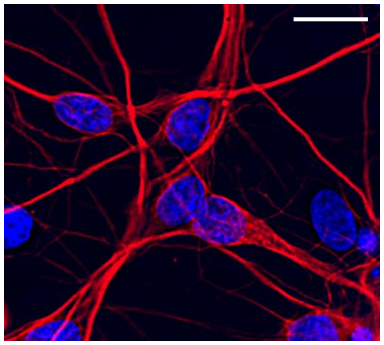
Challenges and opportunities for dementia research



Professor Nigel Hooper
Director of Dementia Research
Institute of Brain, Behaviour and Mental Health
Faculty of Medical and Human Sciences
University of Manchester

Hooper Lab
Our aim: to understand the basic biological processes underlying Alzheimer's disease so as to identify opportunities for intervention, and translate research into practice that improves quality of life.

@HooperLabManc

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Dementia

An umbrella term which describes a serious deterioration in mental functions, such as memory, language, orientation and judgement.

There are many different types of dementia

- **Alzheimer's disease**
- Vascular dementia
- Dementia with Lewy bodies
- Frontotemporal dementia
- Creutzfeldt-Jakob Disease

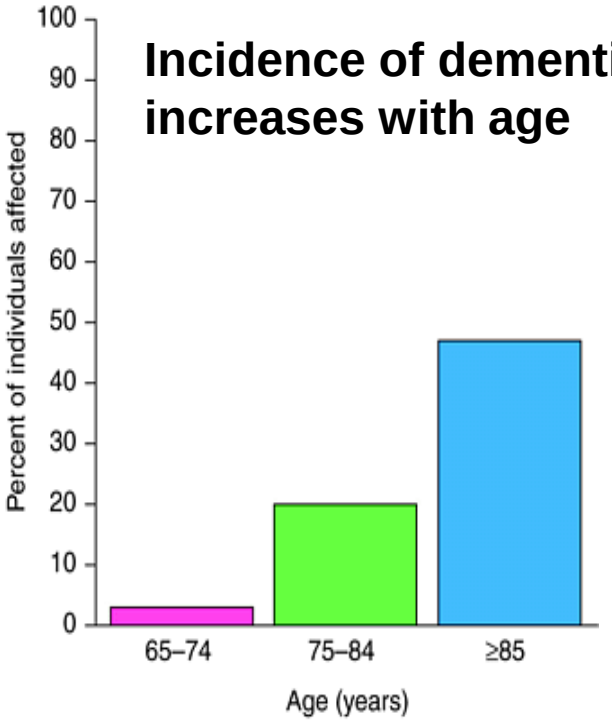
Other neurodegenerative diseases

- Parkinson's disease
- Huntington's disease
- Motor neuron disease (amyotrophic lateral sclerosis)

Dementia in the UK

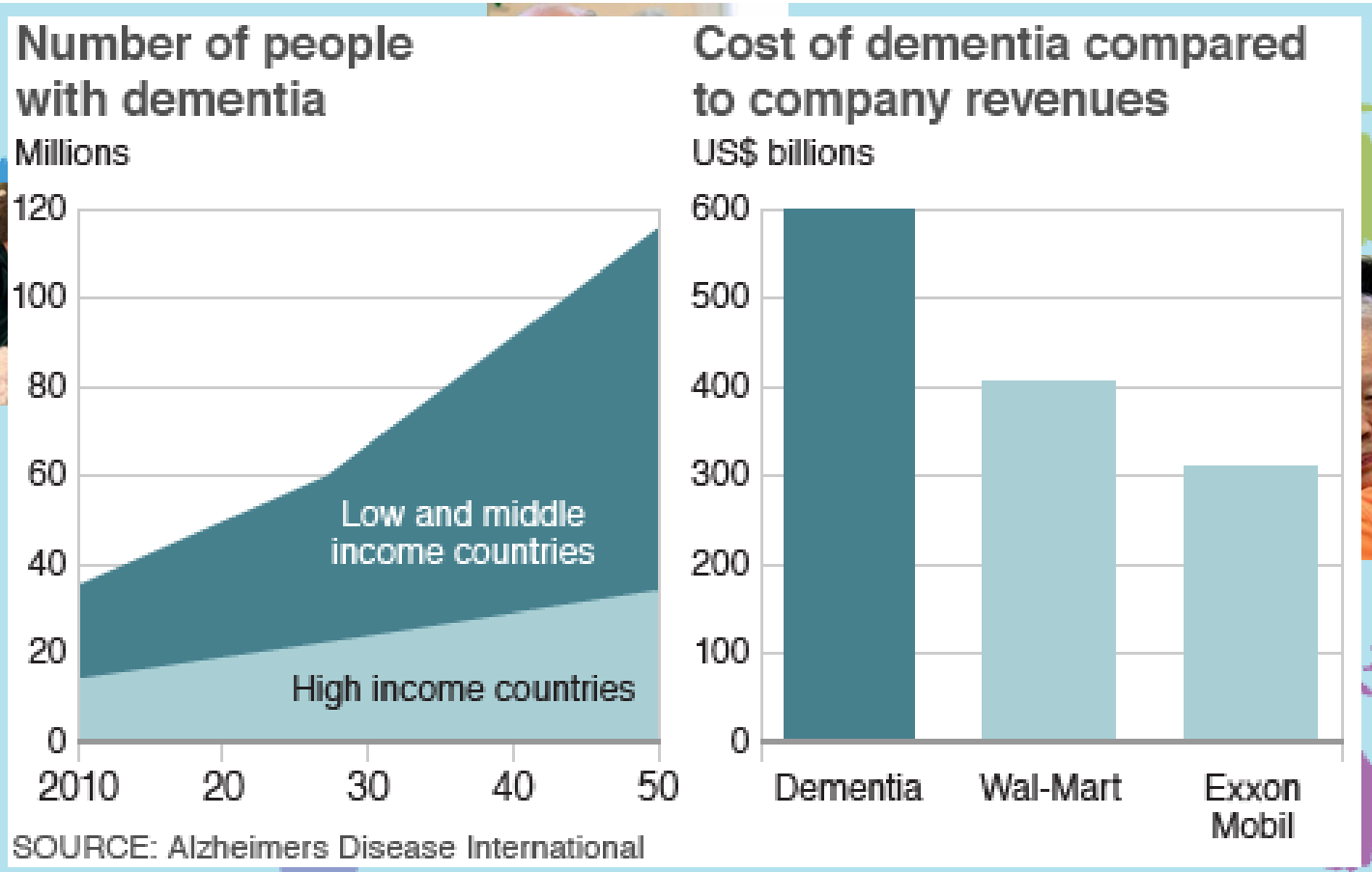
- >800,000 people currently live with dementia
- This number set to double in next 30 years
- 25 million people know a friend or family member with dementia
- Dementia costs the UK economy £23 billion each year (mainly social care costs & unpaid carers
- Highest rates of dementia in the North West (DoH)
- Dementia is the most feared condition amongst those over 50

Incidence of dementia increases with age



Number of people with dementia in minority ethnic groups could rise seven fold by 2051 and yet awareness and support is lacking http://www.alzheimers.org.uk/site/scripts/news_article.php?newsID=1659

Alzheimer's disease is a global problem

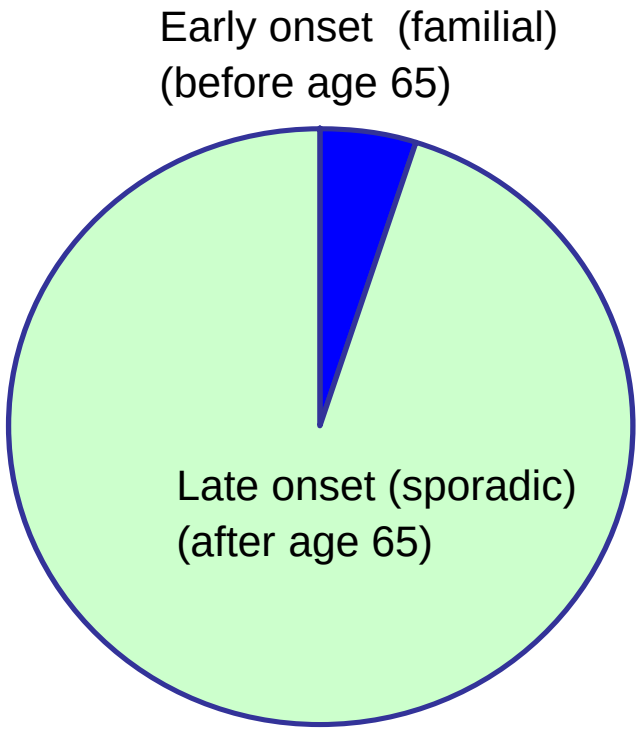


"Dementia poses the most significant health and social crisis of the century as its global financial burden continues to escalate."
The World Alzheimer Report (Sept 2010)

What causes Alzheimer's?

Risk factors:

- Alzheimer's in the family
- Old age
- Poor vascular health
- Trauma to the head
- Insulin resistance/diabetes
- Obesity



"What's good for the heart is good for the brain"

Current drugs for Alzheimer's disease

❖**Cholinesterase inhibitors**
Aricept (donepezil)
Exelon (rivastigmine)
Reminyl (galantamine)

❖**NMDA receptor antagonist**
Ebixa (memantime)

- Do not cure or halt the disease
- Temporarily relieve some of the symptoms

- Need disease modifying drugs

Current status of anti-Alzheimer's drugs

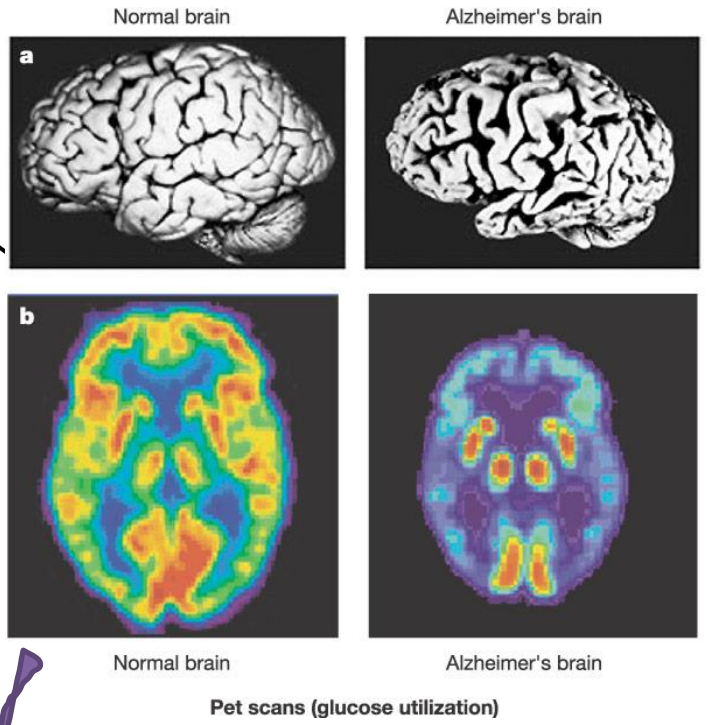
In the last 10 years no new drugs to treat Alzheimer's have come through clinical trials

It takes >10 years and $2billion to bring a new drug into clinical use.

