Turning ideas into medicines: The Alzheimer's Research UK Cambridge Drug Discovery Institute

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SciBar Cambridge 12th September 2017

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Dementia


Alzheimer's
Research UK
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Dementia – a global crisis

1 in 4
hospital beds are occupied by people with dementia

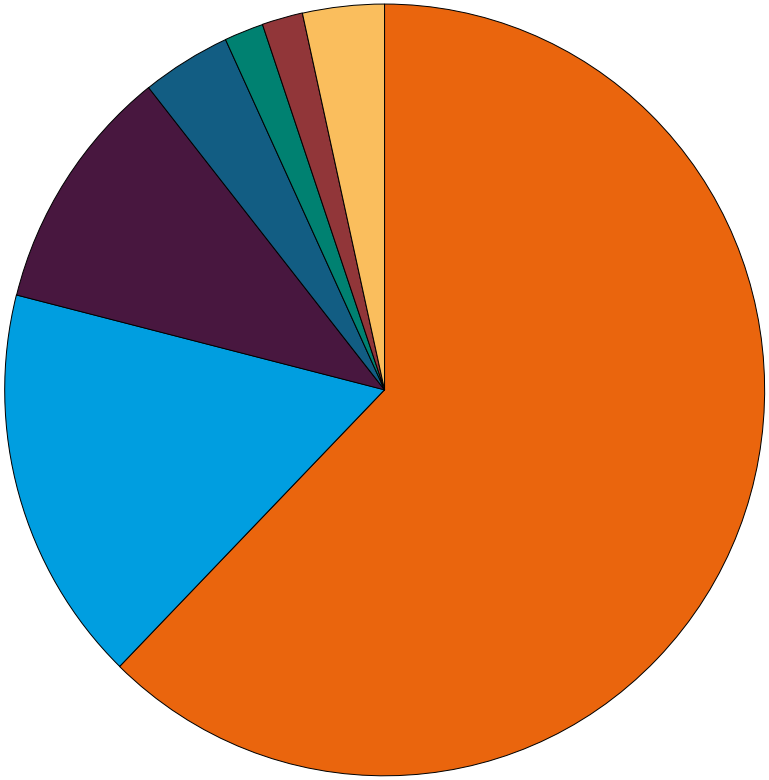
225,000
people will develop dementia in the UK this year – that's one every three minutes

Over **1.5 million** people in the UK, including both people with dementia and their carers, would benefit from dementia treatments today; that's more that the combined populations of the cities of **Manchester**, Sheffield and Bristol

Dementia costs the UK economy
£24bn
a year (more than the cost of cancer and heart disease combined) and had a global cost of US$818bn in 2015

What is dementia?

A collection of symptoms, including a decline in memory, reasoning and communication skills, and a gradual loss of skills needed to carry out daily activities.



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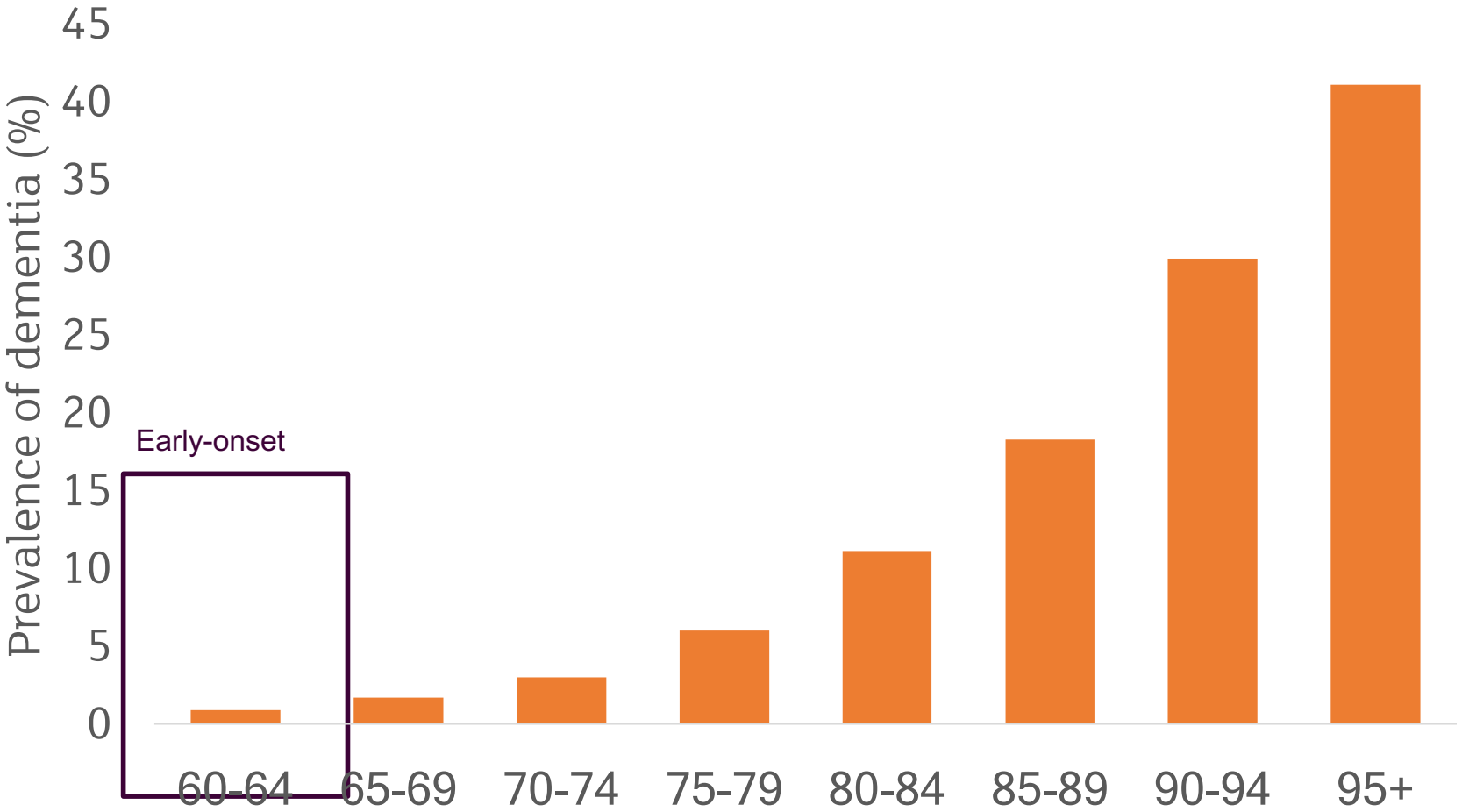
Dementia isn't an inevitable part of ageing



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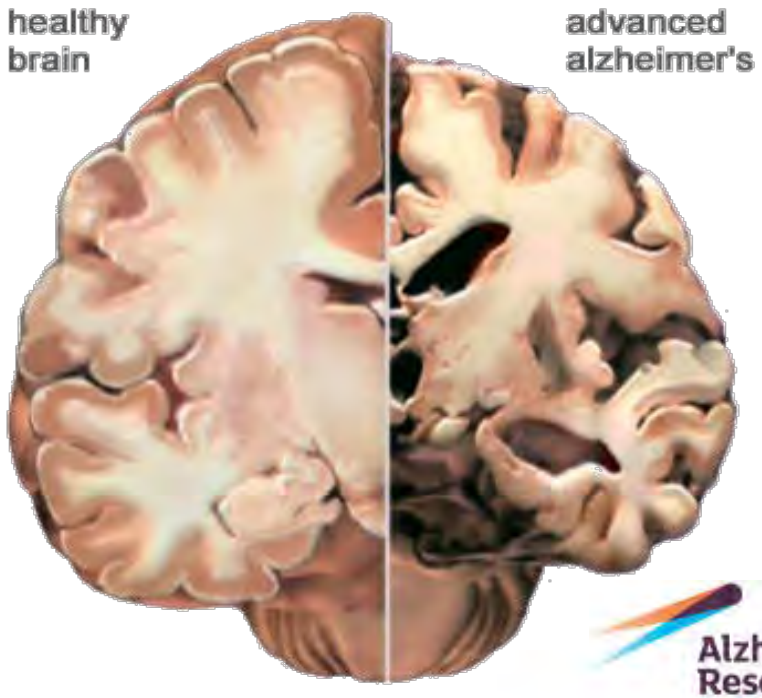
Dementia UK Update, 2014

Why does dementia pose such a challenge?

