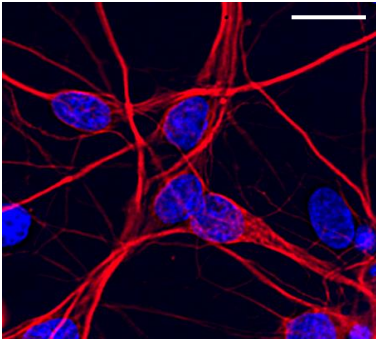


Challenges and opportunities for dementia research



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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.



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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

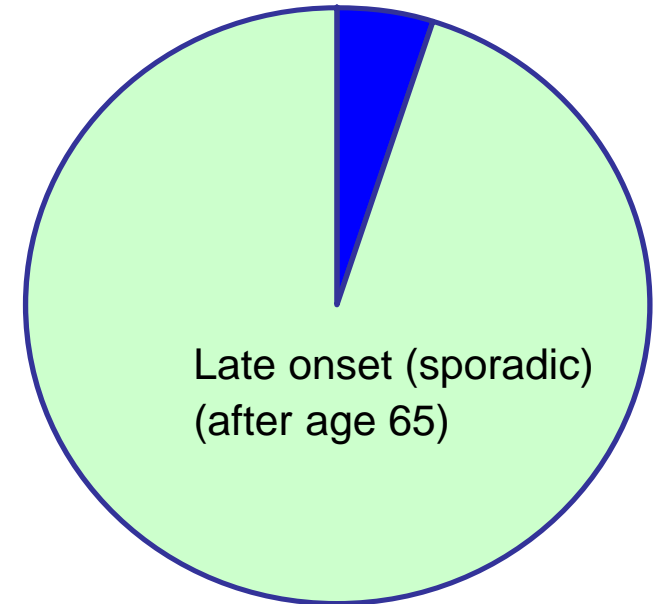
- Parkinson's disease
- Huntington's disease
- Motor neuron disease (amyotrophic lateral sclerosis)

What causes Alzheimer's?

Risk factors:

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

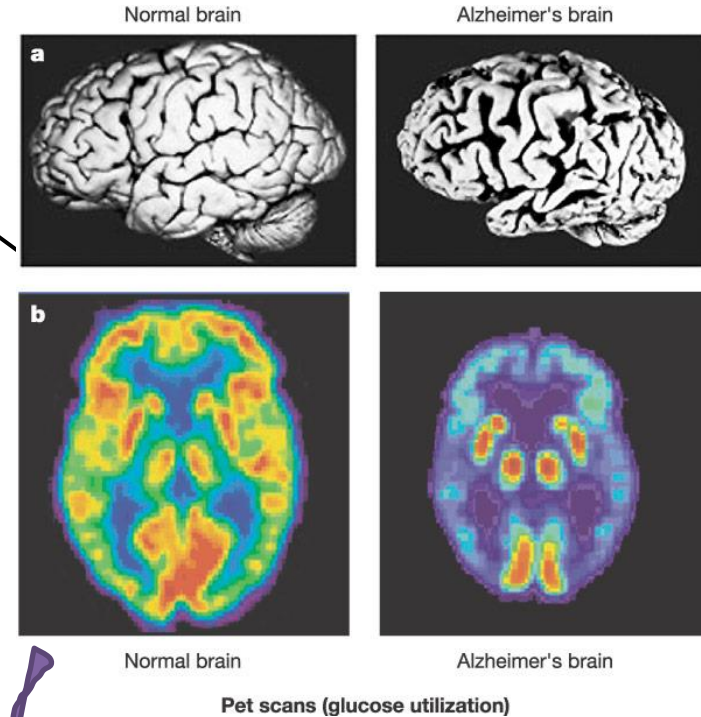
Early onset (familial)
(before age 65)



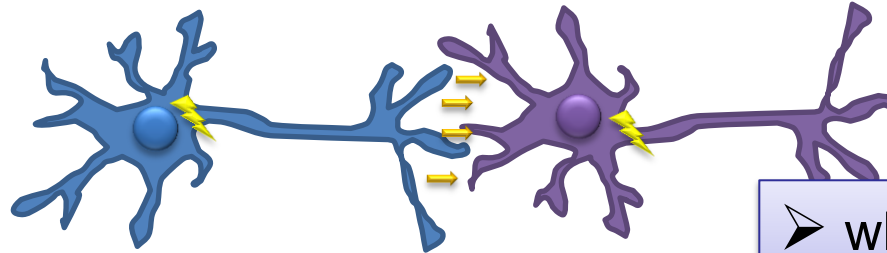
Queen's 100th birthday telegrams:
1917 – 24 (King George V)
1952 – 255
2011 – 9,736
(www.royal.gov.uk)

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.