- Are the experimental models appropriate?
- Are the clinical trials poorly designed?
- Do we need to target multiple sites?

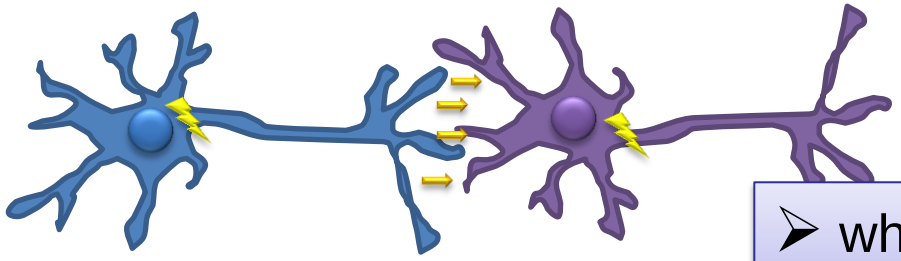
What happens in the brain in Alzheimer's disease?

- The part of the brain dealing with memory (hippocampus) usually affected first
- Reduced brain volume and metabolism
- Symptoms caused by connections between nerve cells degenerating and nerve cells dying.

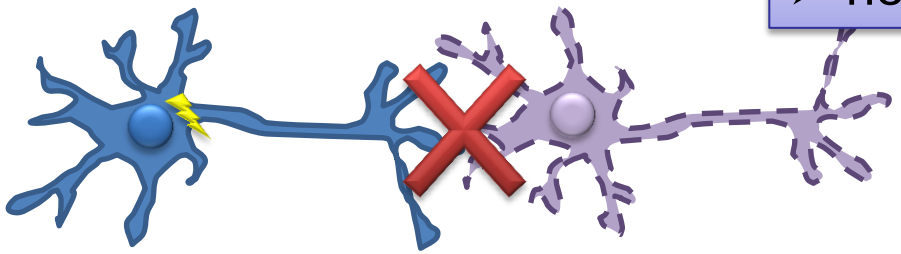


Pet scans (glucose utilization)

Healthy



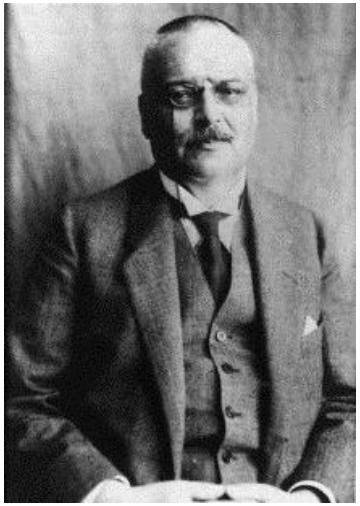
Alzheimer's



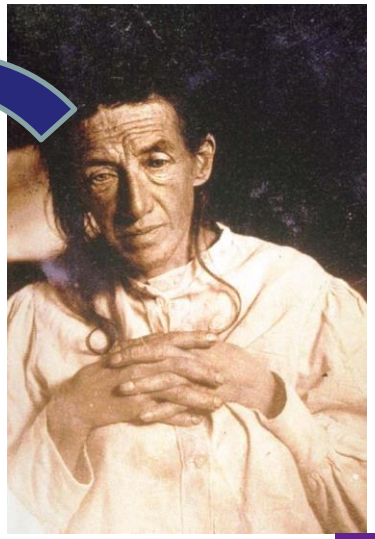
- what initiates this process?
- how can we stop it?

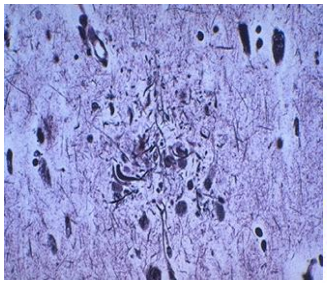
First account of Alzheimer's - 1907

Alois Alzheimer (1864-1915)
published account of 51 year old female

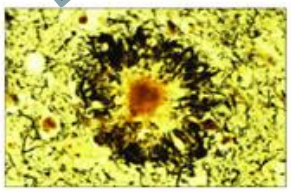


Auguste Deter
- suffered from strong feelings of jealousy towards husband, a banker
- increased memory impairment
- disorientation
- hallucinations
- loud & aggressive behaviour
- 4½ years later died

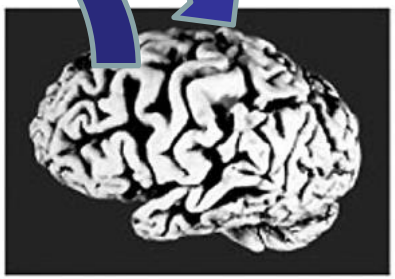




Tangles



Plaques



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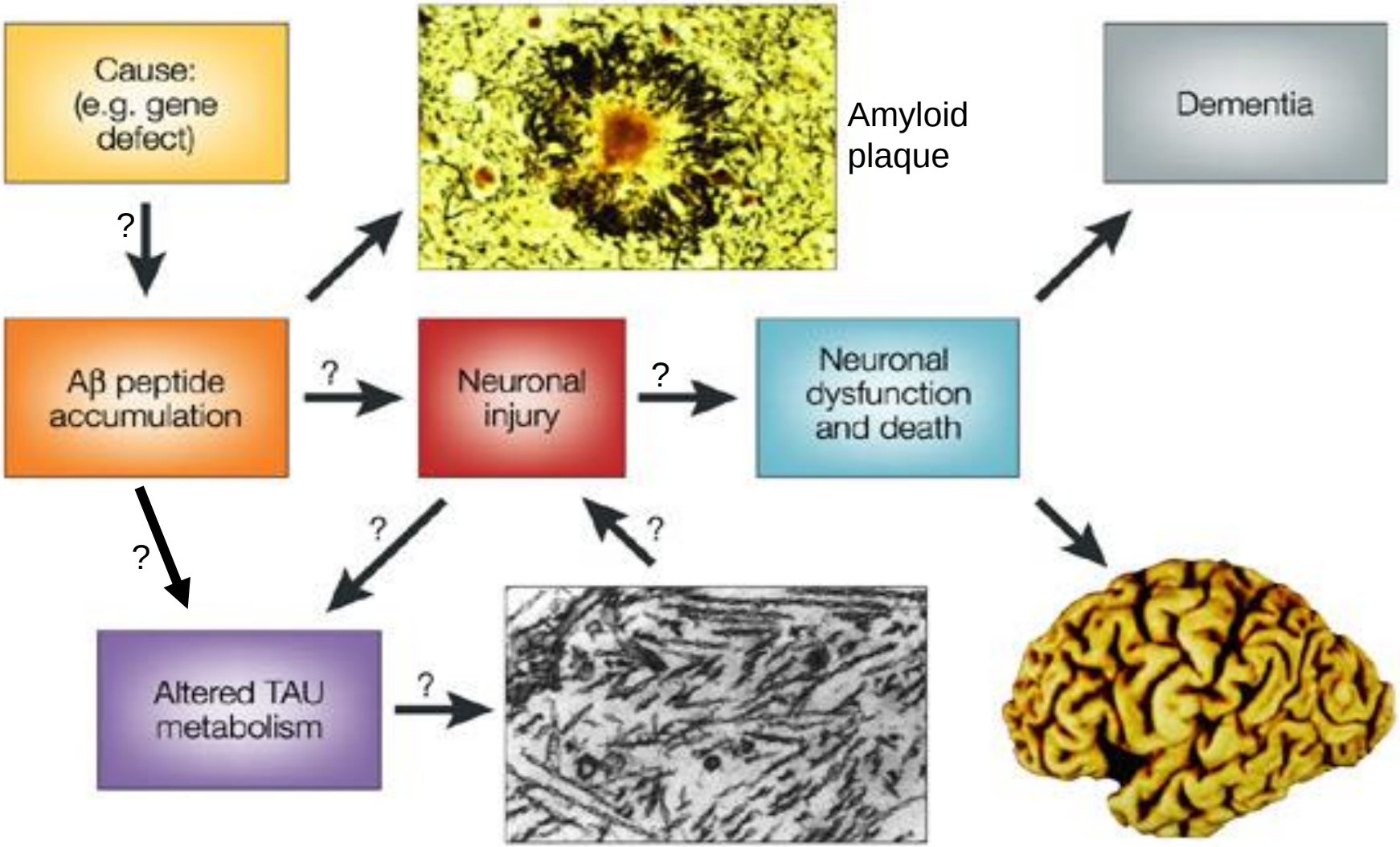
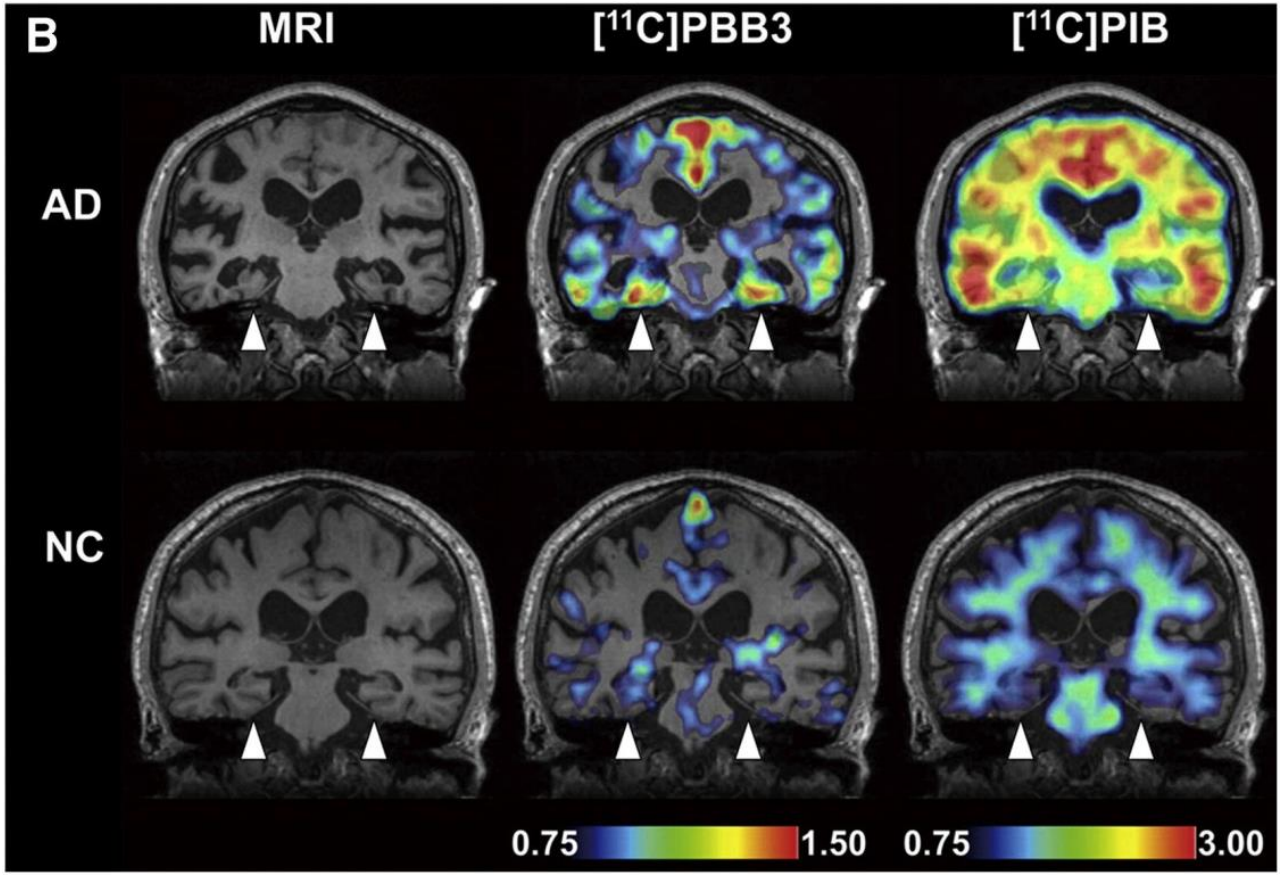
Alzheimer's disease – central role of amyloid (Aβ) and tau