- Dementia is caused by physical and progressive brain diseases.
- Changes in the brain can occur long before symptoms start to show.
- Results from a complex mix of genetic and environmental risk factors which interact over a lifetime.
- Complicated by other processes or conditions which can also accompany the ageing process



The Alzheimer's Society

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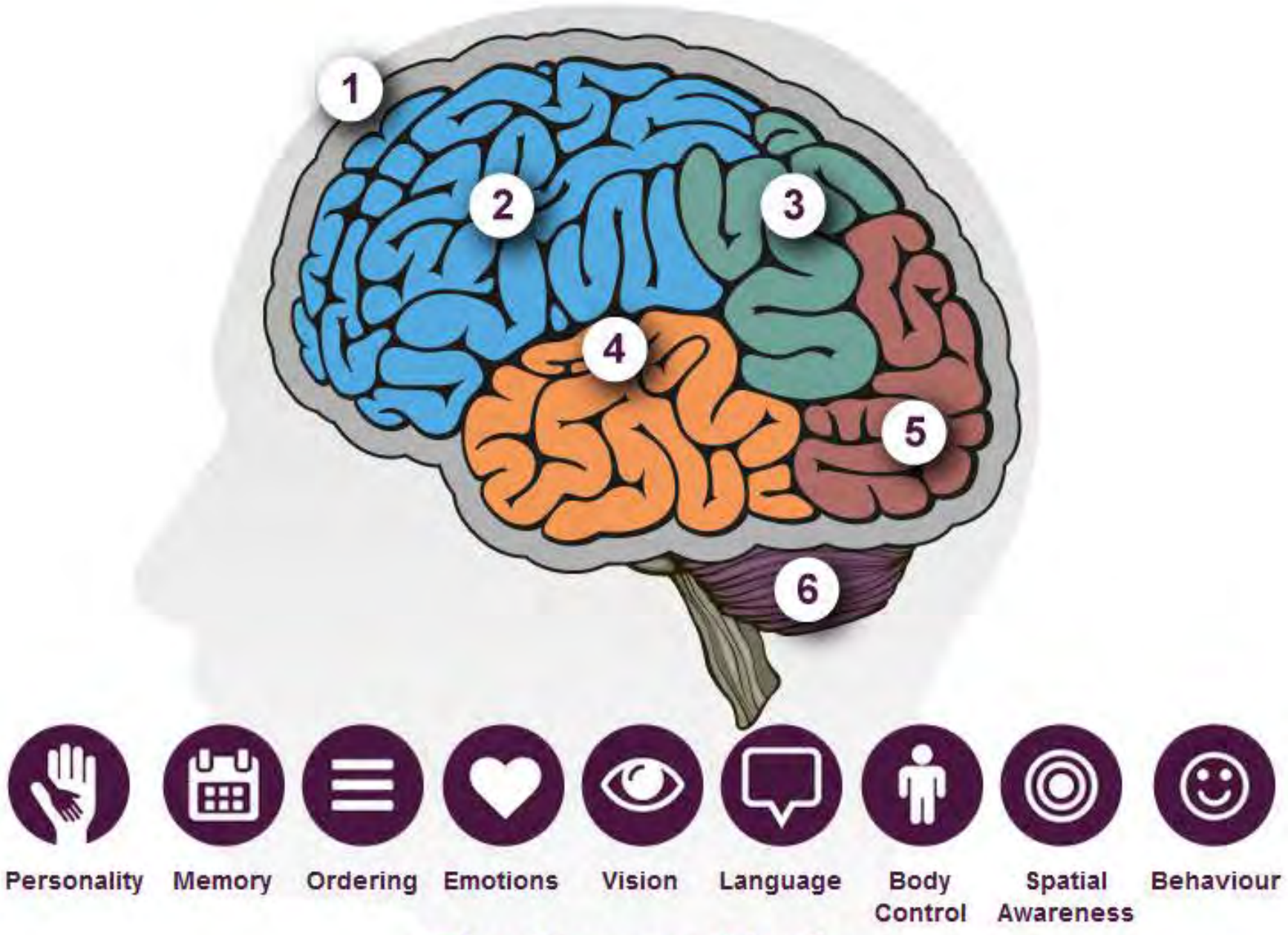
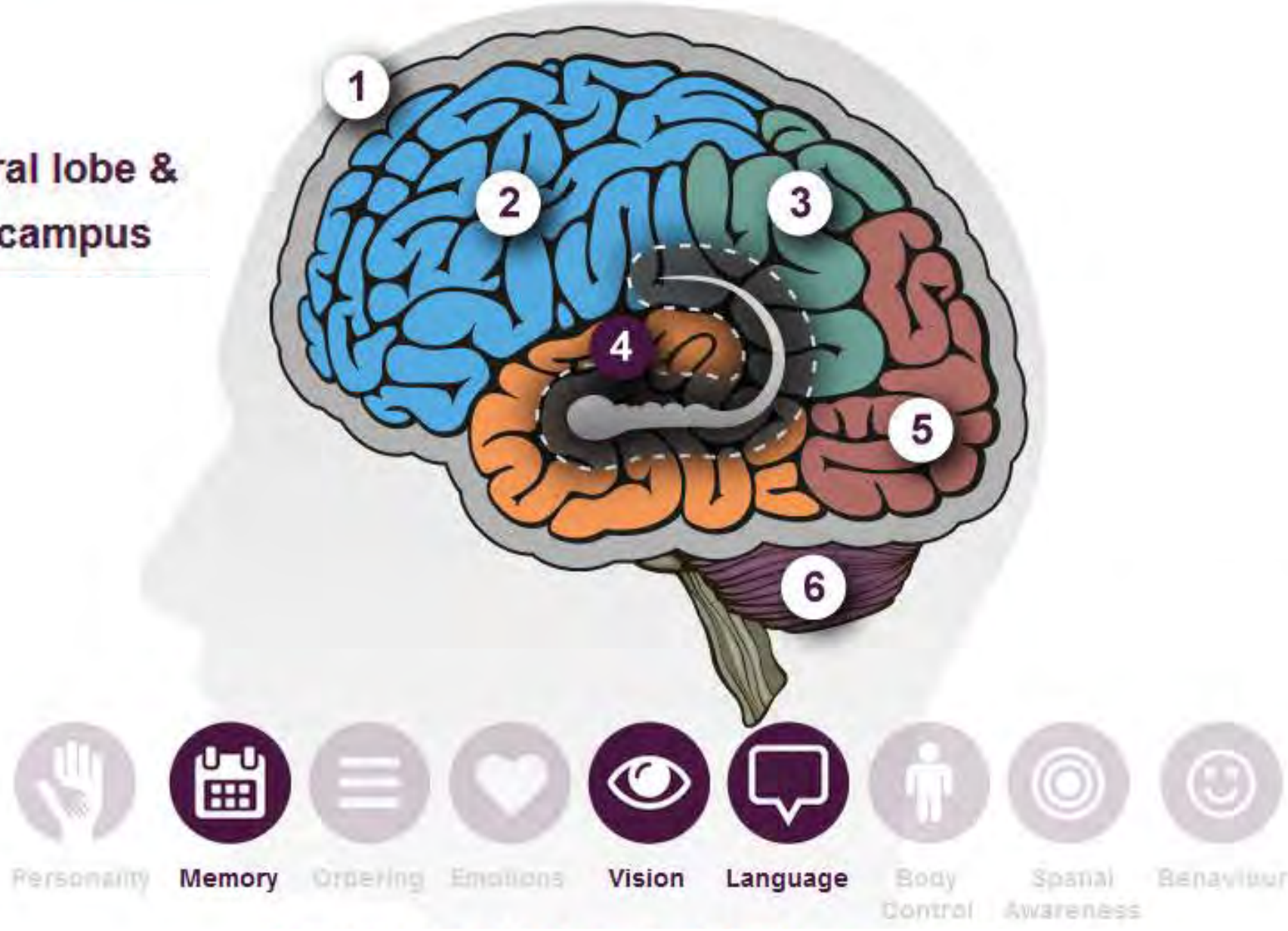
Symptoms of dementia

