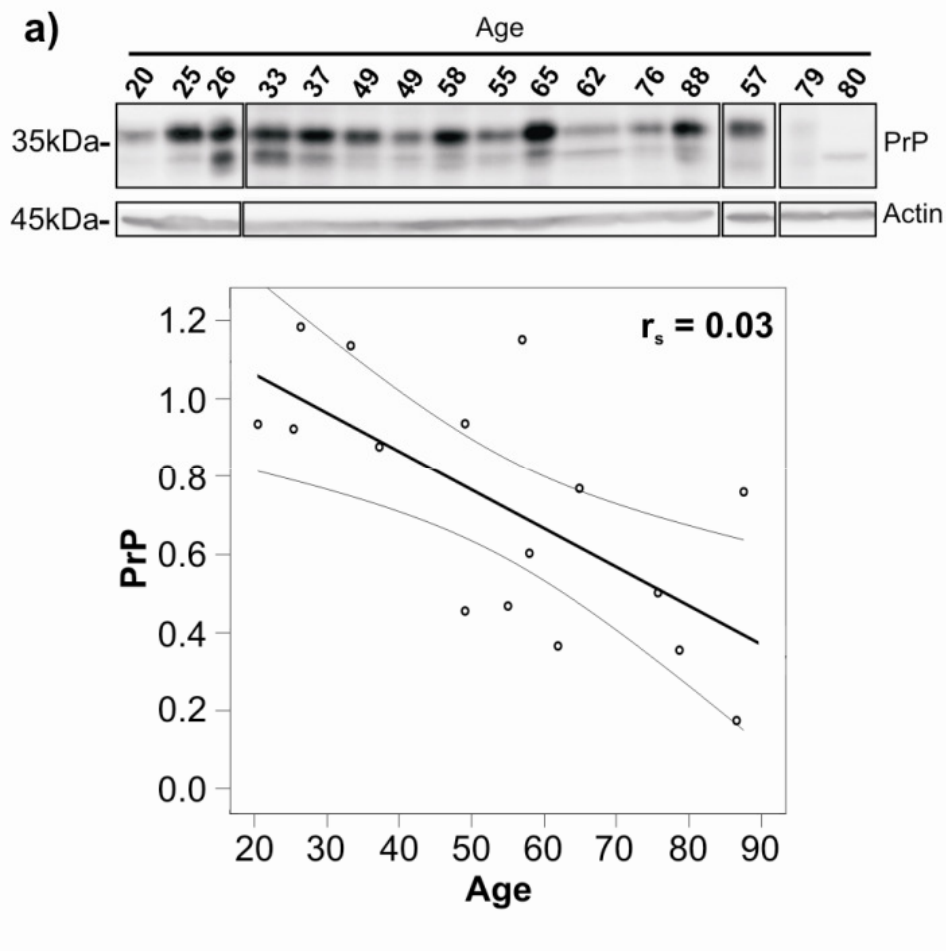




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Whitehouse et al. (2013) PLoS ONE 8: e59554