Imaging amyloid plaques and tau tangles in the human brain

Positron emission tomography (PET)



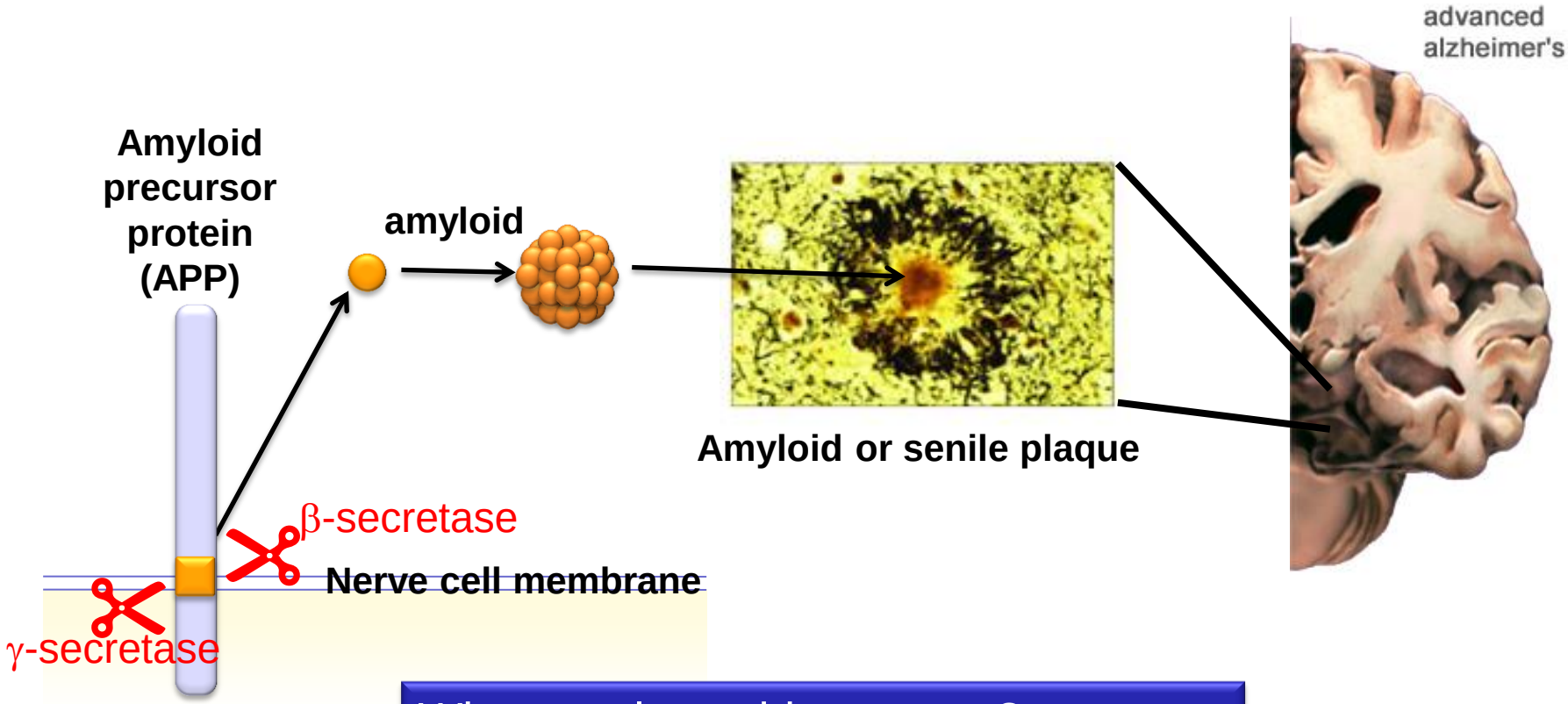
Pittsburgh compound B (PIB) binds to amyloid plaques

PBB3 binds to tau tangles

Maruyama et al. (2013) Neuron 79, 1094-1108

Amyloid plaques appear >15 years before clinical symptoms
http://www.nejm.org/doi/full/10.1056/NEJMoa1202753

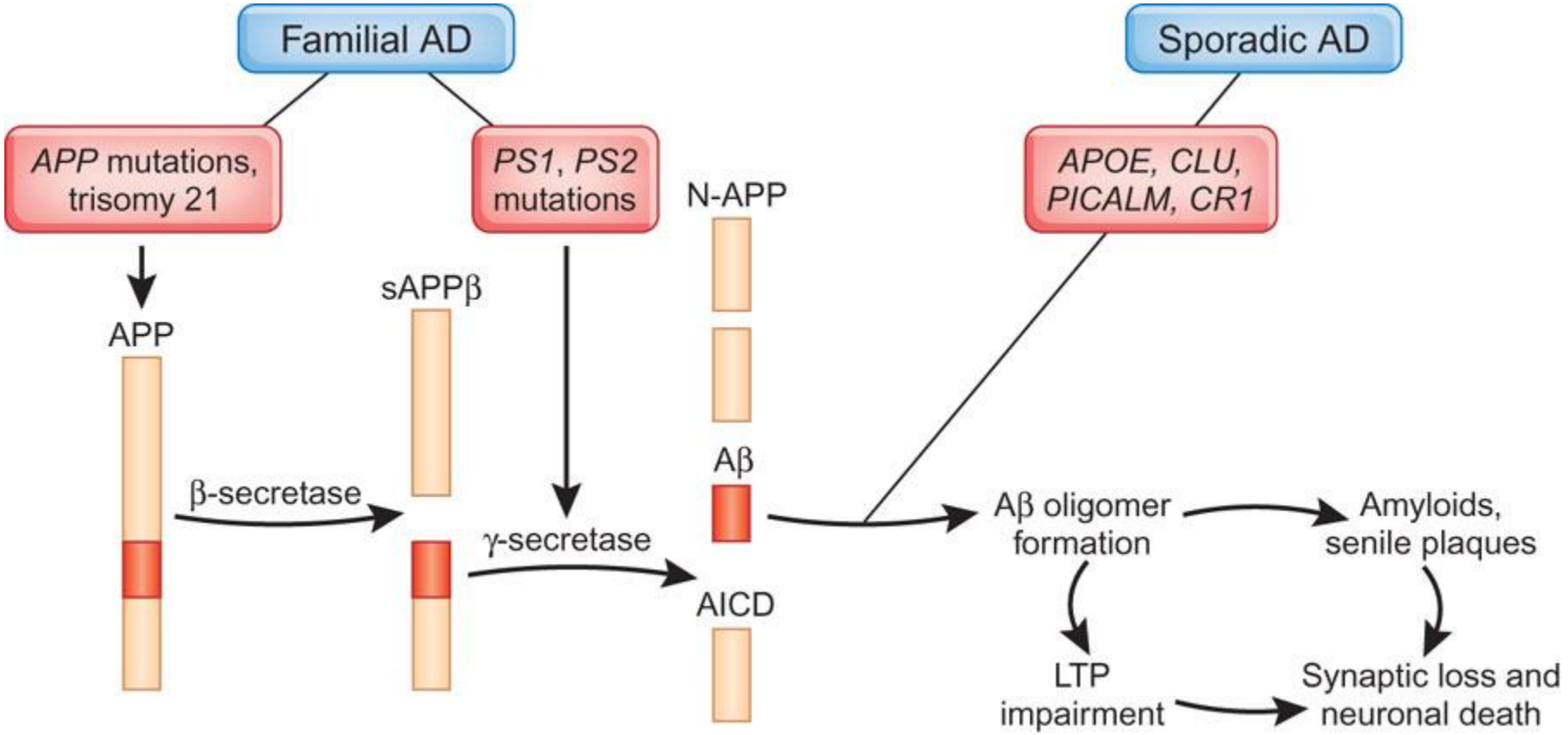
In Alzheimer's disease there is a build up of amyloid in the brain



What regulates this process?

Can we inhibit the build up of amyloid?

Genes that influence Alzheimer's disease



- Some 22 new genes recently found by genome-wide association studies (GWAS)

nature genetics

LETTERS

NATURE GENETICS VOLUME 43 | NUMBER 5 | MAY 2011 429

GWAS – Genome wide association studies

Require samples from thousands of individuals and involve 100s of researchers

Common variants at *ABCA7*, *MS4A6A/MS4A4E*, *EPHA1*, *CD33* and *CD2AP* are associated with Alzheimer's disease