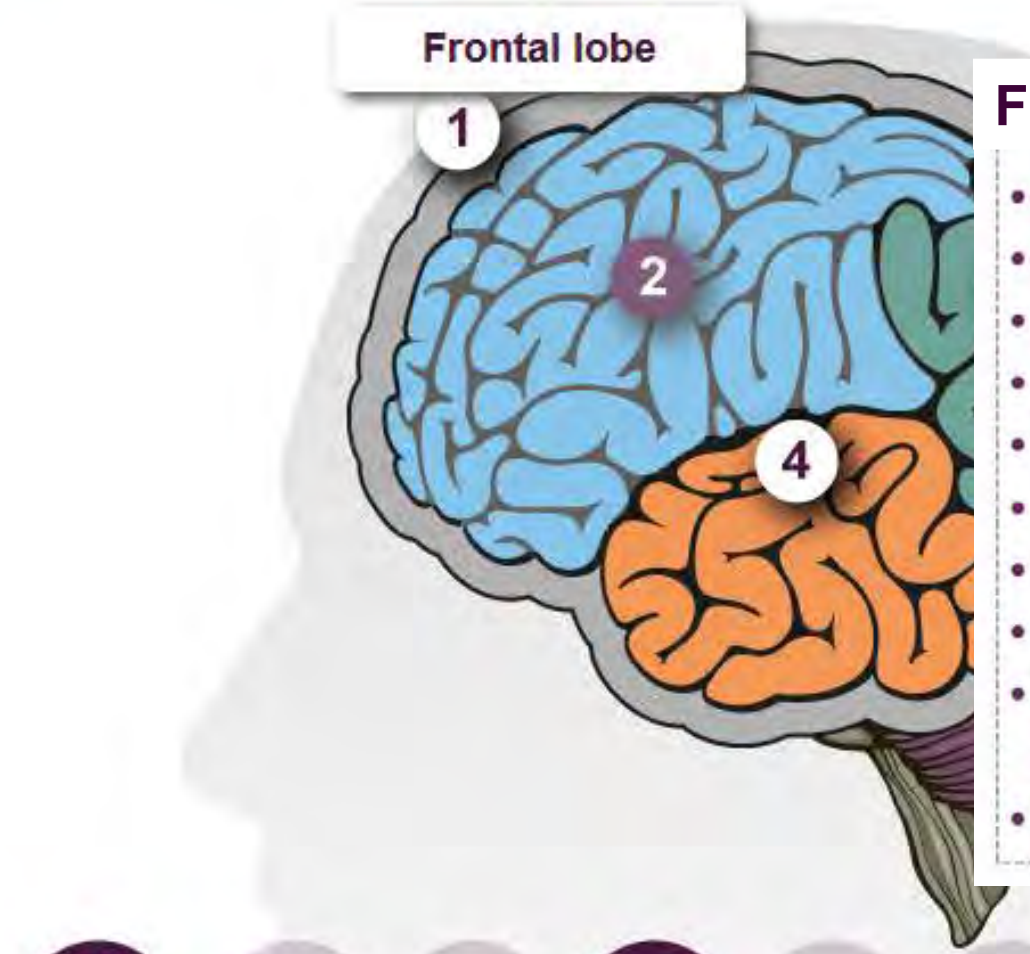


Alzheimer's disease

Temporal lobe & hippocampus



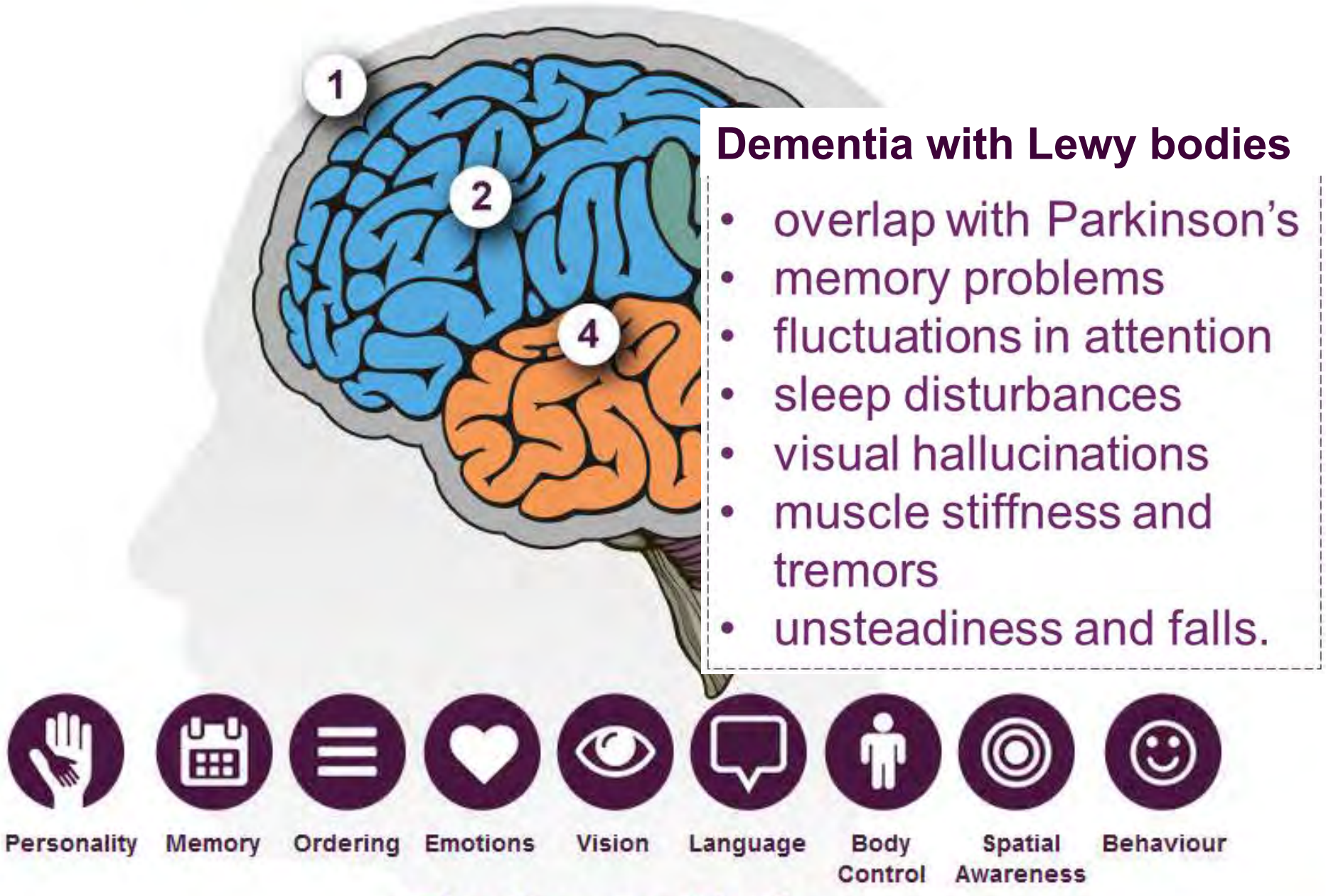
Frontotemporal dementia



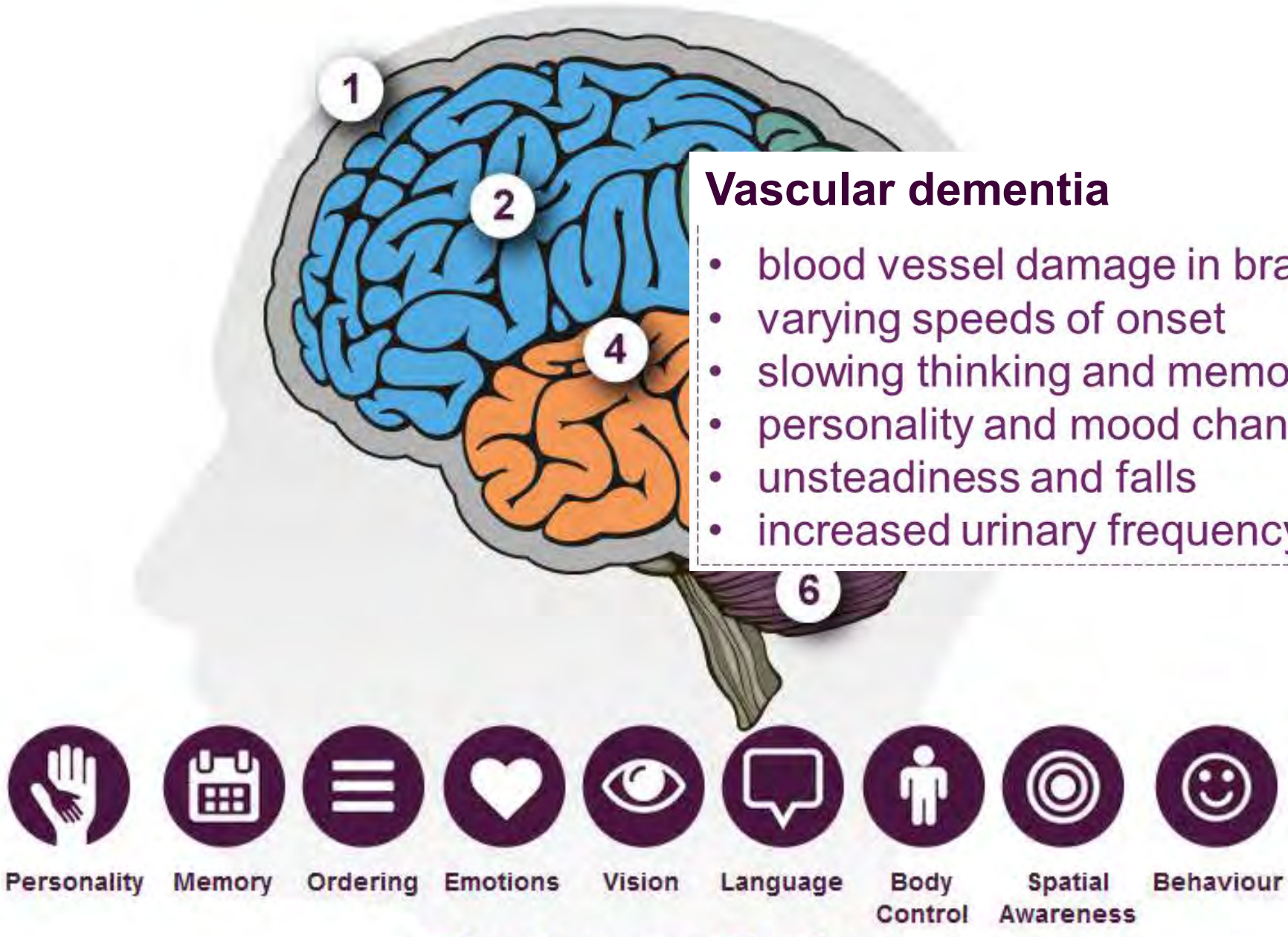
Frontotemporal dementia

- common in under 65s
- stronger family history
- personality changes
- reduced attention
- apathy or overactivity
- change in eating habits
- disinhibited
- lack of personal awareness
- Speech and language problems
- memory affected later.

Dementia with Lewy bodies



Vascular dementia



Vascular dementia

- blood vessel damage in brain
- varying speeds of onset
- slowing thinking and memory
- personality and mood changes
- unsteadiness and falls
- increased urinary frequency.

What causes Dementia?

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What are the risk factors?

- Biggest risk factor is age
- Genetics

    - **Faulty gene** - causes disease in familial early-onset Alzheimer's (>1%) and in frontotemporal dementia (around 10%).