Prion protein in human hippocampus declines with age

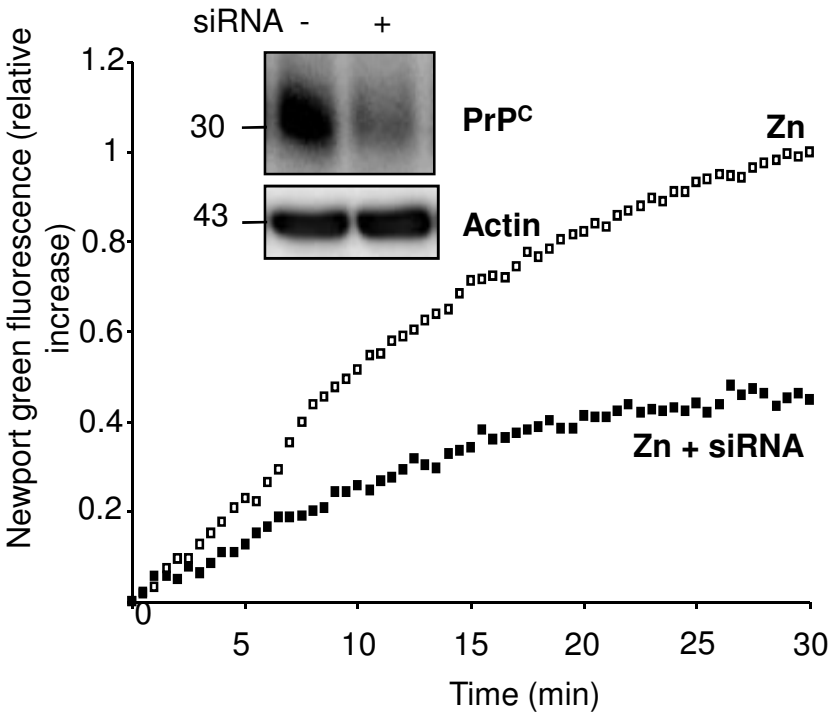


Whitehouse et al. (2010) J. Alz. Dis. **22**, 1023-1031

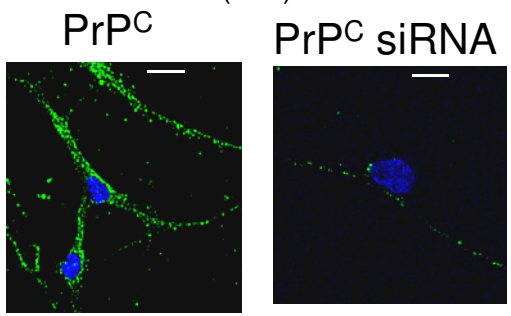
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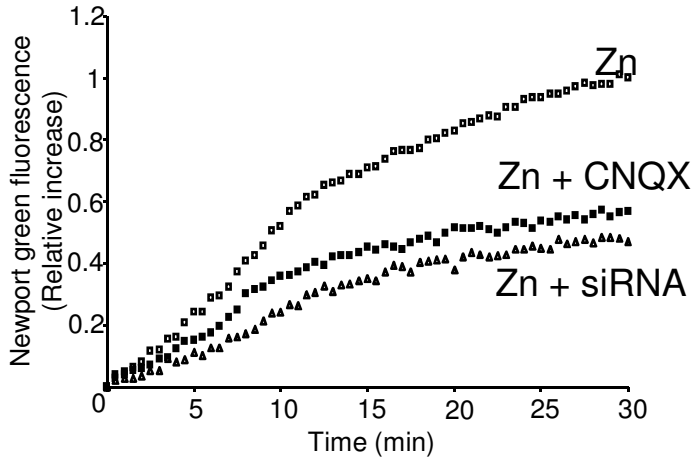
PrP^C facilitates neuronal zinc uptake via AMPA receptors