Paul Hollingworth[1,110], Denise Harold[1,110], Rebecca Sims[1,110], Amy Gerrish[1,110], Jean-Charles Lambert[2–4,110], Minerva M Carrasquillo[5,110], Richard Abraham[1], Marian L Hamshere[1], Jaspreet Singh Pahwa[1], Valentina Moskvina[1], Kimberley Dowzell[1], Nicola Jones[1], Alexandra Stretton[1], Charlene Thomas[1], Alex Richards[1], Dobril Ivanov[1], Caroline Widdowson[1], Jade Chapman[1], Simon Lovestone[6,7], John Powell[7], Petroula Proitsi[7], Michelle K Lupton[7], Carol Brayne[8], David C Rubinsztein[9], Michael Gill[10], Brian Lawlor[10], Aoibhinn Lynch[10], Kristelle S Brown[11], Peter A Passmore[12], David Craig[12], Bernadette McGuinness[12], Stephen Todd[12], Clive Holmes[13], David Mann[14], A David Smith[15], Helen Beaumont[15], Donald Warden[15], Gordon Wilcock[16], Seth Love[17], Patrick G Kehoe[17], Nigel M Hooper[18], Emma R L C Vardy[14,18,19], John Hardy[20,21], Simon Mead[22], Nick C Fox[22], Martin Rossor[22], John Collinge[22], Wolfgang Maier[23,24], Frank Jessen[23], Eckart Rüther[24–26], Britta Schürmann[23,26], Reiner Heun[23,27], Heike Kölsch[23], Hendrik van den Bussche[28], Isabella Heuser[29], Johannes Kornhuber[30], Jens Wiltfang[31], Martin Dichgans[32,33], Lutz Frölich[34], Harald Hampel[35], John Gallacher[36], Michael Hüll[37], Dan Rujescu[37], Ina Giegling[36], Alison M Goate[38–40], John S K Kauwe[41], Carlos Cruchaga[38], Petra Nowotny[38], John C Morris[39], Kevin Mayo[38], Kristel Sleegers[42,43], Karolien Bettens[42,43], Sebastiaan Engelborghs[42,44], Peter P De Deyn[42,44], Christine Van Broeckhoven[42,43], Gill Livingston[45], Nicholas J Bass[45], Hugh Gurling[45], Andrew McQuillin[45], Rhian Gwilliam[46], Panagiotis Deloukas[46], Ammar Al-Chalabi[47], Christopher E Shaw[47], Magda Tsolaki[48], Andrew B Singleton[49], Rita Guerreiro[49], Thomas W Mühleisen[50,51], Markus M Nöthen[25,50,51], Susanne Moebus[52], Karl-Heinz Jöckel[52], Norman Klopp[53], H-Erich Wichmann[53–55], V Shane Pankratz[56], Sigrid B Sando[57,58], Jan O Aasly[57,58], Maria Barcikowska[59], Zbigniew K Wszolek[60], Dennis W Dickson[5], Neill R Graff-Radford[5,60], Ronald C Petersen[61,62], the Alzheimer's Disease Neuroimaging Initiative[63], Cornelia M van Duijn[64,65], Monique M B Breteler[64,65], M Arfan Ikram[64,65], Anita L DeStefano[66,67], Annette L Fitzpatrick[68], Oscar Lopez[69,70], Lenore J Launer[71], Sudha Seshadri[67,72], CHARGE consortium, Claudine Berr[73], Dominique Campion[74], Jacques Epelbaum[75], Jean-François Dartigues[76], Christophe Tzourio[77], Annick Alpérovitch[77], Mark Lathrop[78,79], EADI1 consortium, Thomas M Feulner[80], Patricia Friedrich[80], Caterina Riehle[80], Michael Krawczak[81–83], Stefan Schreiber[82,83], Manuel Mayhaus[80], S Nicolhaus[83], Stefan Wagenpfeil[84], Stacy Steinberg[85], Hreinn Stefansson[85], Kari Stefansson[86], Jon Snædal[87], Sigurbjörn Björnsson[87], Palmi V Jonsson[87], Vincent Chouraki[2–4], Benjamin Genier-Boley[2–4], Mikko Hiltunen[88], Hilkka Soininen[88], Onofre Combarros[89,90], Diana Zelenika[91], Marc Delepine[91], Maria J Bullido[90,92], Florence Pasquier[4,93], Ignacio Mateo[89,90], Ana Frank-Garcia[90,94], Elisa Porcellini[95], Olivier Hanon[96], Eliecer Coto[97], Victoria Alvarez[97], Paolo Bosco[98], Gabriele Siciliano[99], Michelangelo Mancuso[99], Francesco Panza[100], Vincenzo Solfrizzi[100], Benedetta Nacmias[101], Sandro Sorbi[101], Paola Bossù[102], Paola Piccardi[103], Beatrice Arosio[104], Giorgio Annoni[105], Davide Seripa[106], Alberto Pilotto[106], Elio Scarpini[107], Daniela Galimberti[107], Alexis Brice[108], Didier Hannequin[109], Federico Licastro[95], Lesley Jones[1], Peter A Holmans[1], Thorlakur Jonsson[85], Matthias Riemenschneider[80], Kevin Morgan[11], Steven G Younkin[5], Michael J Owen[1], Michael O'Donovan[1], Philippe Amouyel[2–4,92] & Julie Williams[1]

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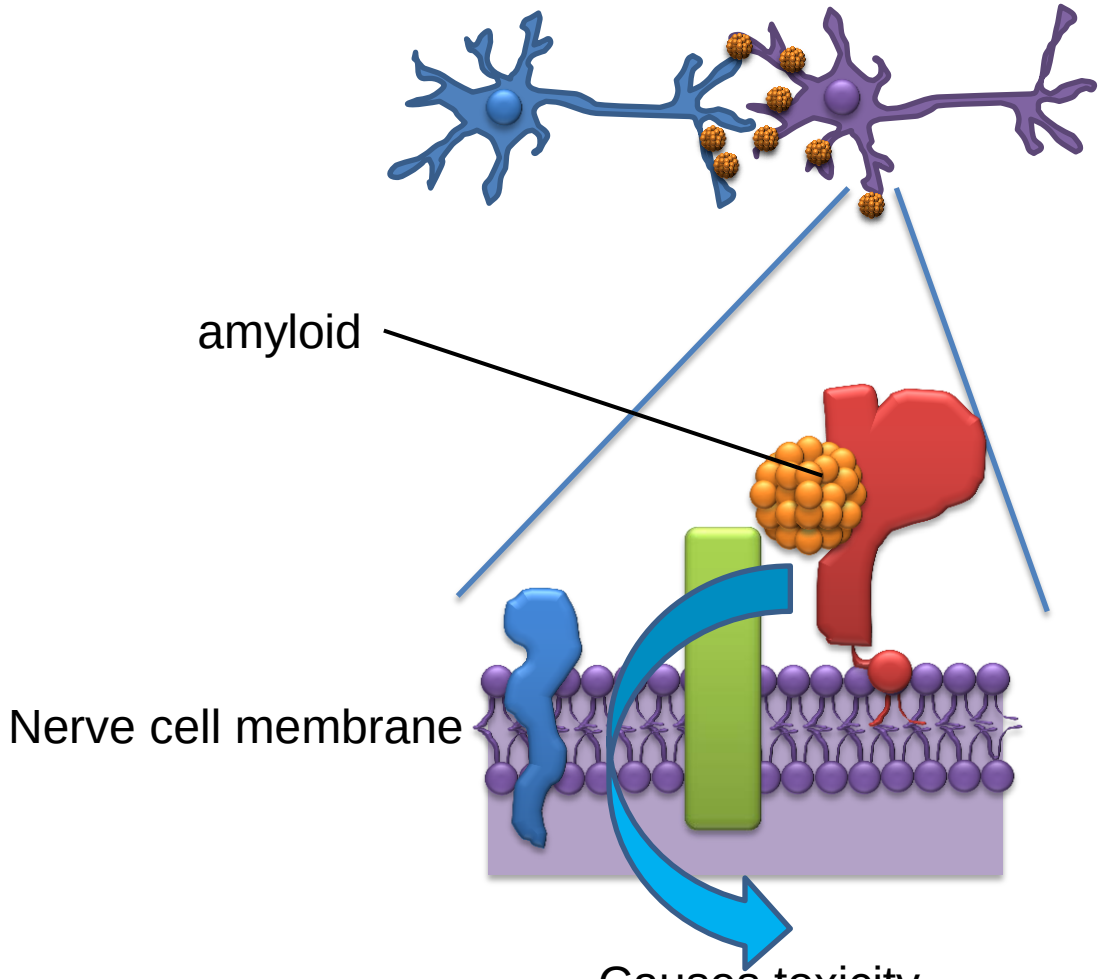
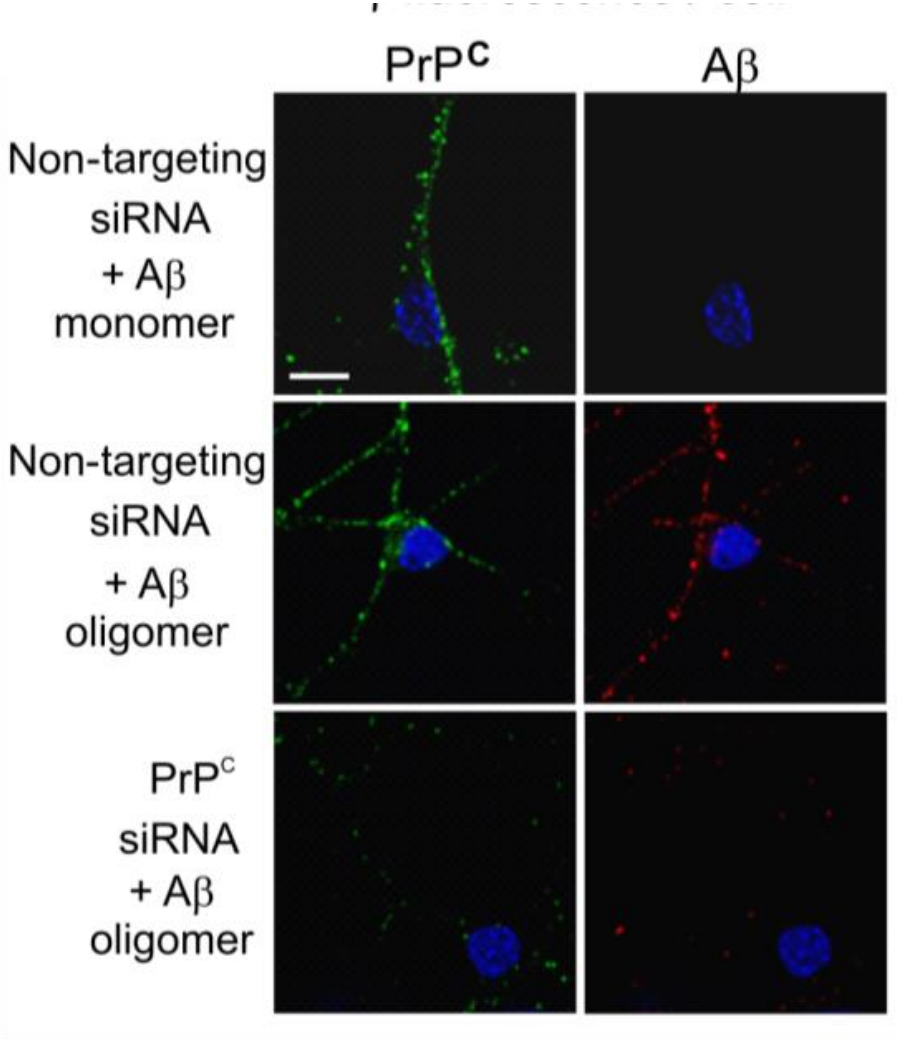
Amyloid sticks to specific proteins on the surface of nerve cells and causes damage



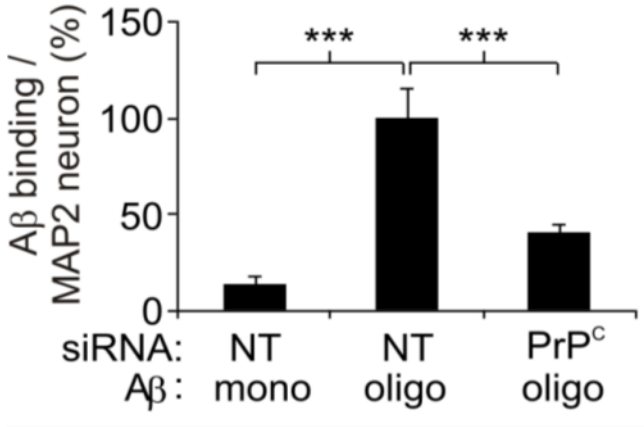
What receptors/signalling proteins are involved?

Can we disrupt these interactions?