    - **Risk genes** - common in the population and normally have a relatively small effect on risk on their own. Linked to late-onset Alzheimer's and other dementias.

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Lifestyle risk factors

- Biggest risk factor is **age**.
- Genetics.
- Lifestyle.

Where is the evidence?

- What is good for your heart is good for your head.
  Vascular risk factors:

Lack of exercise	Poor diet
Obesity	Heavy alcohol intake
High blood pressure	High cholesterol
Smoking	Diabetes

- Suggested additional risk factors:

Lack of social engagement	Low educational attainment
Depression	Head injury

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What causes dementia?

- Damage to blood vessels – stroke, small vessel disease

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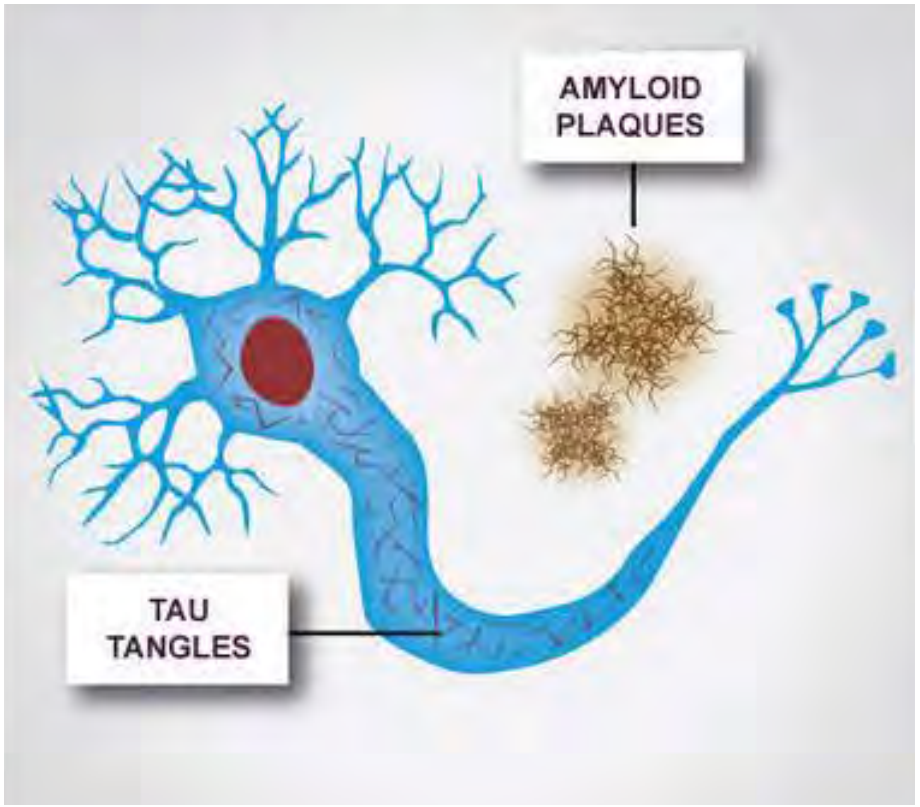
What causes dementia?

- Damage to blood vessels – stroke, small vessel disease.
- Build-up of abnormal proteins in the brain.



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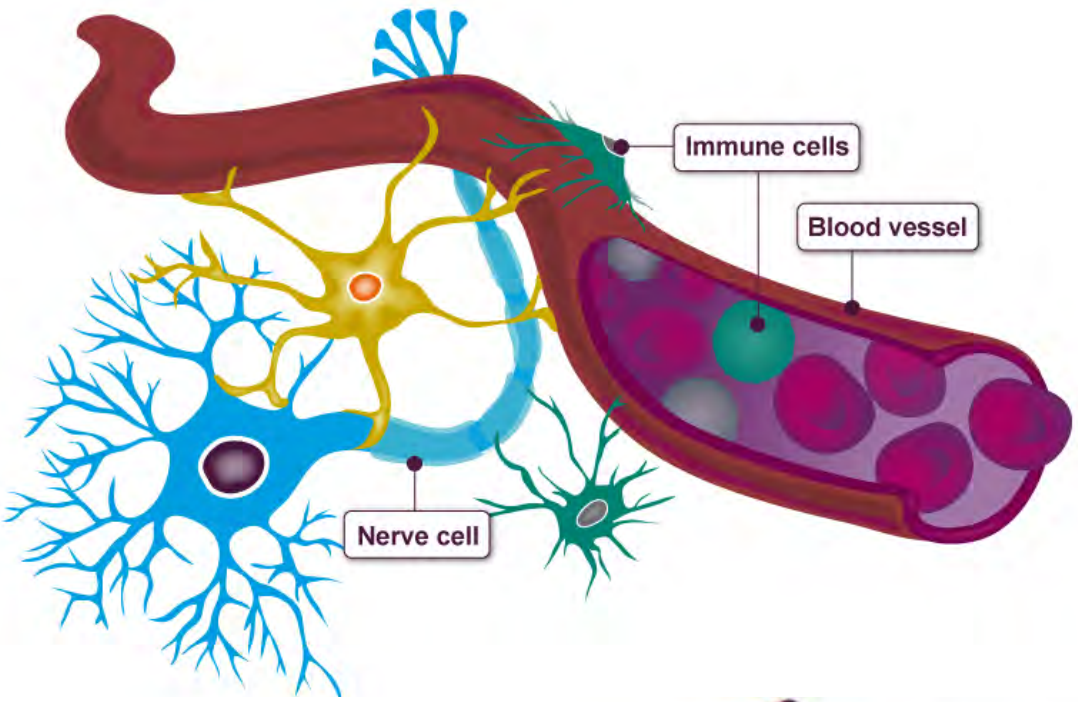
What causes dementia?