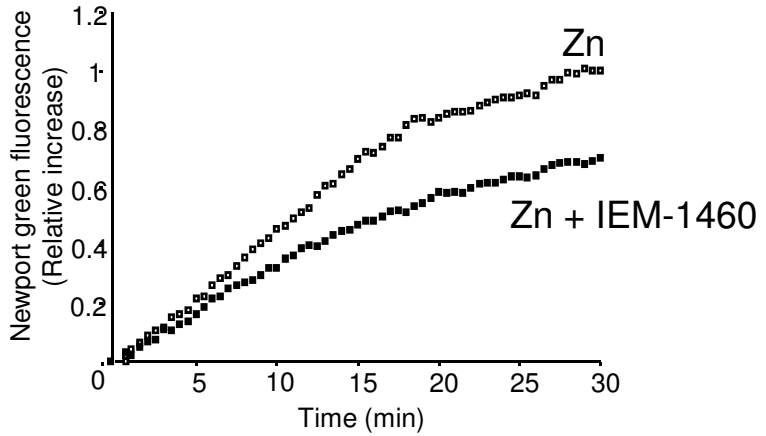
Rat hippocampal neurons



Newport green staining





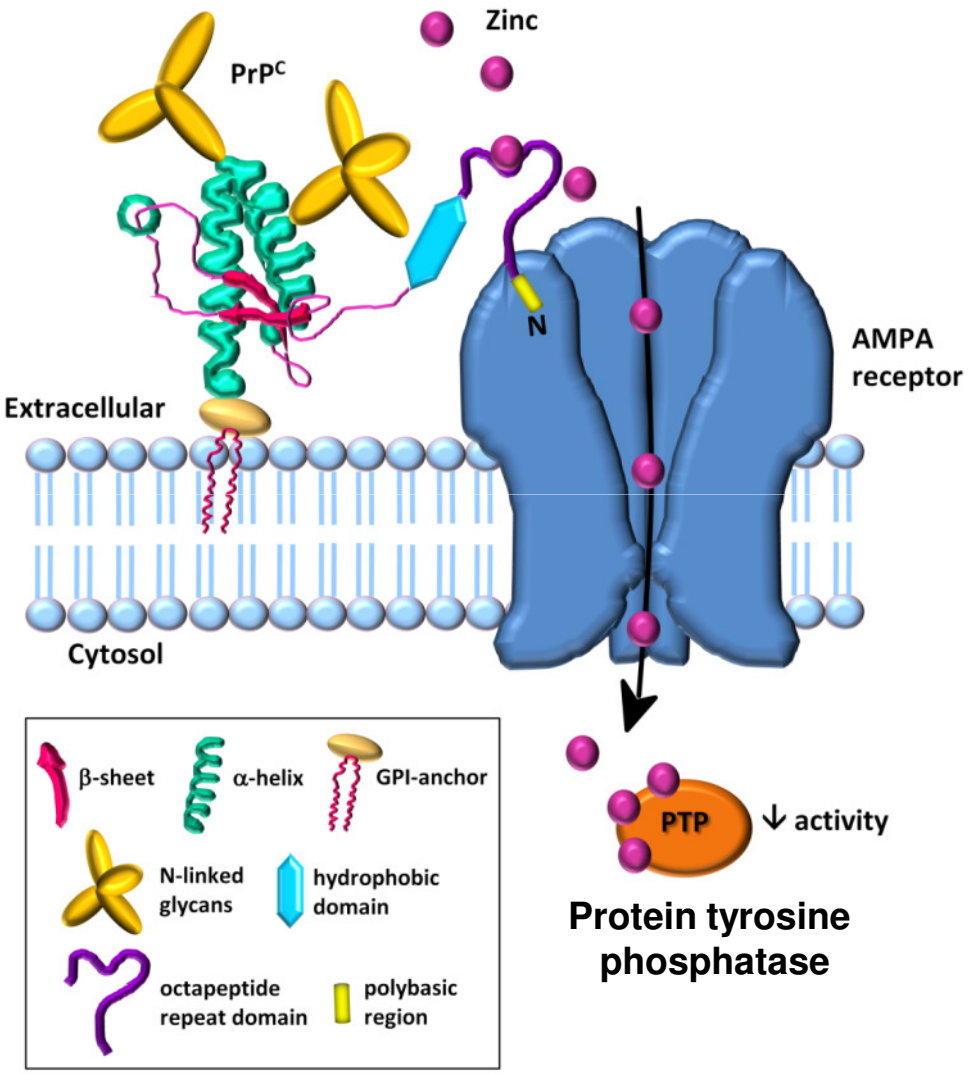


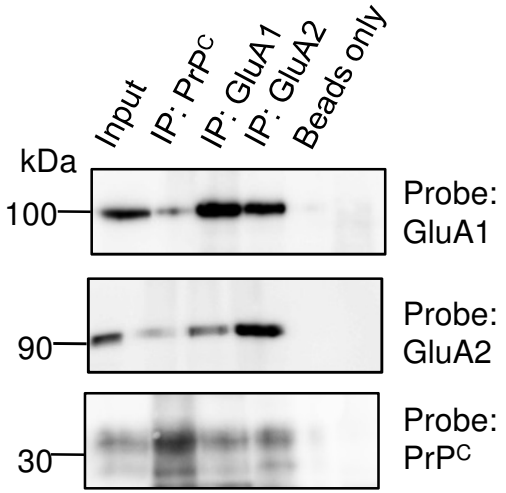
GluA2-lacking, Ca^{2+} and Zn^{2+} permeable AMPAR