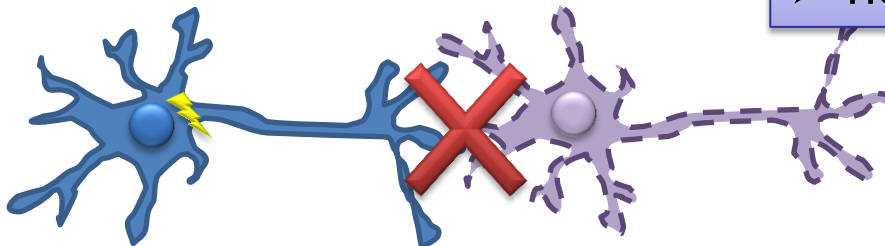


Healthy

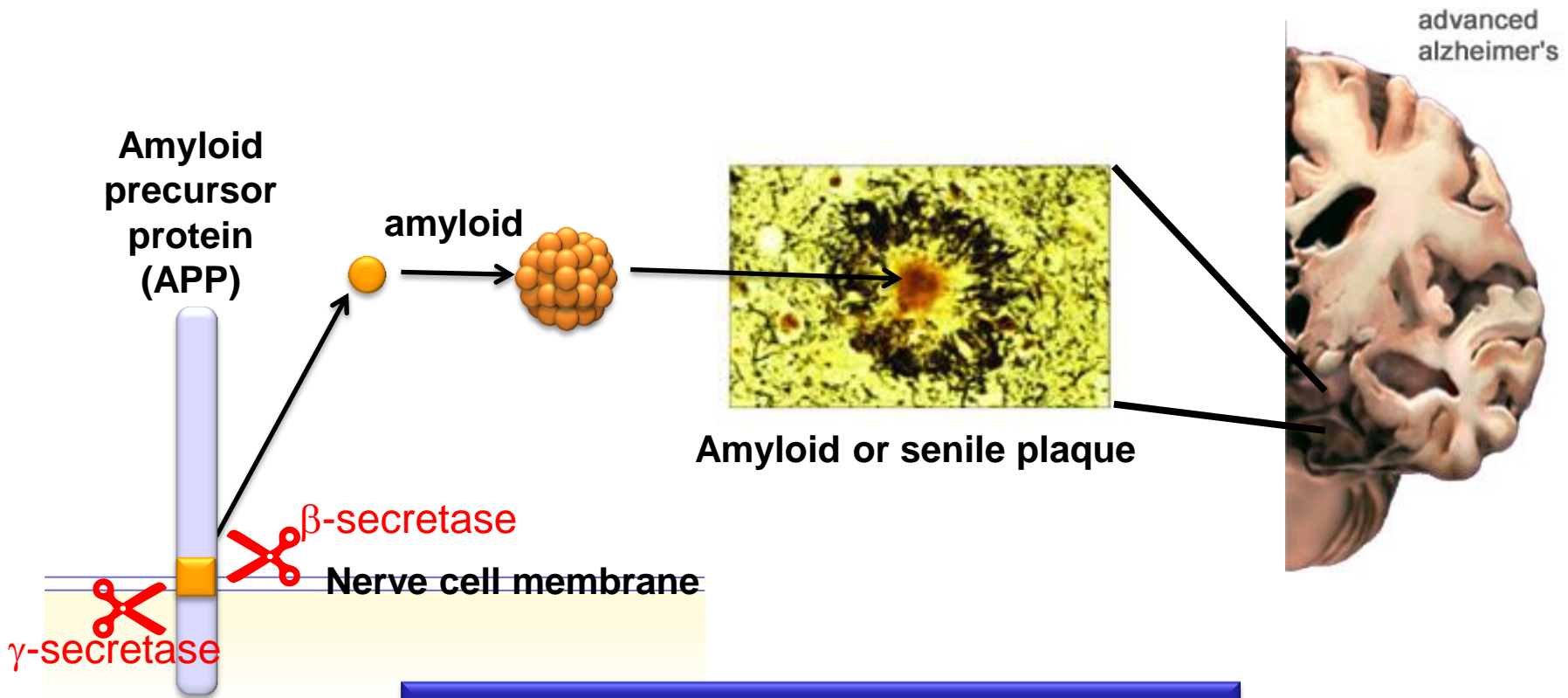


- what initiates this process?
- how can we stop it?

Alzheimer's



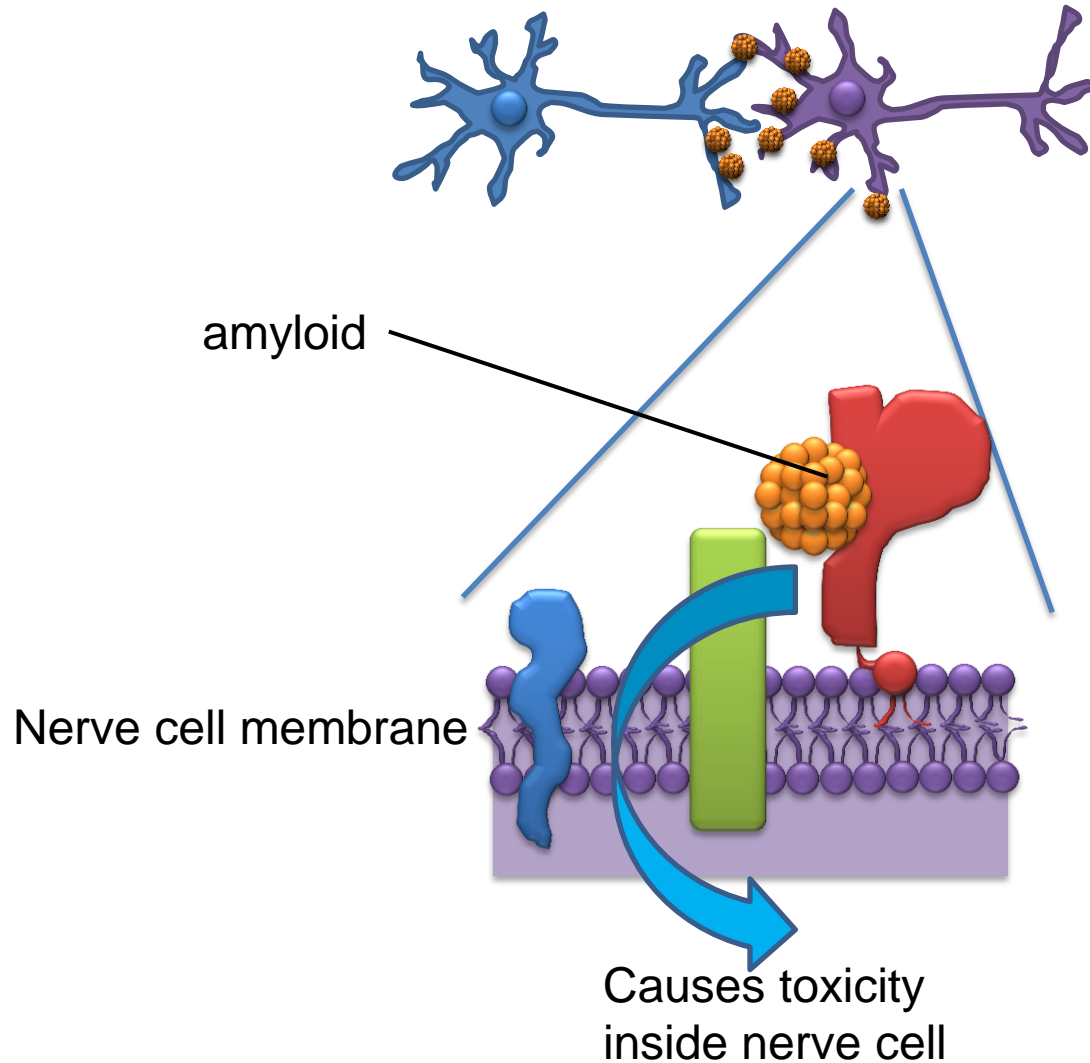
In Alzheimer's disease there is a build up of amyloid in the brain