- Damage to blood vessels – stroke, small vessel disease.
- Build-up of abnormal proteins in the brain
- Changes in the immune system, metabolism, other brain cells.



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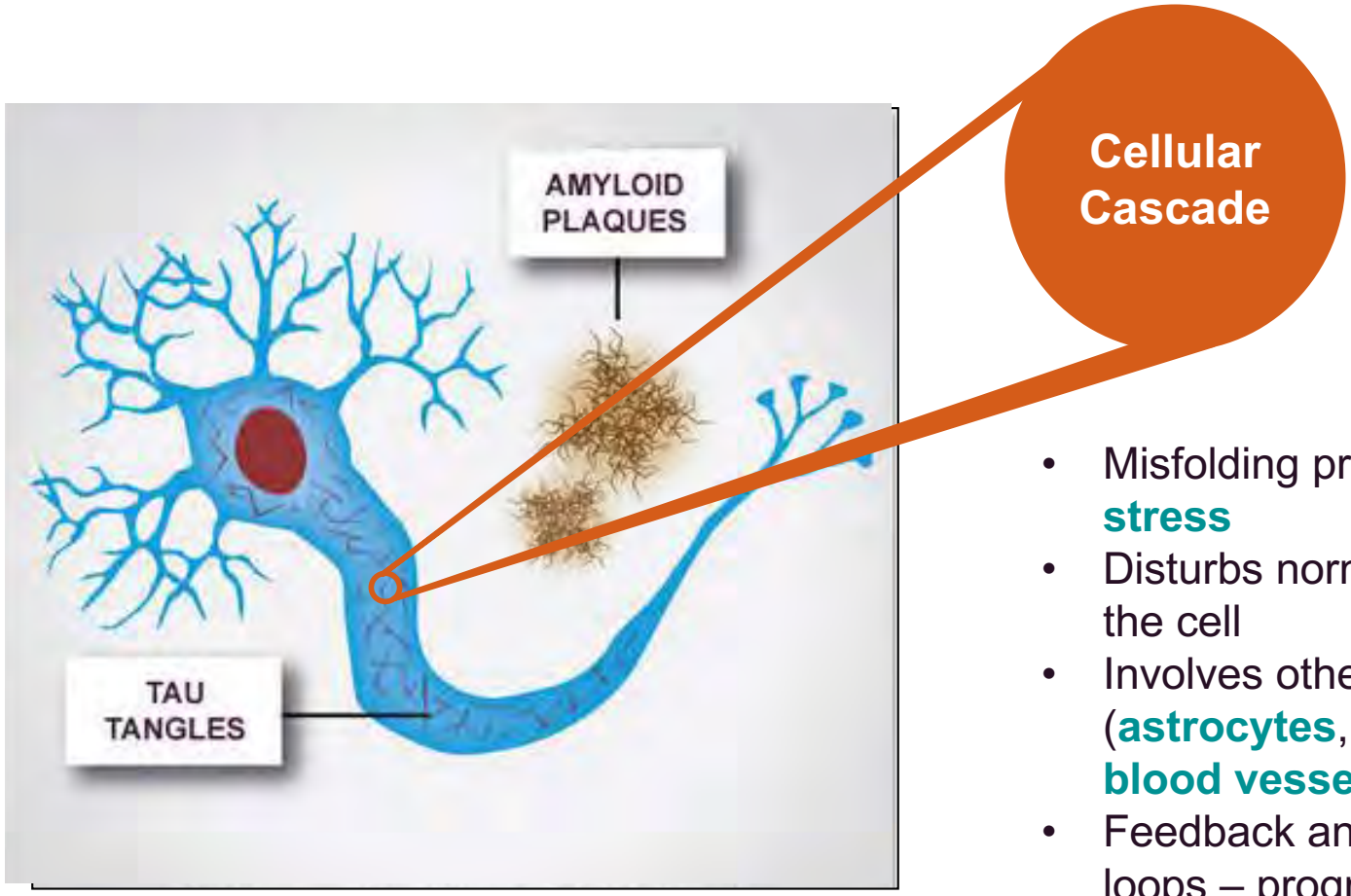
What Causes AD – cascade of events



- Misfolding proteins cause **stress**
- Disturbs normal behaviour of the cell
- Involves other brain cells (**astrocytes**, **microglia**) and **blood vessels**
- Feedback and feedforward loops – progression may no longer require the plaques and tangles

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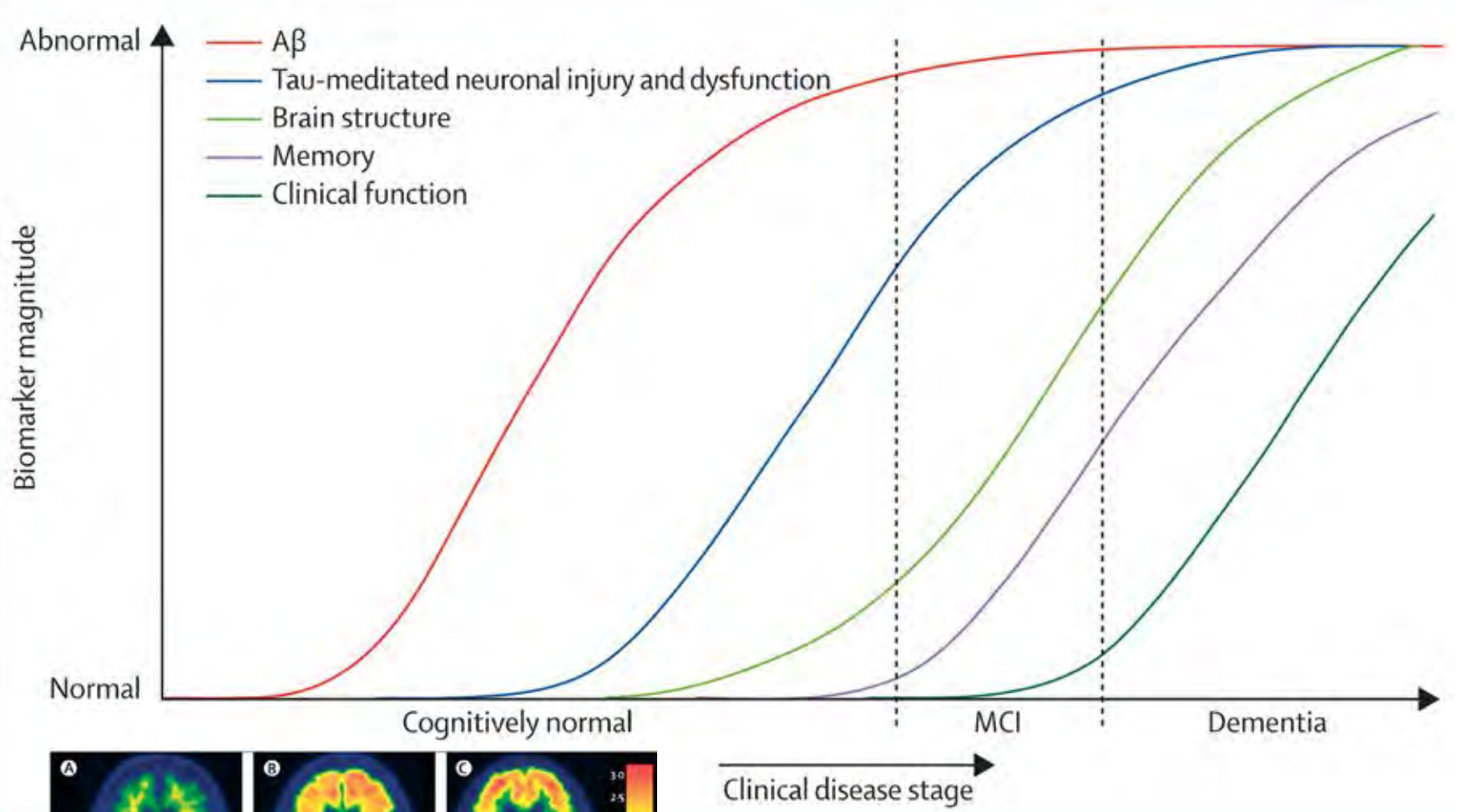
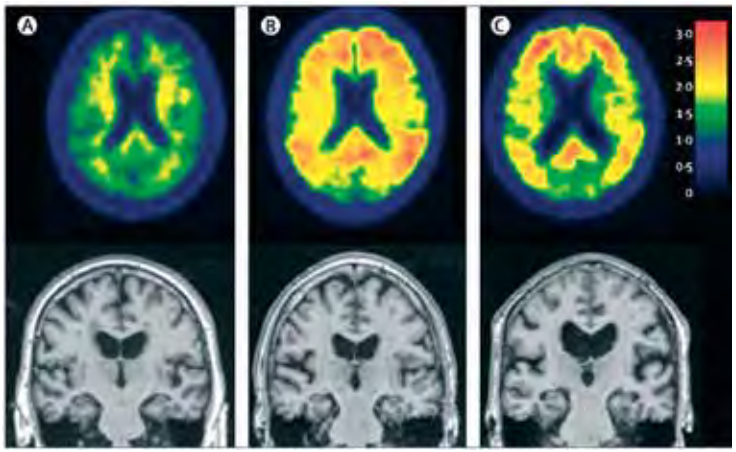
Forlenza *et al. BMC Medicine* 2010 **8**:89 doi:10.1186/1741-7015-8-89