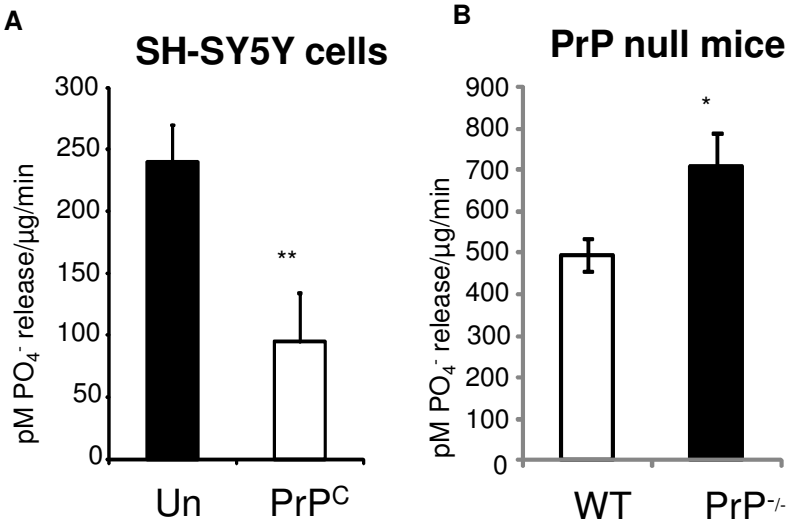
Watt et al. (2012) Nat. Commun. 3:1134

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Potential mechanism by which prion protein facilitates zinc uptake into cells through the AMPA receptor







Watt et al. (2012) Nat. Commun. 3:1134
Watt et al. (2013) Prion 7, 203-208

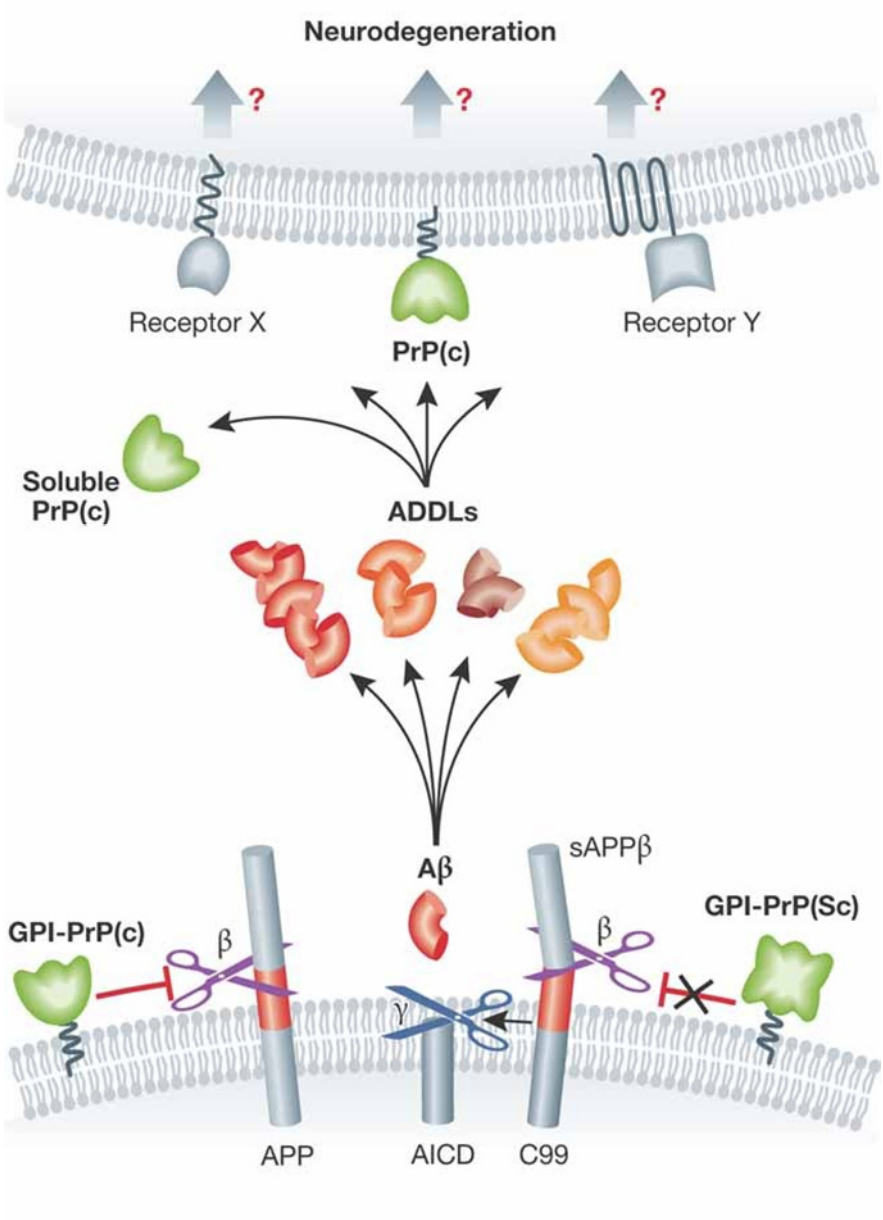
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Impact of reduced prion protein on zinc metabolism in sporadic Alzheimer's disease and ageing