Amyloid binds to prion protein (PrP^C) on the surface of neurons



Rat hippocampal neurons

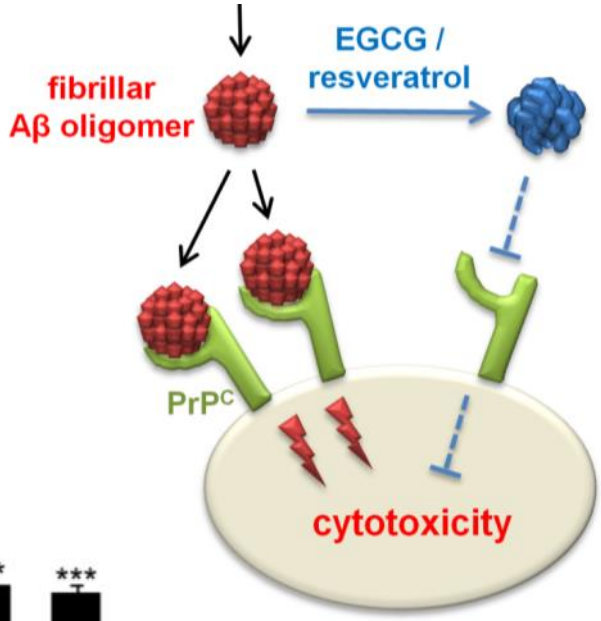


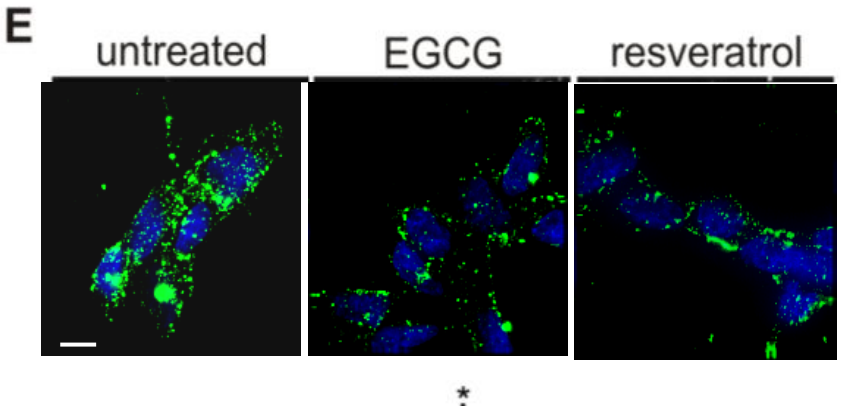
Rushworth et al. (2013) J Biol Chem 288, 8935

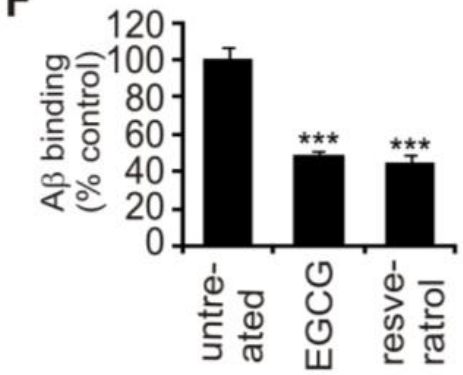
EGCG and resveratrol reduce the binding of amyloid to neurons

EGCG [(-)-epigallocatechin gallate]

Resveratrol







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

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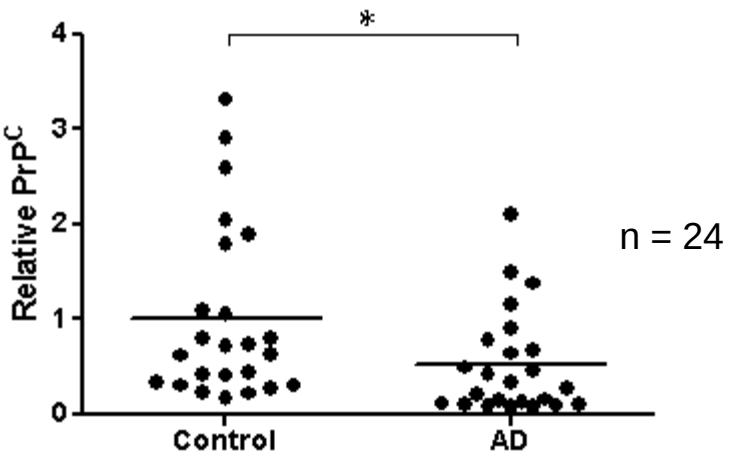
Prion protein is reduced in human brain and inversely correlates with amount of amyloid



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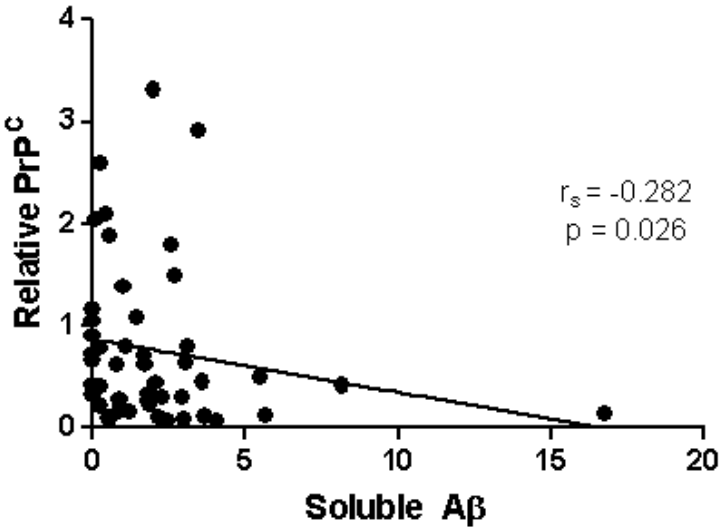

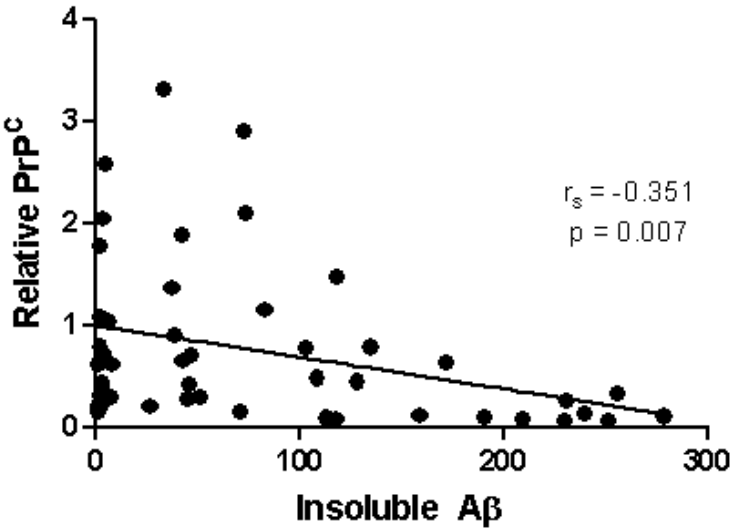

Whitehouse et al. (2013) PLoS ONE 8: e59554

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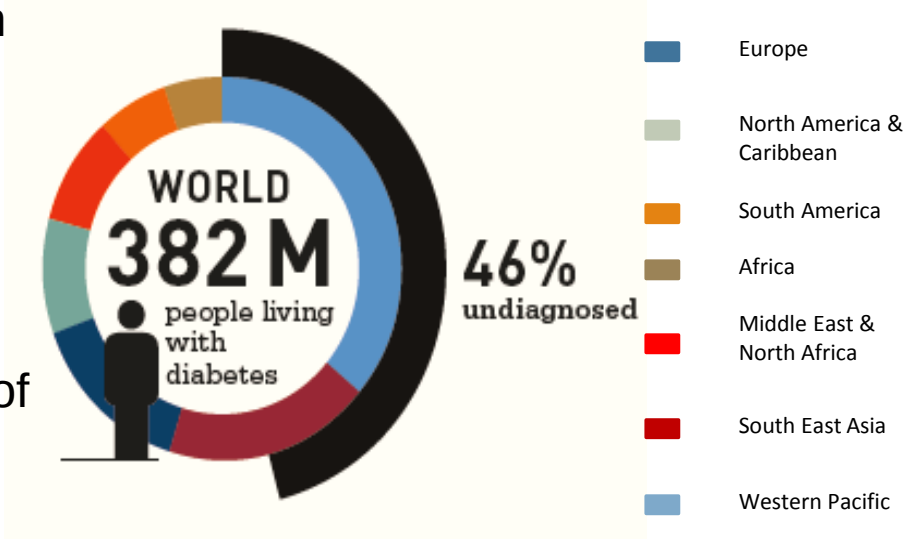
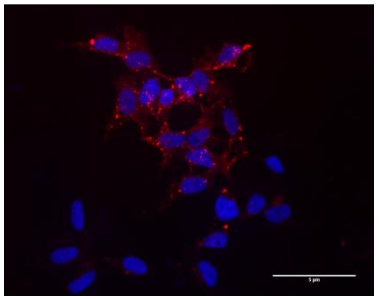
Diabetes and Alzheimer's disease: a link?

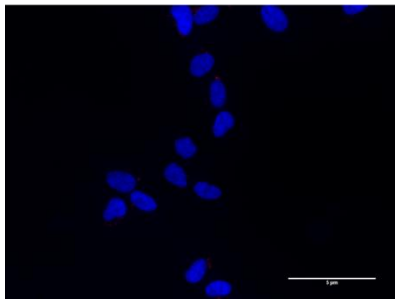
- Death of pancreatic β-cells coupled with amylin fibril formation
- Amylin present in brain with amyloid-β
- Amylin and amyloid-β have similar properties
- Small drug that blocks the toxic effects of both amylin and amyloid-β
- Potential treatment for diabetes and Alzheimer's?