What regulates this process?

Can we inhibit the build up of amyloid?

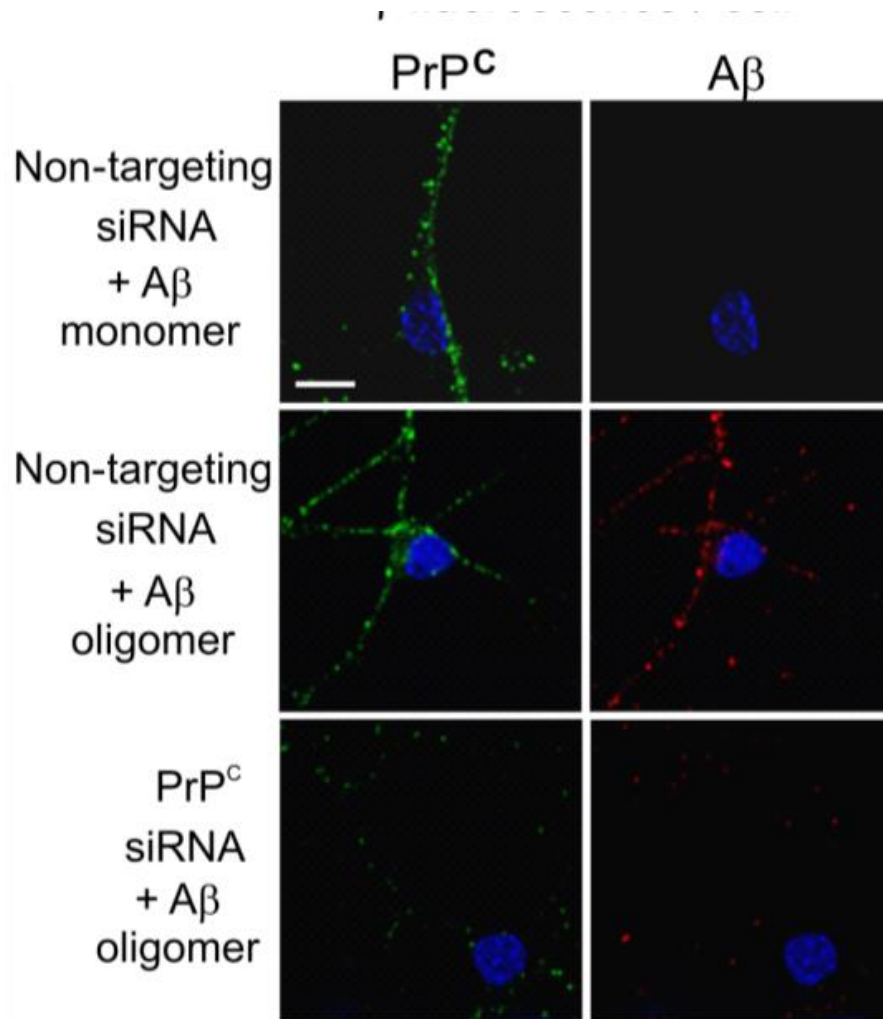
Amyloid sticks to specific proteins on the surface of nerve cells and causes damage



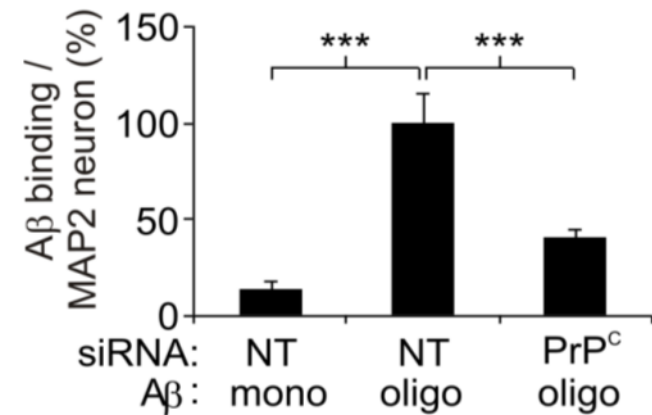
What receptors/signalling proteins are involved?

Can we disrupt these interactions?