1) ⇧ intracellular protein tyrosine phosphatase activity leading to neurotoxicity
2) ⇧ extracellular Zn promotes Aβ oligomer formation and neurotoxicity
3) ⇧ binding of Aβ oligomers to PrP^C further ⇩ zinc uptake

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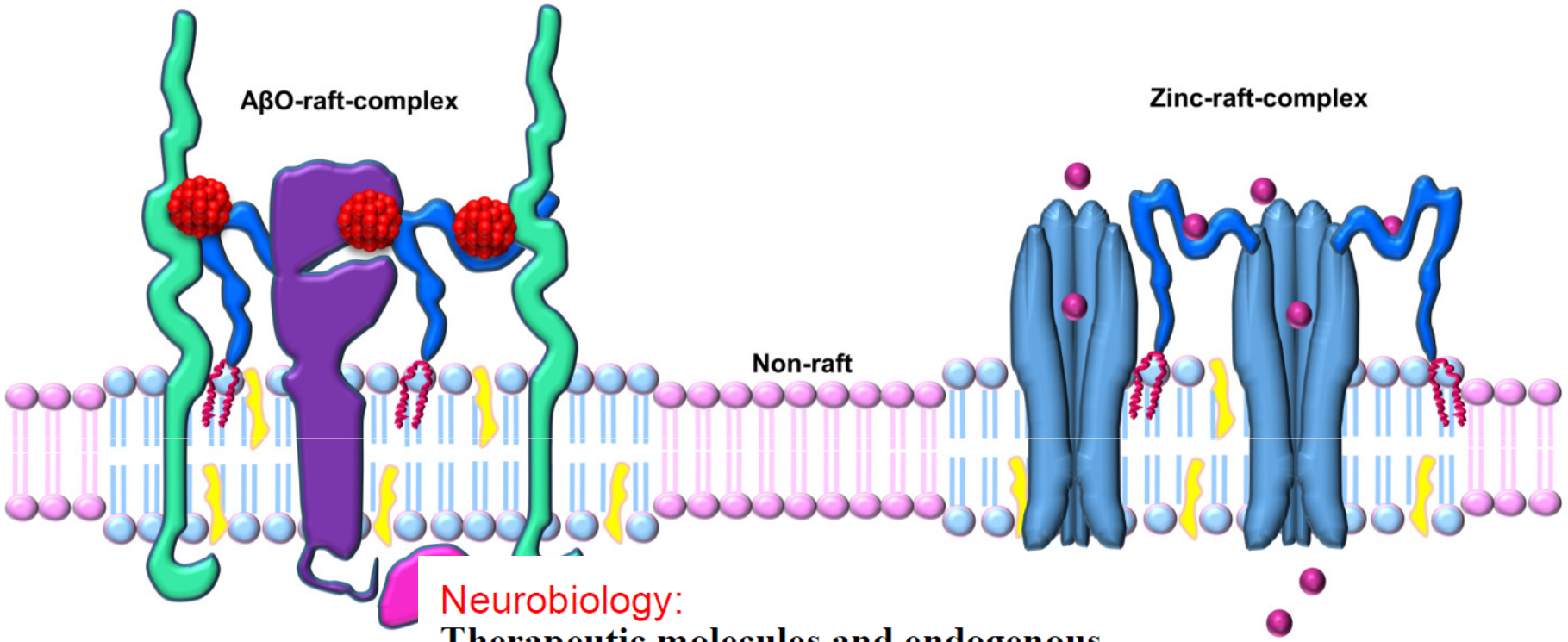
Prion protein in Alzheimer's disease - neuroprotective, neurotoxic or both!