Progression of AD over time





Jack *et al Lancet Neurol,* 2010, 119-128

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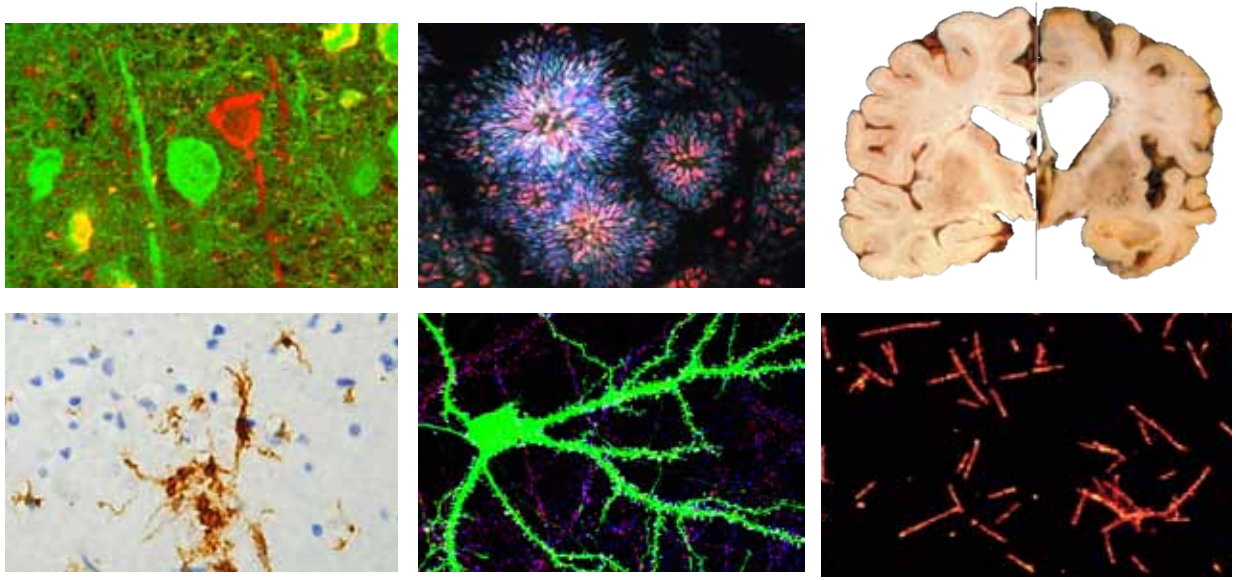
Research into the causes of dementia

- What time do these events start?
- Which events are the most toxic?
- How do we stop them?

£14.7m research fundamental biology of dementia



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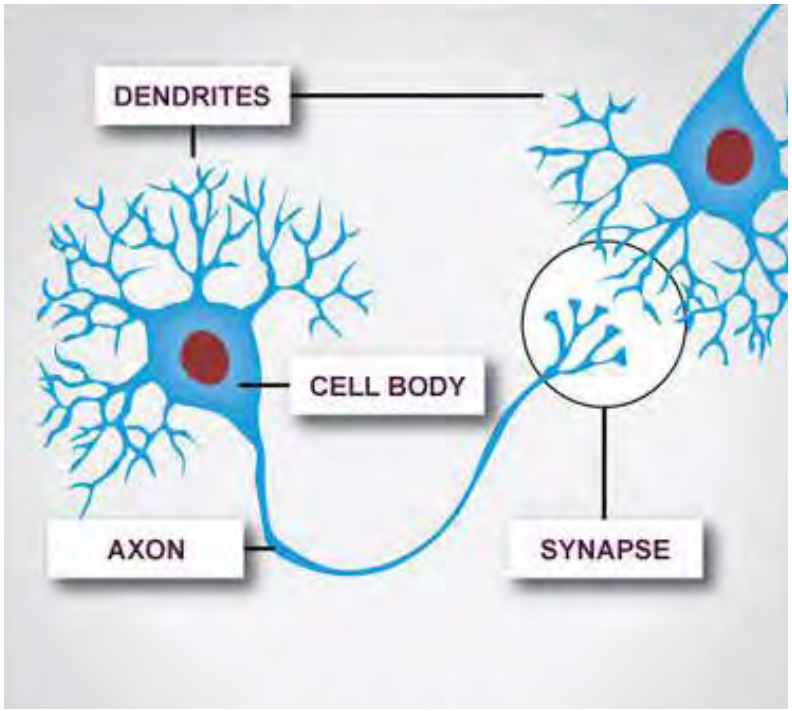
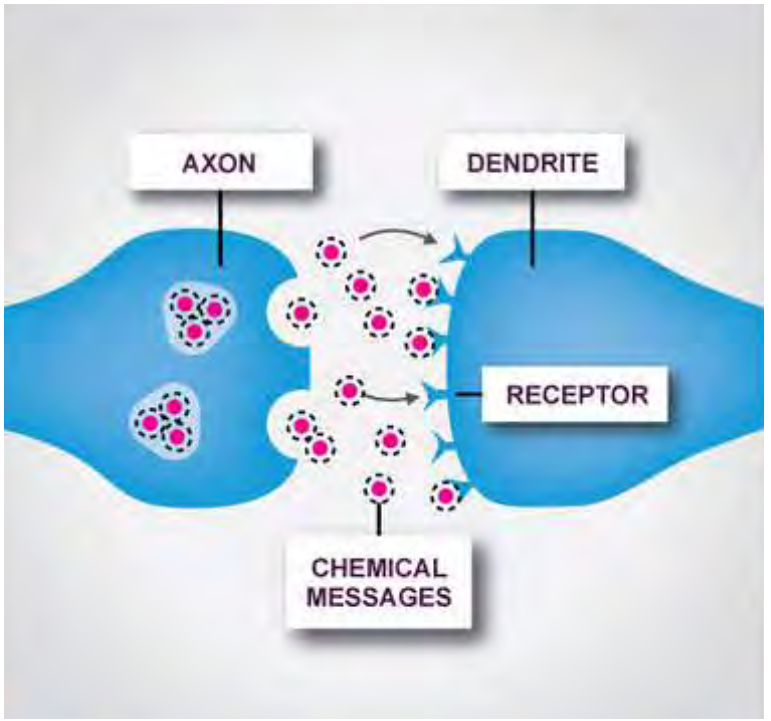
Current treatments for Alzheimer's Disease

- Current treatments help with symptoms
- Donepezil, rivastigmine, galantamine, memantine
- There are no treatments that can slow or stop the disease process





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What are medicines?

How do they work?

How do we ~~discover~~ invent them?