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



Rat hippocampal neurons

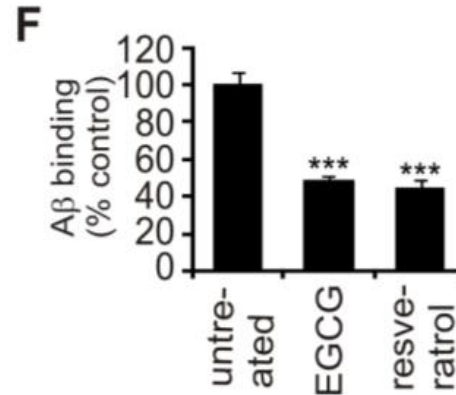
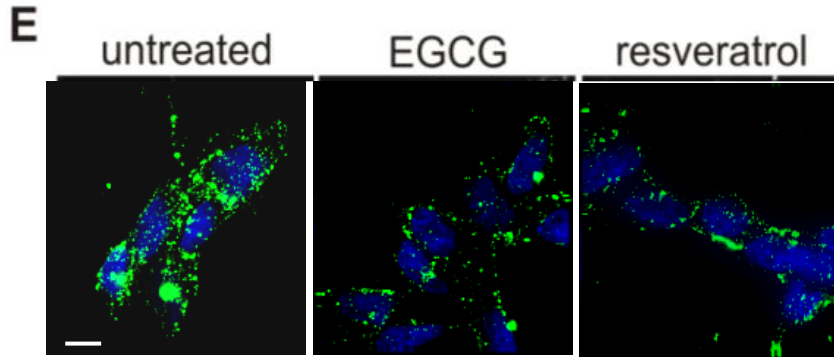
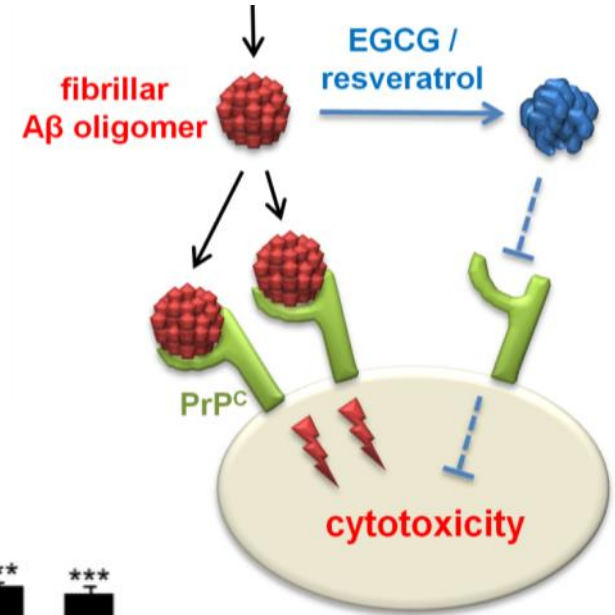


EGCG and resveratrol reduce the binding of amyloid to neurons

EGCG
[(-)-epigallocatechin
gallate]

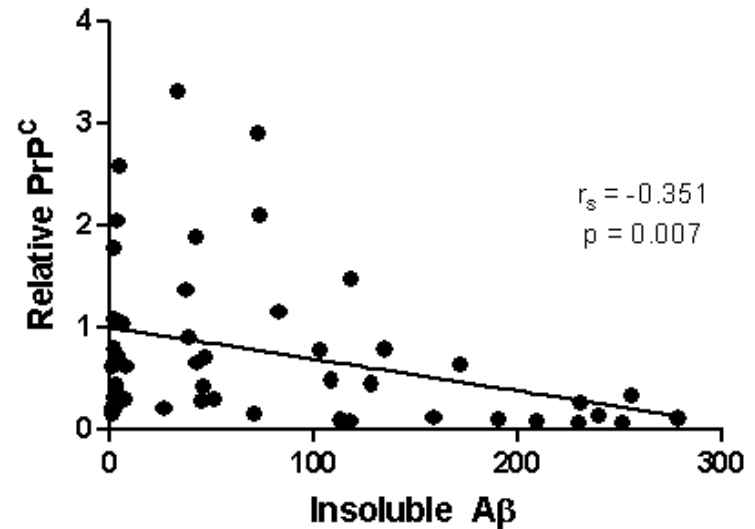
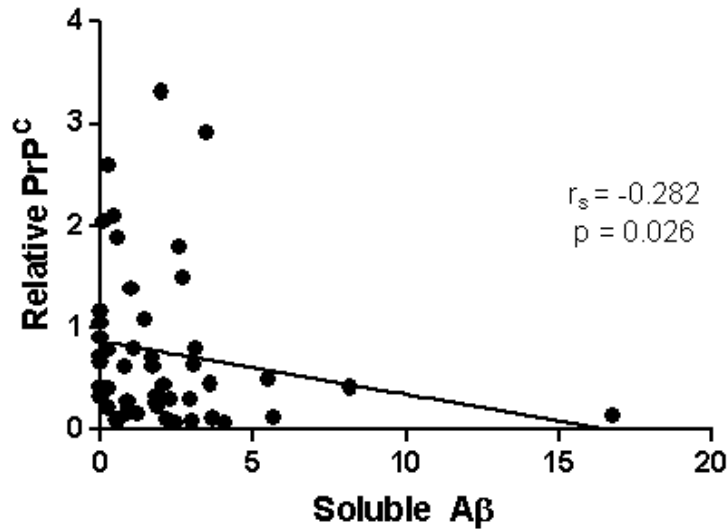
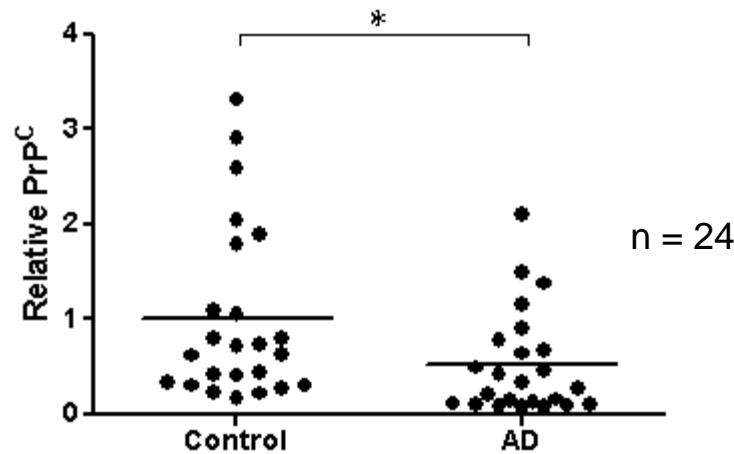