Benilova & De Strooper (2010) EMBO Mol. Med. 2, 289

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PrP^C forms multiple cell surface, raft-based complexes



Neurobiology:

Therapeutic molecules and endogenous ligands regulate the interaction between brain cellular prion protein (PrP^C) and metabotropic glutamate receptor 5 (mGluR5)

Laura T. Haas, Mikhail A. Kostylev and Stephen M. Strittmatter

J. Biol. Chem. published online August 22, 2014

Watt et al. (2014) Frontiers Cell Develop. Biol. 2

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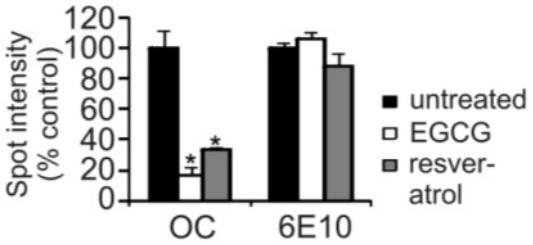
EGCG and resveratrol reduce the cellular binding of Aβ oligomers and their downstream cytotoxicity

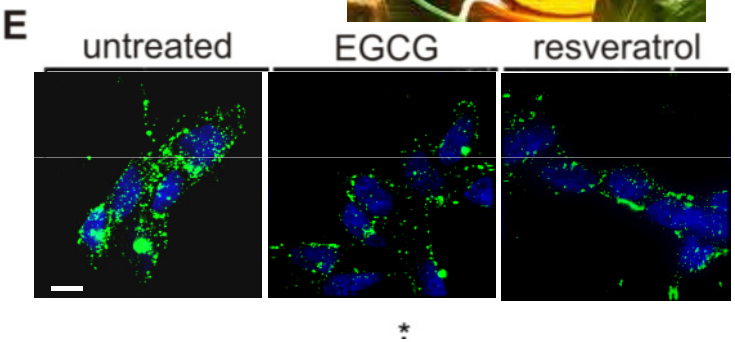
EGCG [(-)-epigallocatechin gallate]