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Designing a medicine for dementia

Proteins – thousands of large molecules with different functions in our bodies
Disease – often caused by malfunctioning proteins
Drug – usually binds to a particular type of protein and changes its function
Medicine – a drug designed to treat disease

1. **Activity**
   - Strong interaction with target protein
   - Limited interactions with other targets
2. **Pharmacokinetics**
   - Gets into the blood when taken as a pill
   - Not degraded by enzymes in liver or blood
3. **Can get into the brain**
   - Brain has special protective “blood-brain barrier”
4. **Safe**
   - No toxic side effects
   - No interactions with other drugs

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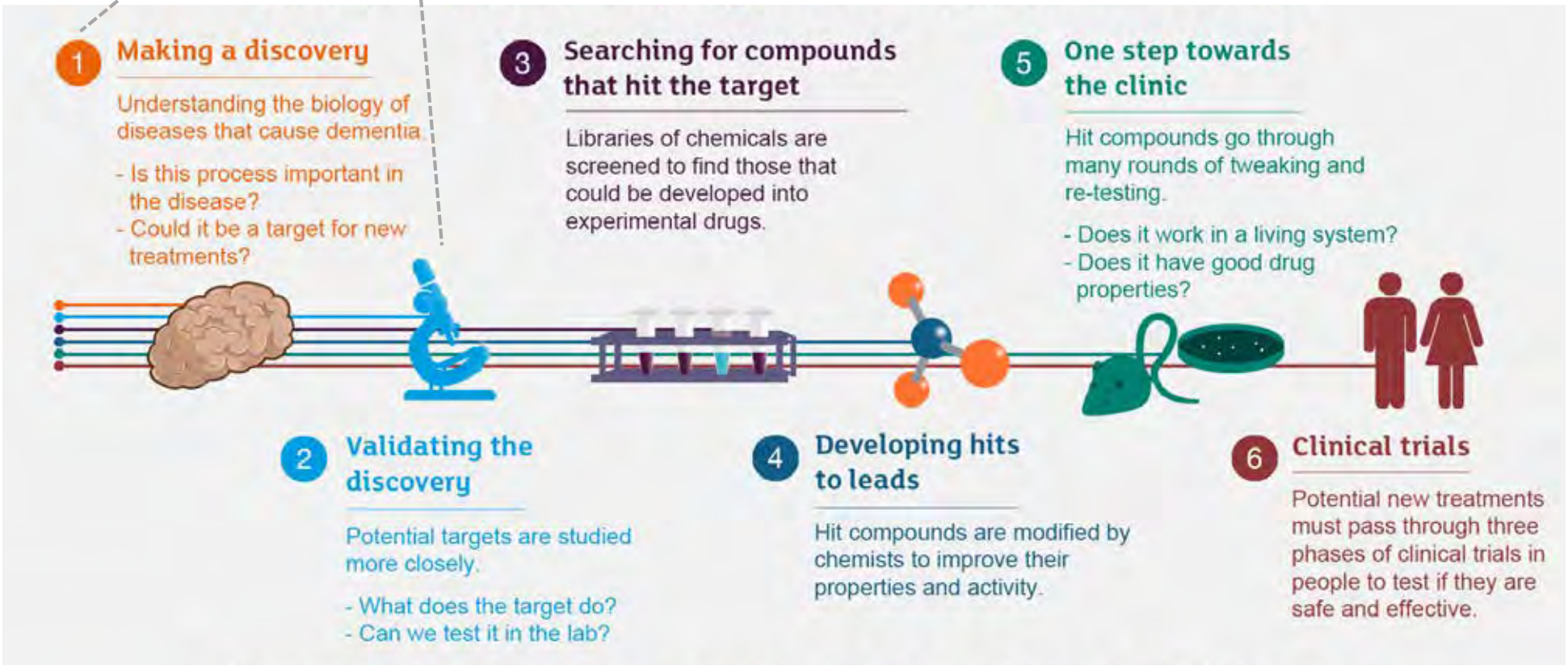
How are we working to find medicines to treat dementia?

Who discovers a drug?

Academia

Biotech and Pharma



Not-for-Profit Drug Discovery

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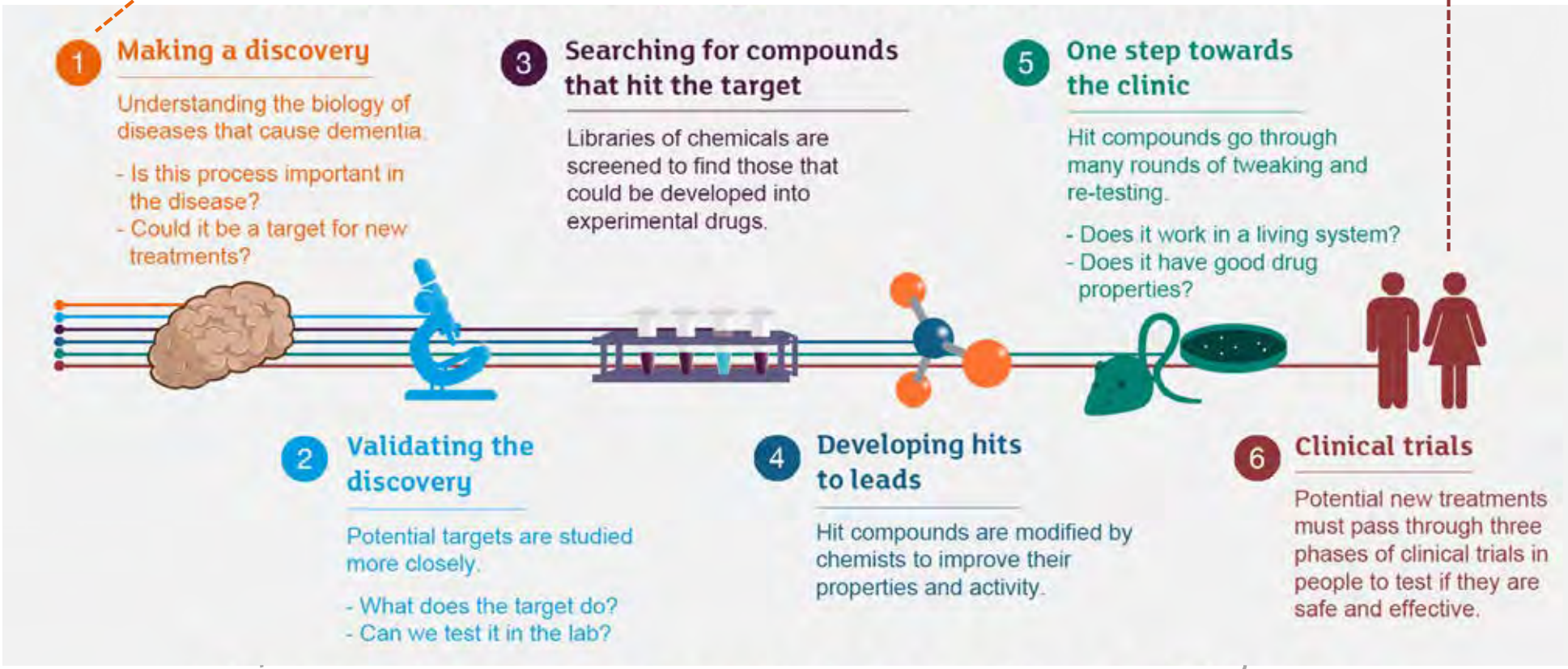
Time and money

It typically takes >15 years to go from a discovery to a medicine and costs > £2Bn

Funded by ARUK

£1.2Bn on drug development for each successful medicine launch



£900 M spent on drug discovery for each medicine launch.

Cost per project is nearer £10M

ARUK funds DDI

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The Alzheimer's Research UK Drug Discovery Alliance

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UCL

- Three independent drug discovery institutes
- Each led by a Chief Scientific Officer and one or more Lead Academics
- Interacting directly and through the coordination of ARUK