Resveratrol

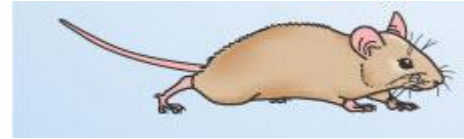
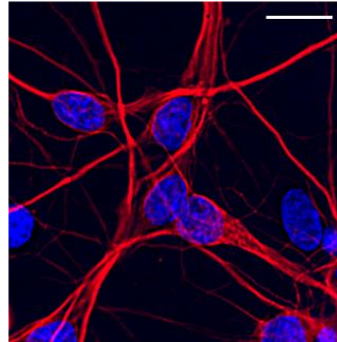
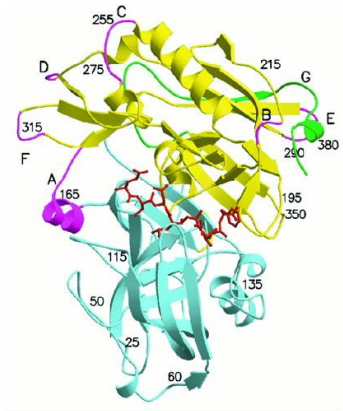


*

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



Experimental approaches to Alzheimer's disease



Molecules



Cells



Animal models



Humans

- Genes
- mRNA
- Proteins
- Lipids

- Immortalised human cells
- Rodent primary neurons
- **induced pluripotent stem cells (iPSCs)**