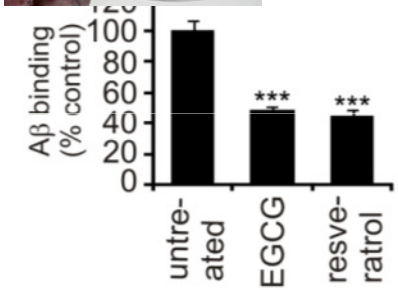


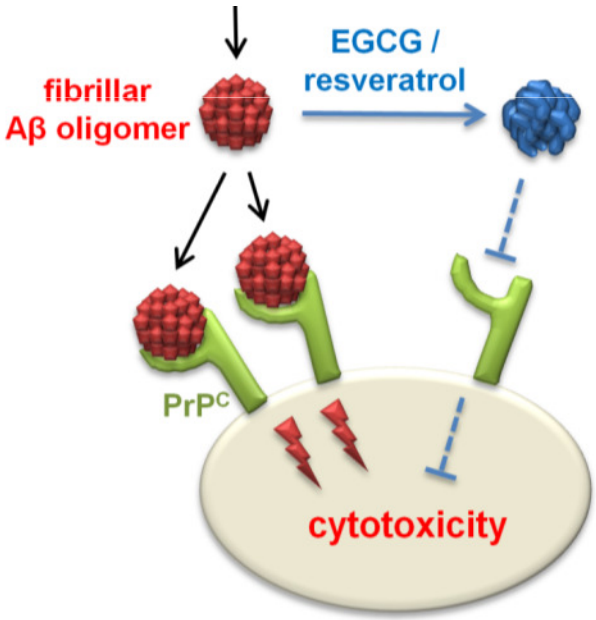
Resveratrol

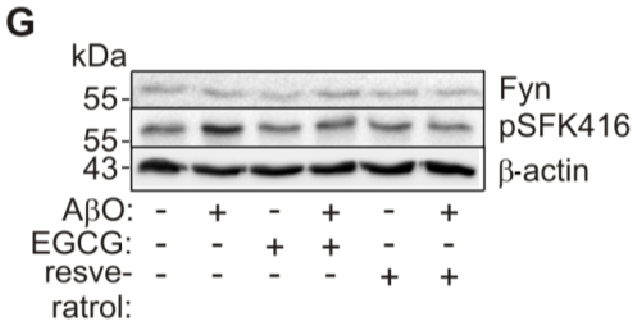


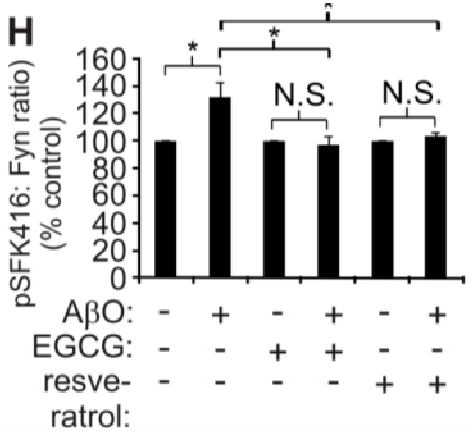










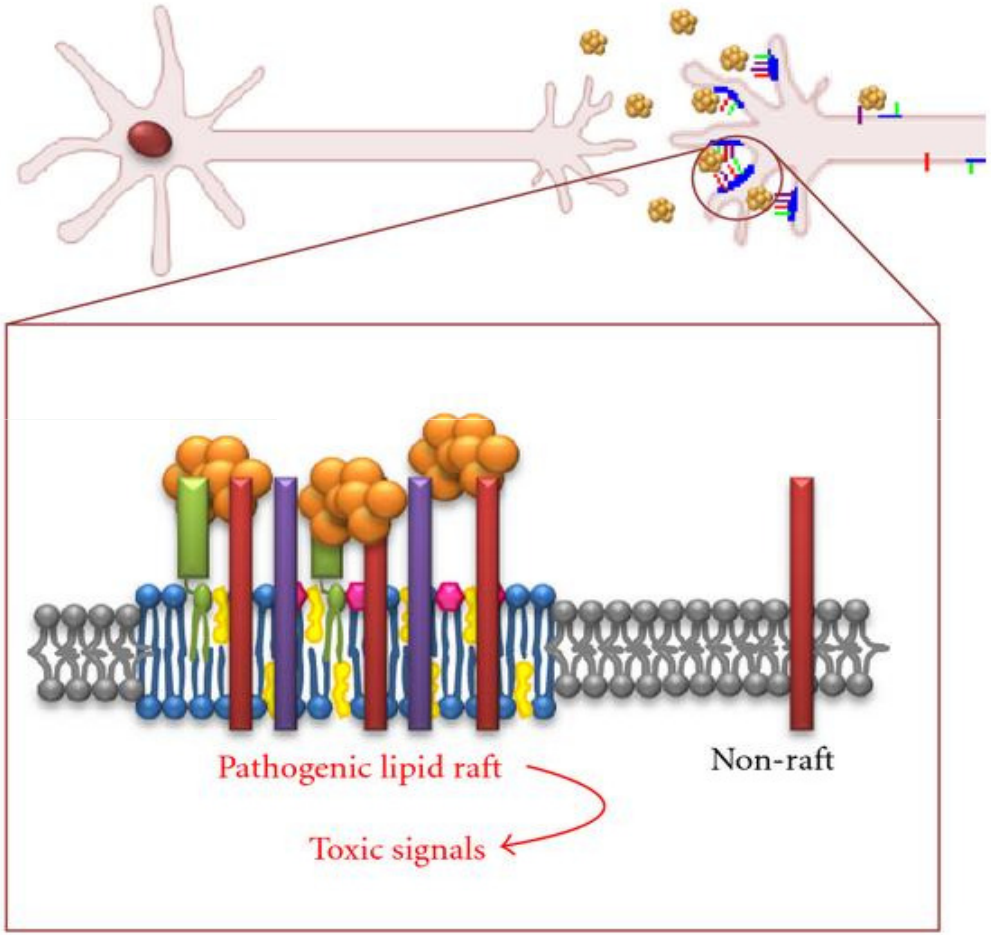


Rushworth et al. (2013) J. Biol. Chem. 288, 8935

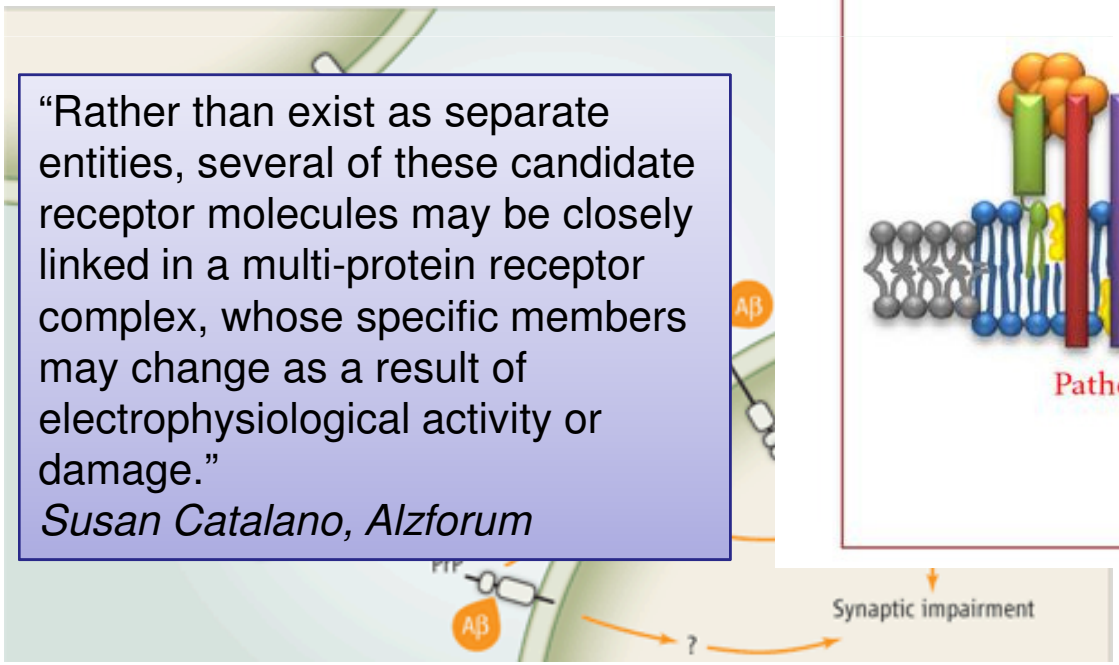
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Prion protein as a therapeutic target in Alzheimer's disease - issues to consider

- Targeting disease vs normal functions of PrP^C
- Receptors other than PrP^C
- Type ("strains") and concentration of Aβ oligomer



"Rather than exist as separate entities, several of these candidate receptor molecules may be closely linked in a multi-protein receptor complex, whose specific members may change as a result of electrophysiological activity or damage."
Susan Catalano, Alzforum



Benilova & DeStrooper (2013) Science 341, 1354

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Alzheimer's Research UK Defeating Dementia

Alzheimer's Society Leading the fight against dementia

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