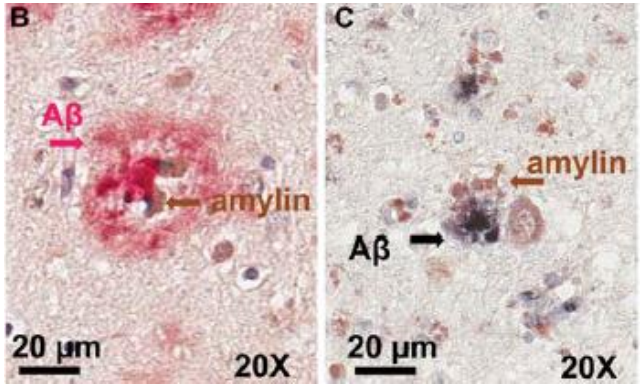


Amyloid



Amyloid + drug





Jackson et al. 2013

Ben Allsop, Garth Cooper, Richard Unwin

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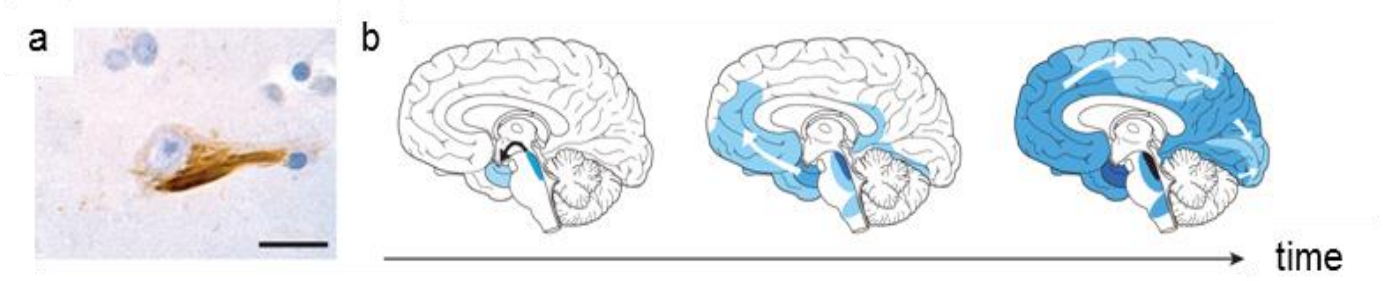
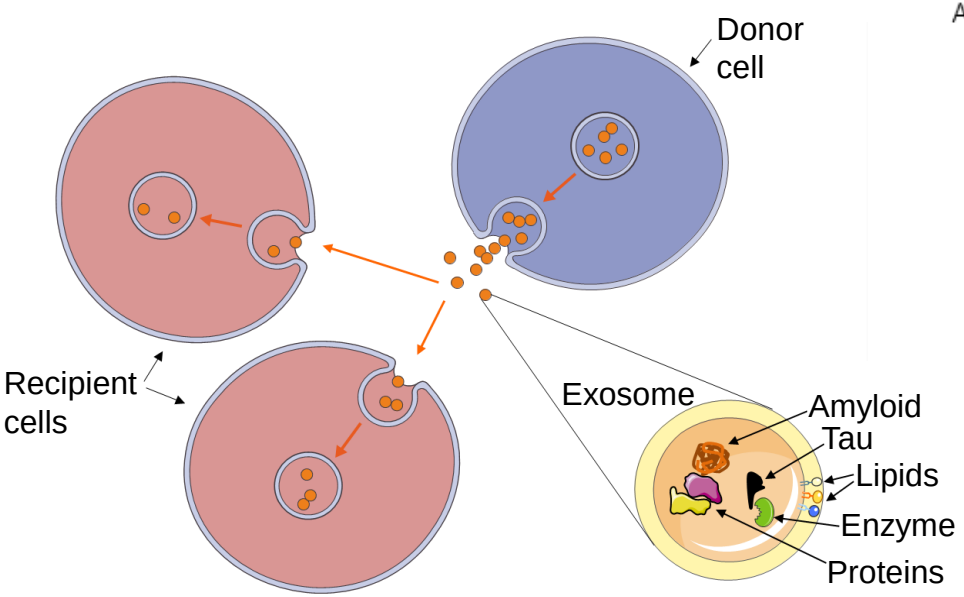
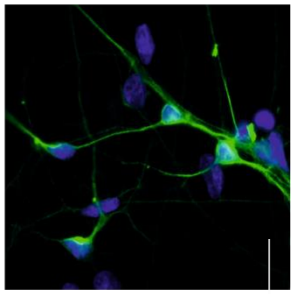
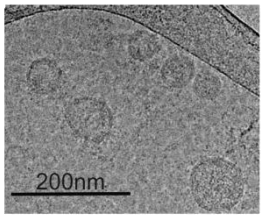
Exosomes: targeting the spread of Alzheimer's disease

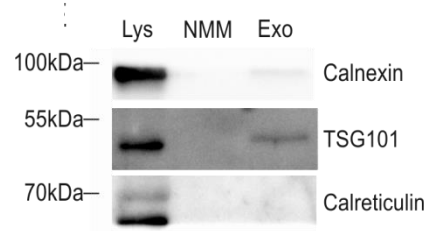


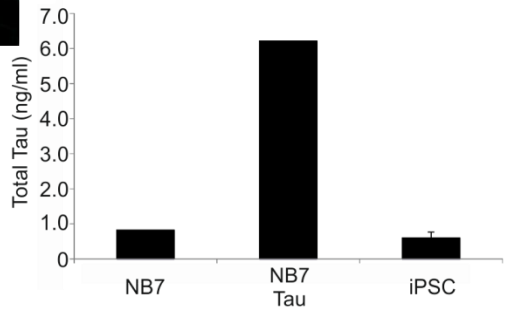
Adapted from Jucker & Walker *Nature* **501**, 45-51 (2013)











- Exosomes (membrane carriers) transfer tau from neuron to neuron
- Can we intervene in this process to prevent the development of disease?

Kate Kellett

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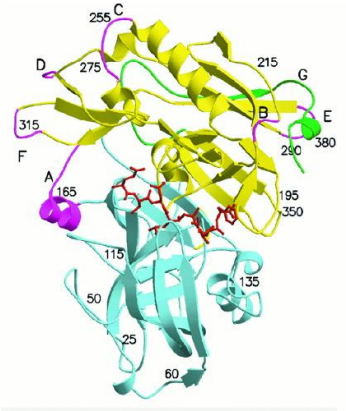
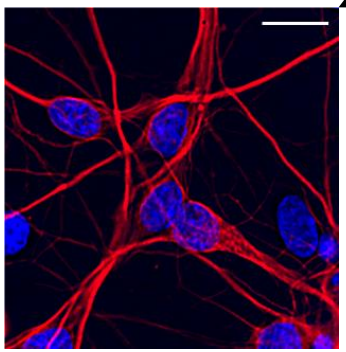
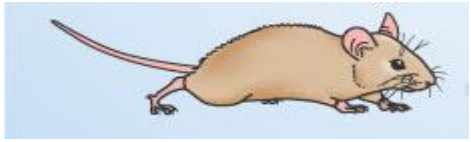
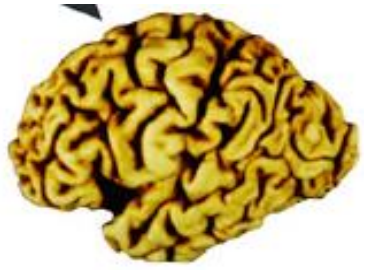
Our multi-experimental approach to tackle Alzheimer's disease





induced pluripotent stem cells (iPSCs)





Molecules ⟷ **Cells** ⟷ **Animal models** ⟷ **Humans**

- Genes
- Proteins
- Lipids

- Immortalised human cells
- Rodent neurons

- Wild type rats
- Transgenic mice
- Transgenic rats

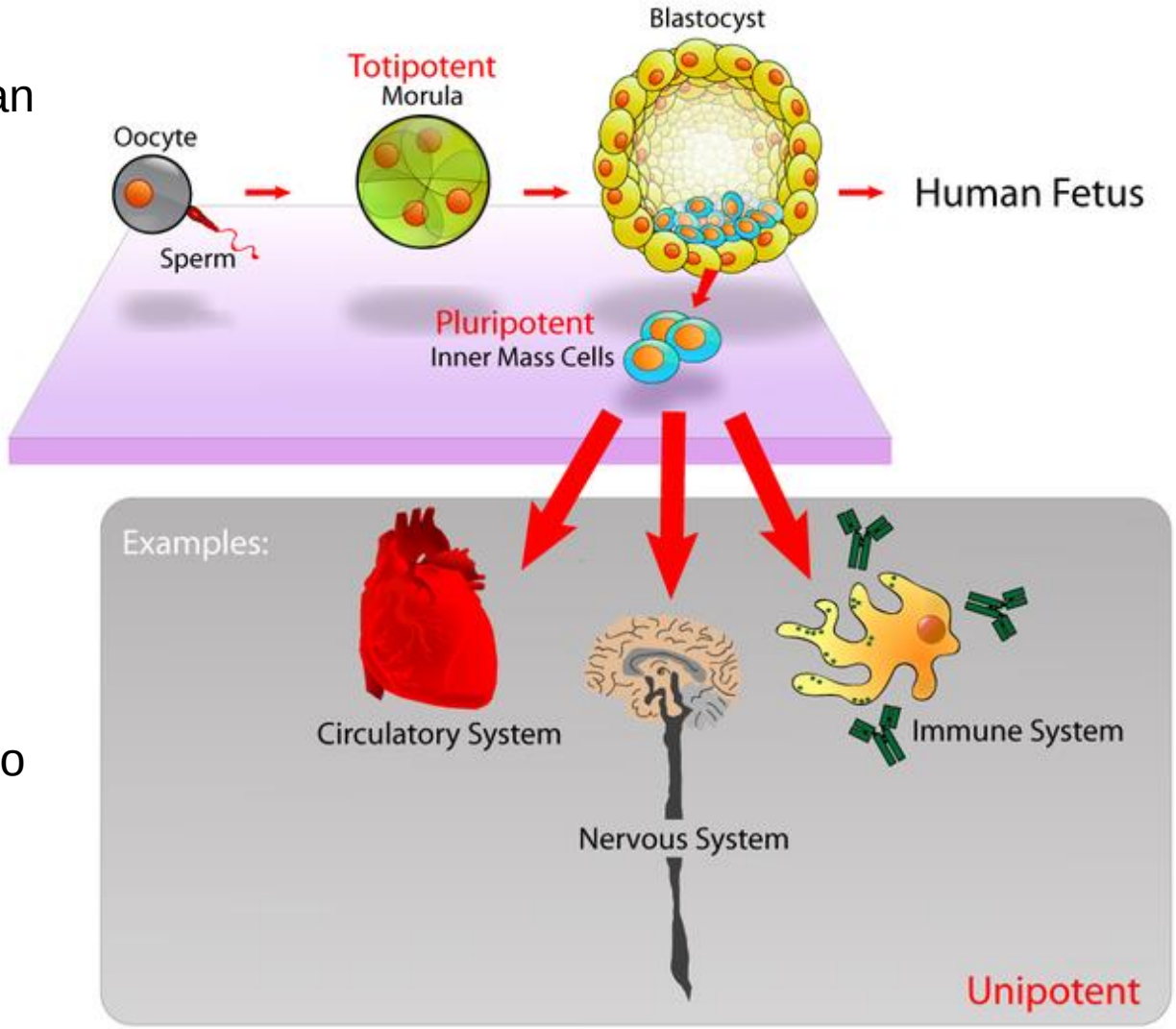
- Brain tissue
- CSF/plasma
- Brain imaging