- Transgenic mice
- Transgenic rats

- Brain tissue
- CSF/plasma
- Brain imaging

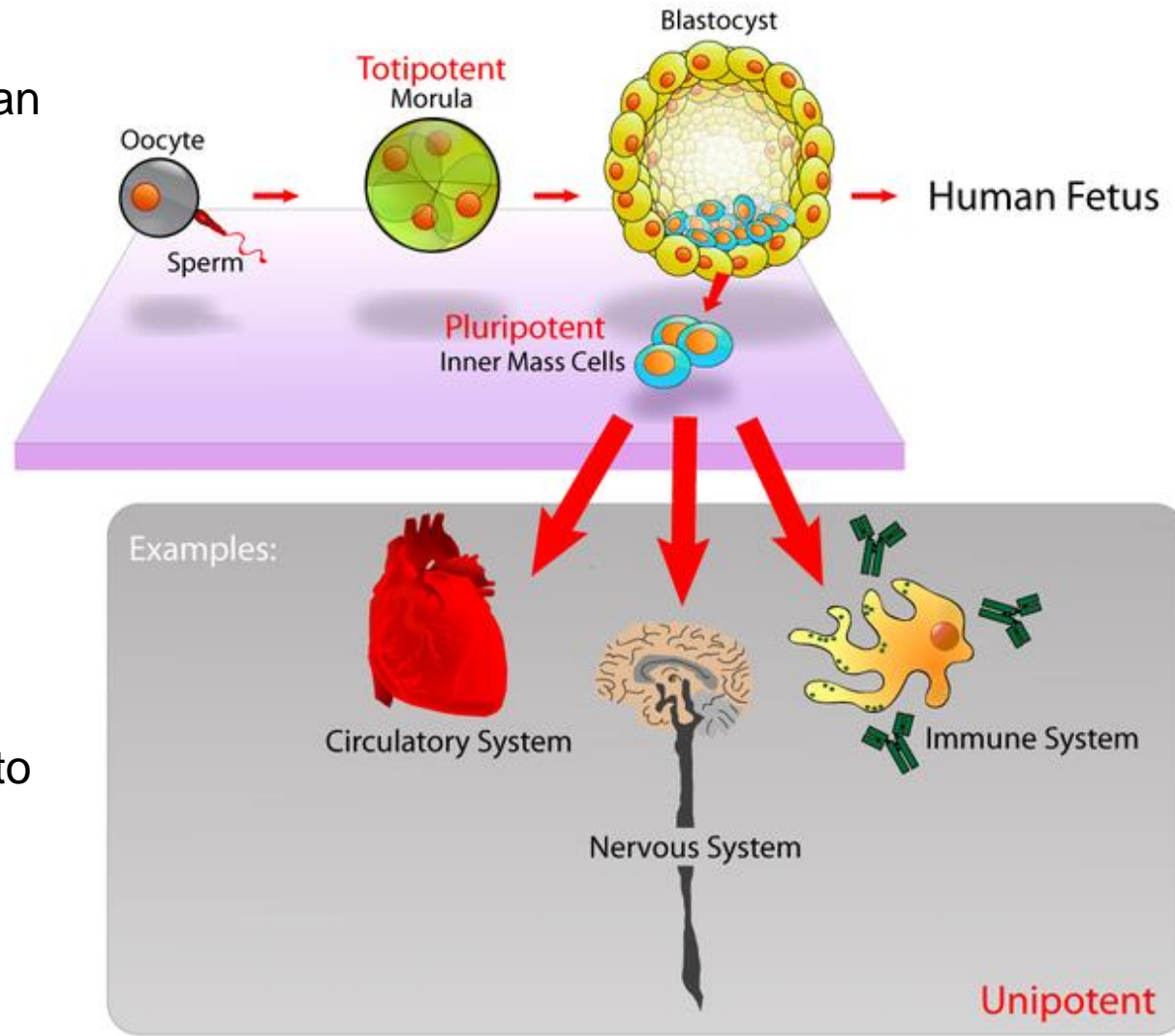
Stem cells

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

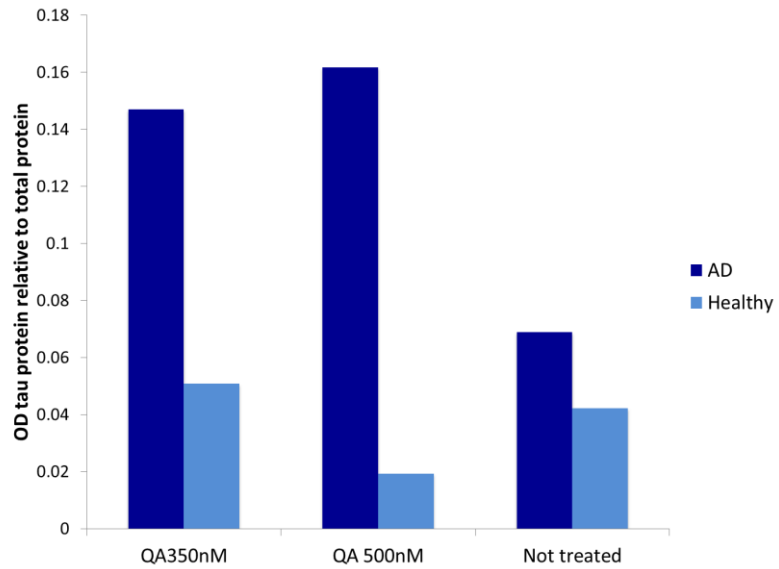
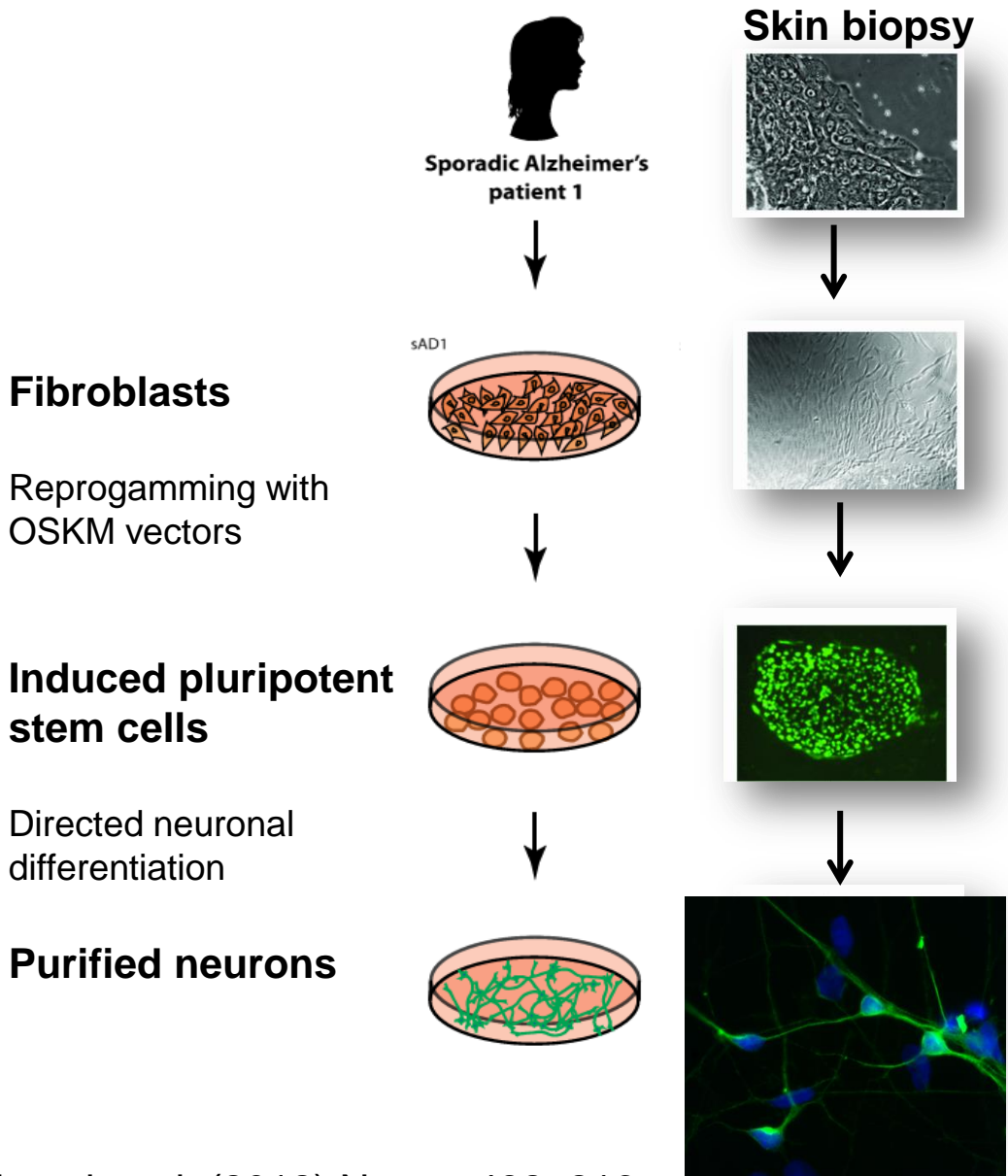
- Embryonic stem cells
- Adult stem cells