Stem cells

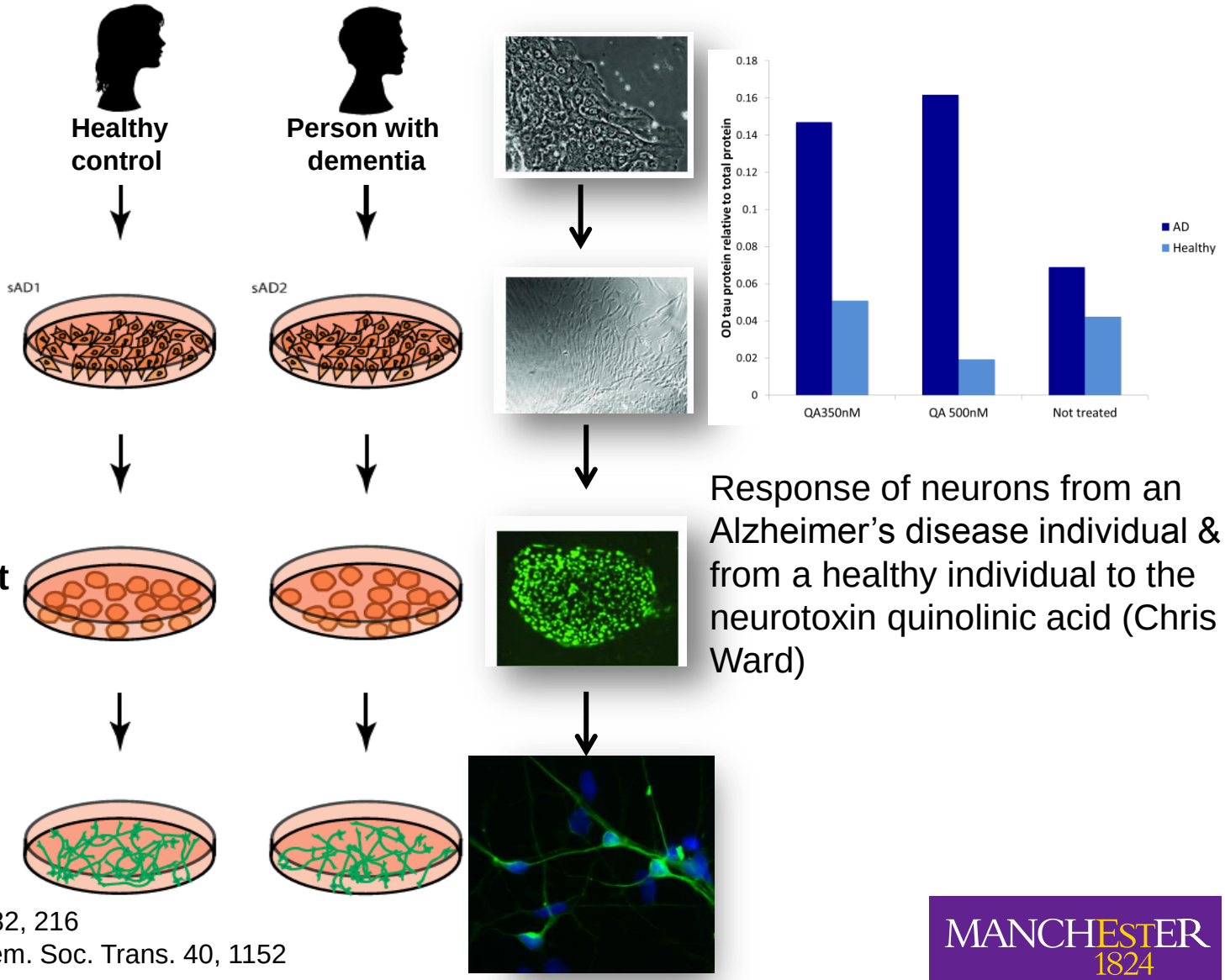
- Undifferentiated cells that can differentiate into specialized cells and divide to produce more stem cells

- Embryonic stem cells
- Adult stem cells

Induced pluripotent stem cells (iPSCs)
- adult cells (e.g. epithelial cells) can be reprogrammed to give rise to pluripotent capabilities



“Dementia-in-a-dish”



Response of neurons from an Alzheimer’s disease individual & from a healthy individual to the neurotoxin quinolinic acid (Chris Ward)

Israel et al. (2012) Nature 482, 216
Hartfield et al. (2012) Biochem. Soc. Trans. 40, 1152

Kate Kellett, Alys Jones

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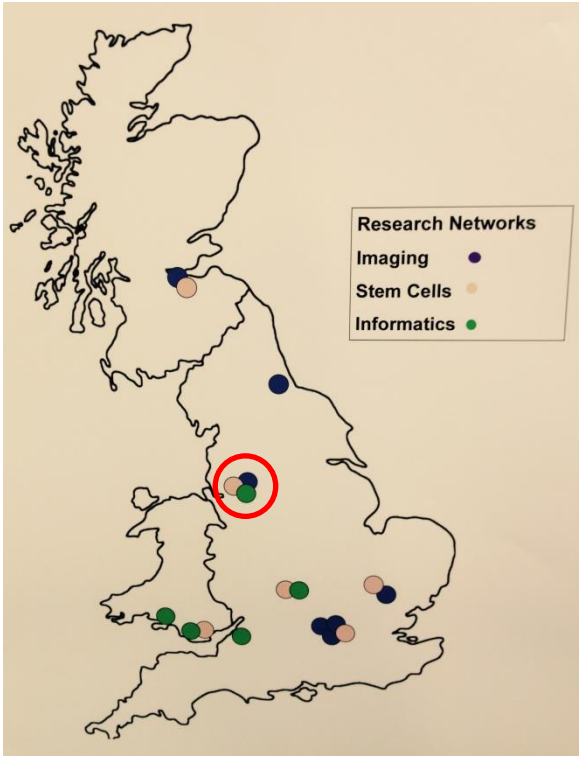
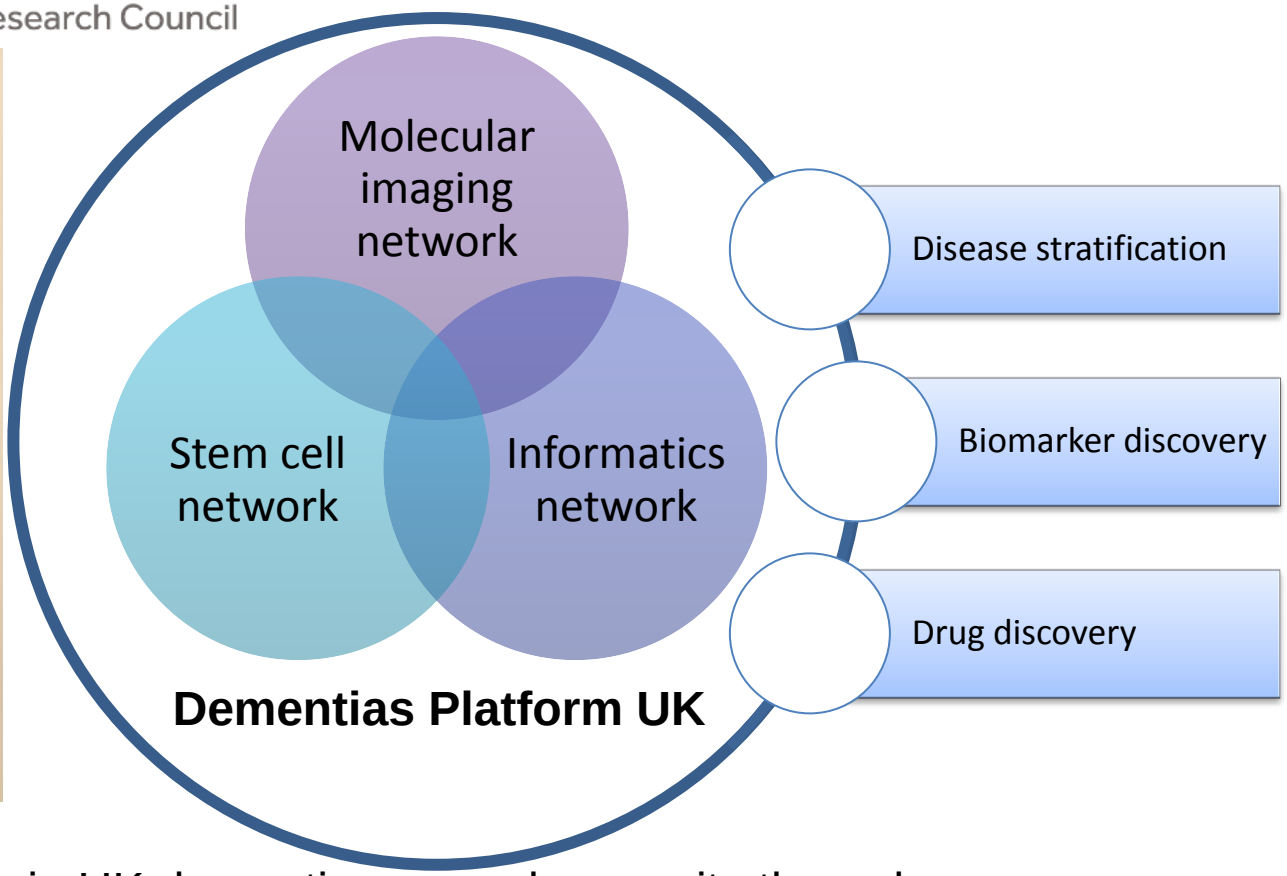
Dementias Platform UK
Medical Research Council





"to achieve a step-change in UK dementia research capacity through establishing national networks of existing and emerging centres of excellence in imaging (PET/MR), informatics and cell biology"

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Dementia@Manchester network

Professor Nigel Hooper, Director of Dementia Research

Dementia@Manchester aims to:

- contribute significantly to understanding neurodegenerative mechanisms;
- identify potential treatments for, and evidence for prevention of, dementia;
- discover and inform on how to live well with dementia at an individual, family and society level.