Induced pluripotent stem cells (iPSCs)

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



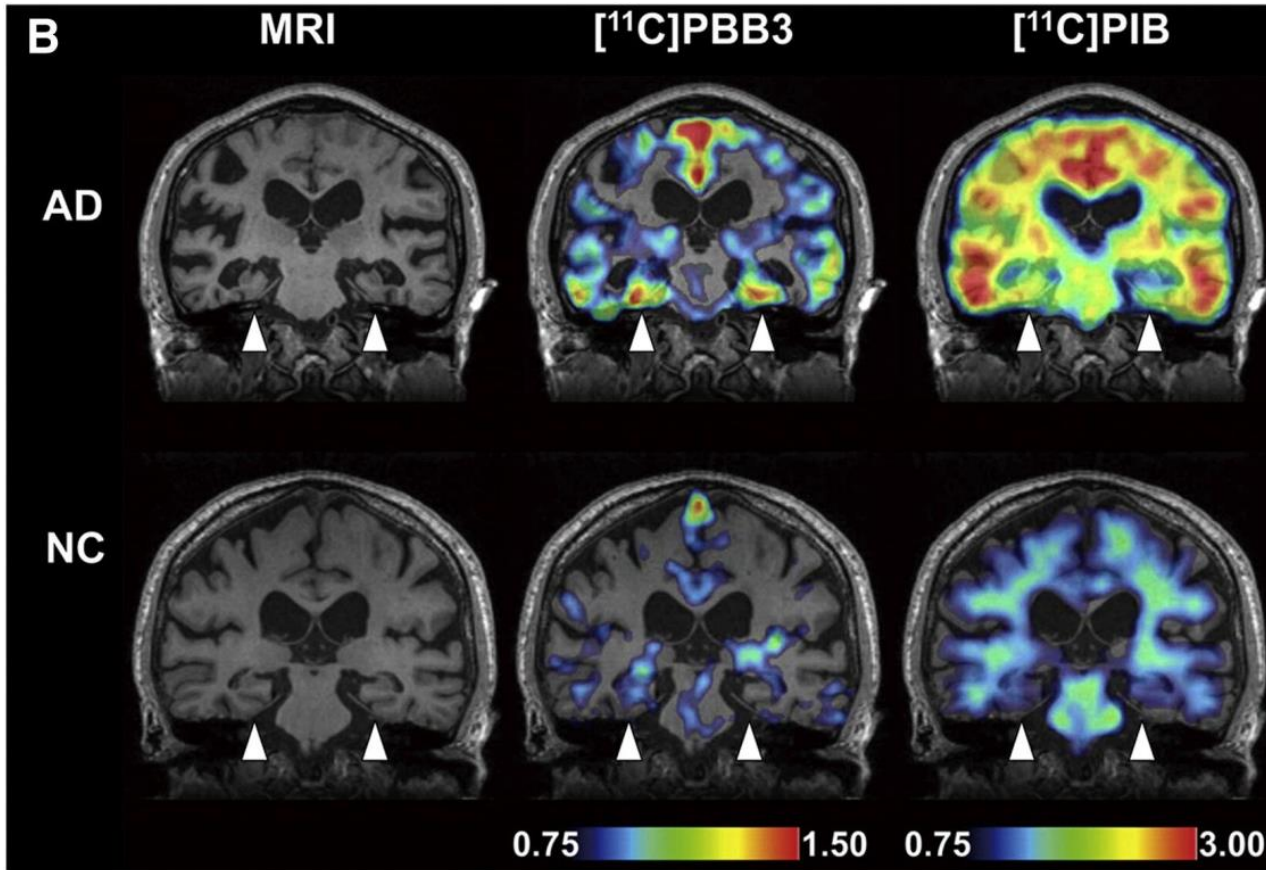
“Neurodegeneration-in-a-dish”



Response of neurons from an AD individual (PSEN2 mutation) & from a healthy individual to the neurotoxin quinolinic acid (Chris Ward)

Imaging amyloid plaques and tau tangles in the human brain

Positron emission tomography (PET)