http://www.dementia.manchester.ac.uk/

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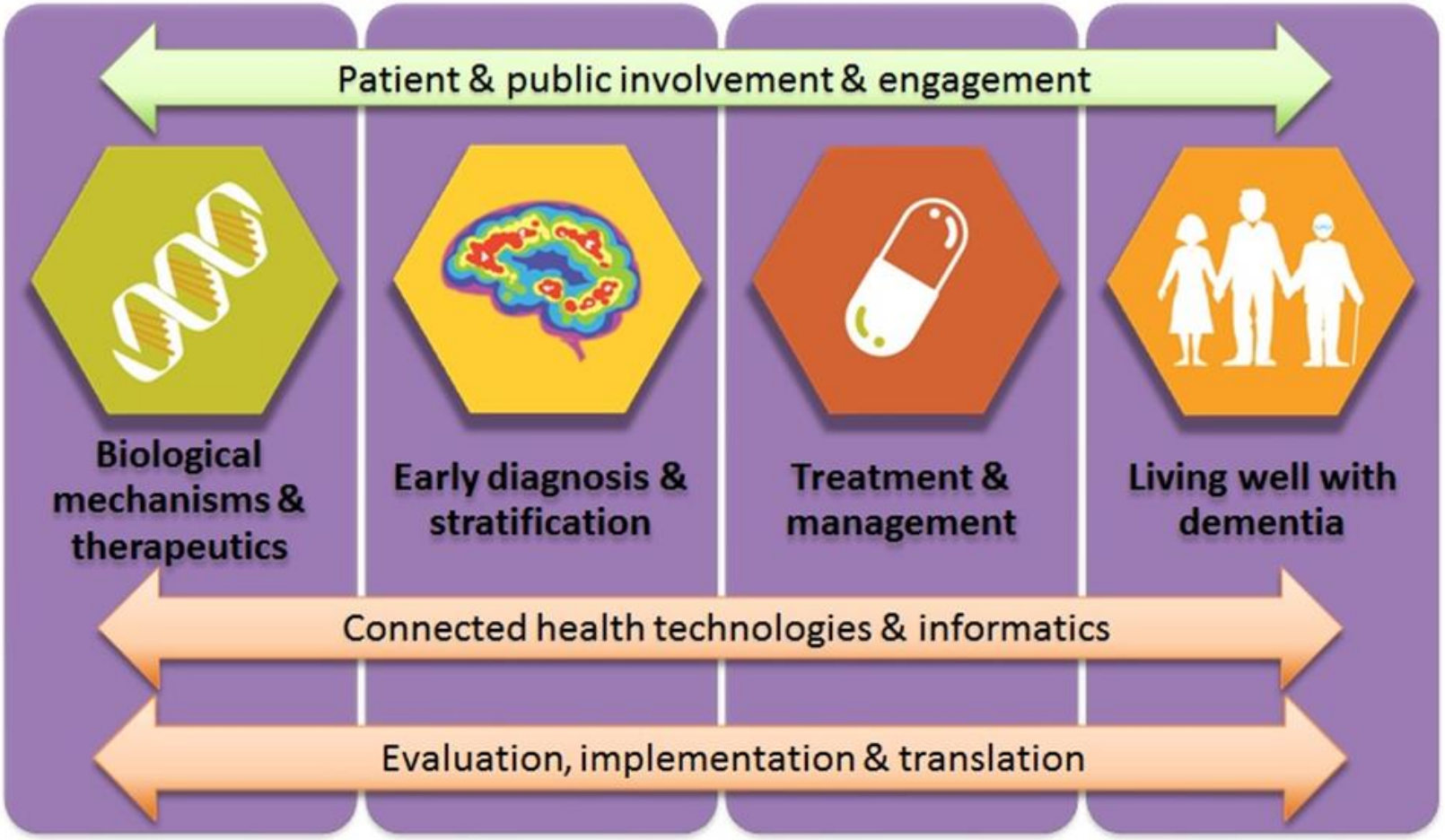
Dementia@Manchester



- bringing forward real benefits to people living with dementia

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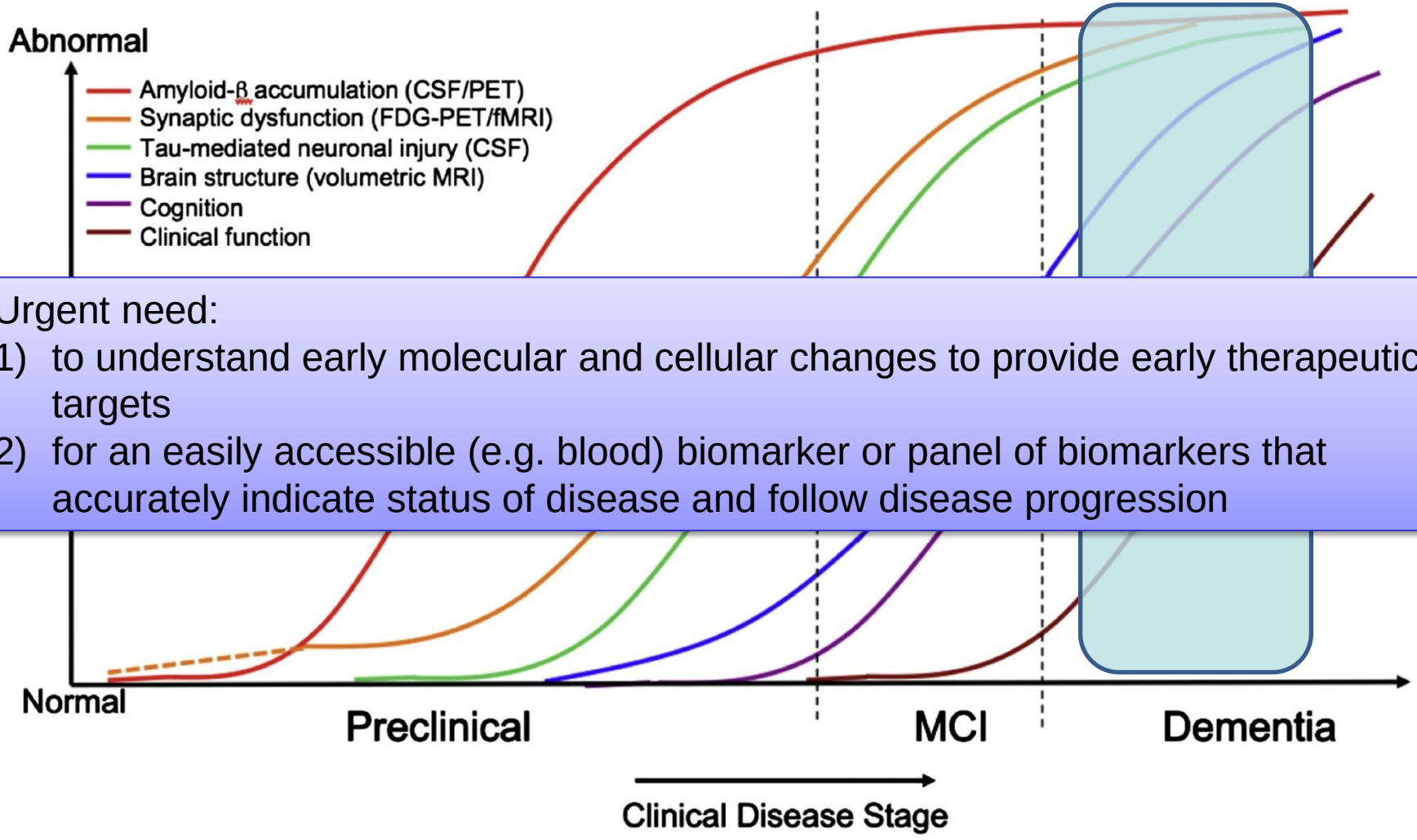
When is the ideal time to intervene in Alzheimer's disease?

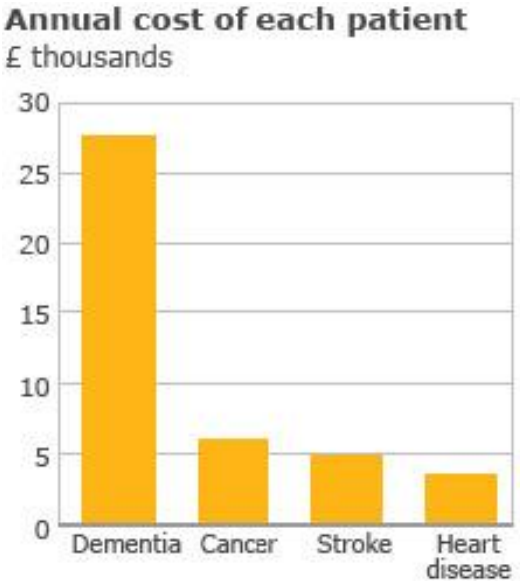


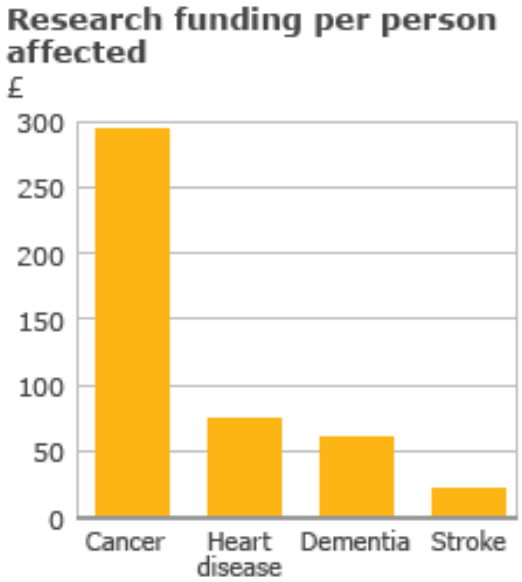
Urgent need:

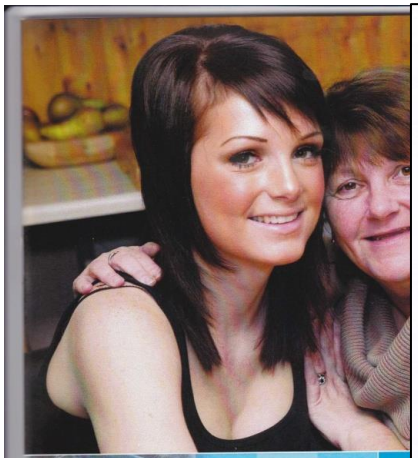
1) to understand early molecular and cellular changes to provide early therapeutic targets
2) for an easily accessible (e.g. blood) biomarker or panel of biomarkers that accurately indicate status of disease and follow disease progression

Sperling et al. (2011) Alz. & Dem. 7, 280-292
Sperling et al. (2011) ScienceTranslationalMedicine 3, 1-5

Research funding on dementia







The Prime Minister

requests the pleasure of the company of

Professor Nigel Hooper

at a reception to mark the publication of the first progress report on his challenge on dementia
at 10 Downing Street, Thursday 8th November, from 12.15pm to 2.15pm

An answer is requested to:
Events Office
10 Downing Street
London, SW1A 2AA
email: rsvp1@no10.x.gsi.gov.uk

1. Creating unities
2. Driving i care
3. Better re

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How you can get involved in dementia research

BRAINS FOR DEMENTIA RESEARCH

Increasing knowledge - Finding a cure

A partnership between Alzheimer's Research UK and Alzheimer's Society
In association with the Medical Research Council

http://www.brainsfordementiaresearch.org.uk/

Alzheimer's Research UK

The Power to Defeat Dementia

Alzheimer's Society

Leading the fight against dementia

Join dementia research

https://www.joindementiaresearch.nihr.ac.uk/

age UK

Love later life

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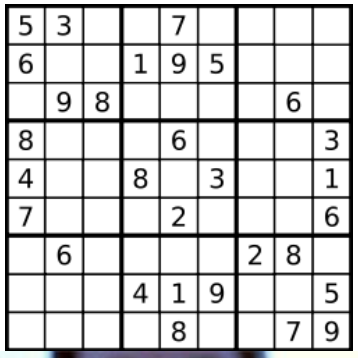
Possible protective factors for Alzheimer's disease



- Education & occupation
- Use it or lose it
- Regular exercise (e.g. ballroom dancing, walking)
- Social networks
- Not smoking
- Not drinking to excess
- Keep blood pressure & cholesterol in check
- Balanced diet (Mediterranean-style diet, anti-oxidants - curcumin, blueberries, cocoa, red wine, oily fish)

Acknowledgements

Hooper Lab

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Beth Noble
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Mike Harte & John Gigg
Cath Lawrence
Anna Nicolaou
Fernando Ortega
Stuart Pickering-Brown
Tao Wang
Chris Ward
Tony Whetton

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MRC Medical Research Council

Alzheimer's Research UK
The Power to Defeat Dementia

Alzheimer's Society
Leading the fight against dementia

Dr Donald Dean Fund in Dementia Research

BBSRC
bioscience for the future

Engaging with dementia
http://www.fbs.leeds.ac.uk/blogs/dementia/