Pittsburgh compound B (PIB) binds to amyloid plaques

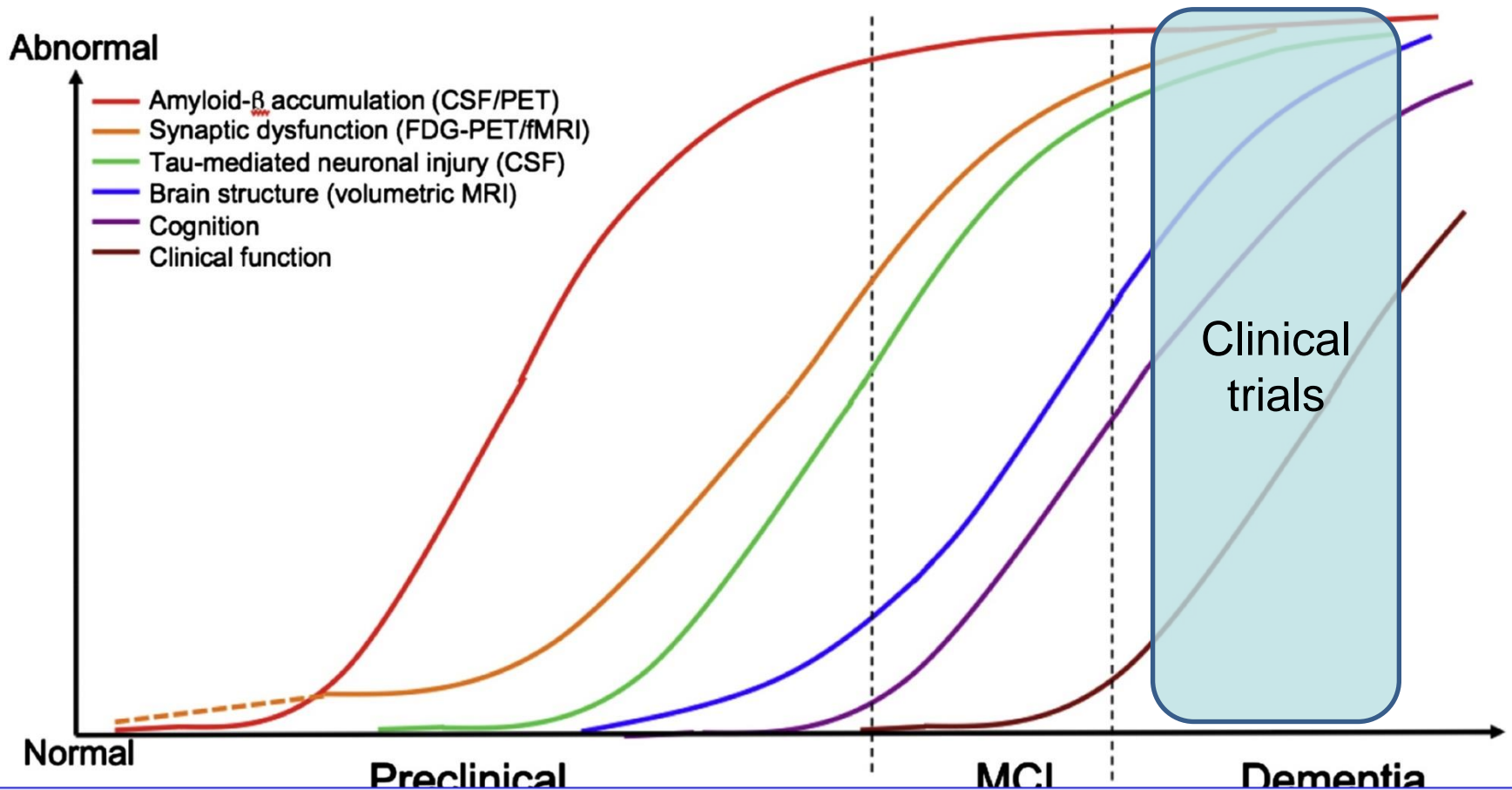
PBB3 binds to tau tangles

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

Amyloid plaques appear >15 years before clinical symptoms

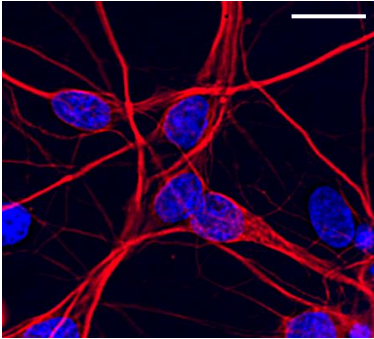
<http://www.nejm.org/doi/full/10.1056/NEJMoa1202753>

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

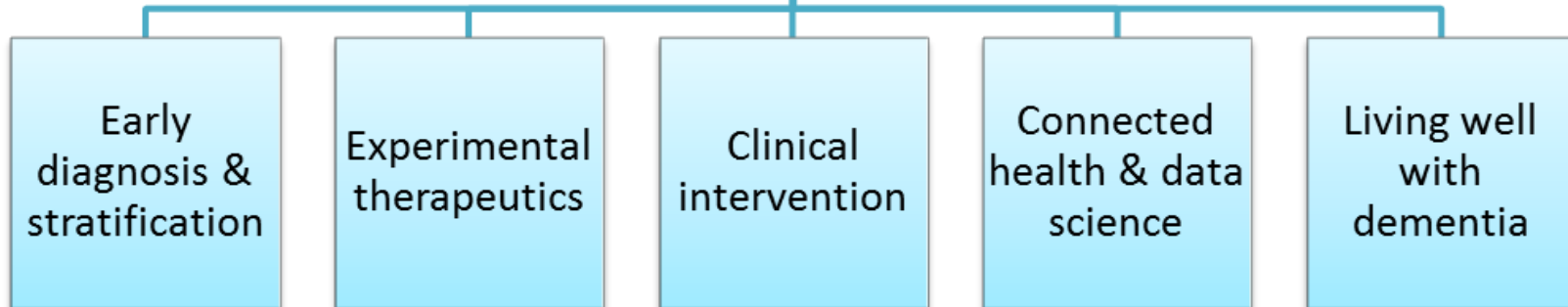


Urgent need for an easily accessible (e.g. blood) biomarker or panel of biomarkers that accurately indicate status of disease and follow disease progression

Dementia@Manchester – from cell to society



Patient and public involvement



Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, motor neuron disease, vascular dementia, ageing

Acknowledgements

Hooper Lab

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Cath Lawrence
Stuart Pickering-Brown

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Defeating Dementia

Alzheimer's
Society
Leading the
fight against
dementia

welcome trust

BBSRC
bioscience for the future

Engaging with dementia

<http://www.fbs.leeds.ac.uk/blogs/dementia/>