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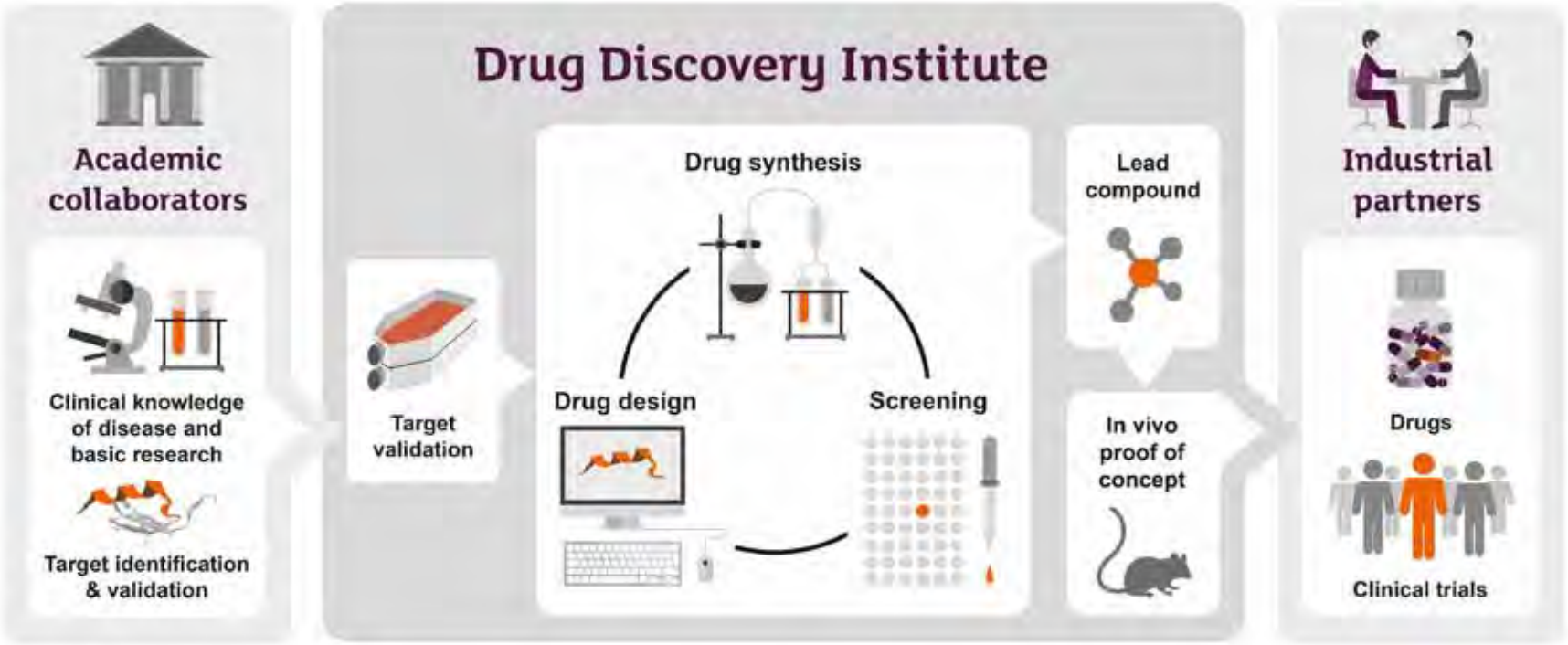
The role of the Drug Discovery Alliance

Mission:

- Take the latest science into dementia and turn it into new drug discovery projects
- Generate molecules that are the seeds for the next generation of medicines
- Explore new and exciting areas not yet investigated by industry

Funding: £30M over 5 years



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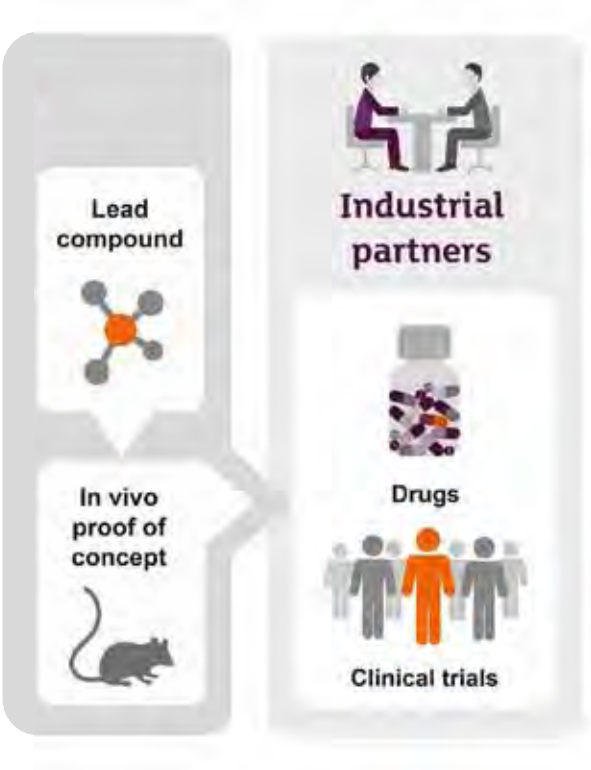
What will happen to our projects?



What will happen next?

- Our molecules will be optimised to find **new drugs** which will be ready for **clinical trials**
- To do this will will partner our projects with industry or get further funding to support late-stage drug discovery
- The University can help run clinical trials to get our new drugs to the patients that need them.

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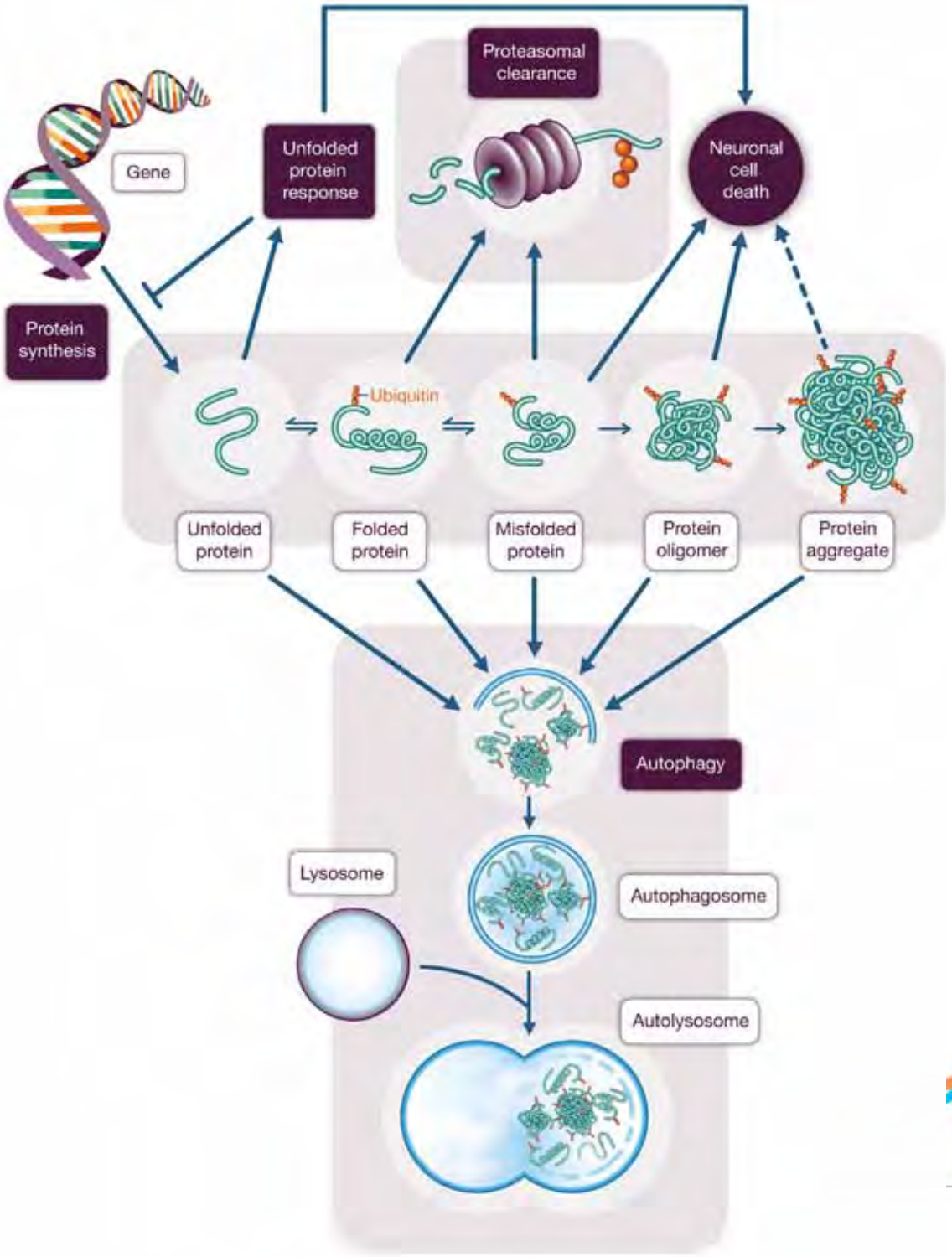

Our focus on proteostasis

The Cambridge DDI is exploring approaches to **stopping the formation of the misfolded proteins** for diseases such as **Alzheimer's**, **Parkinson's** and **Lewy Body disease** and **Huntington's**

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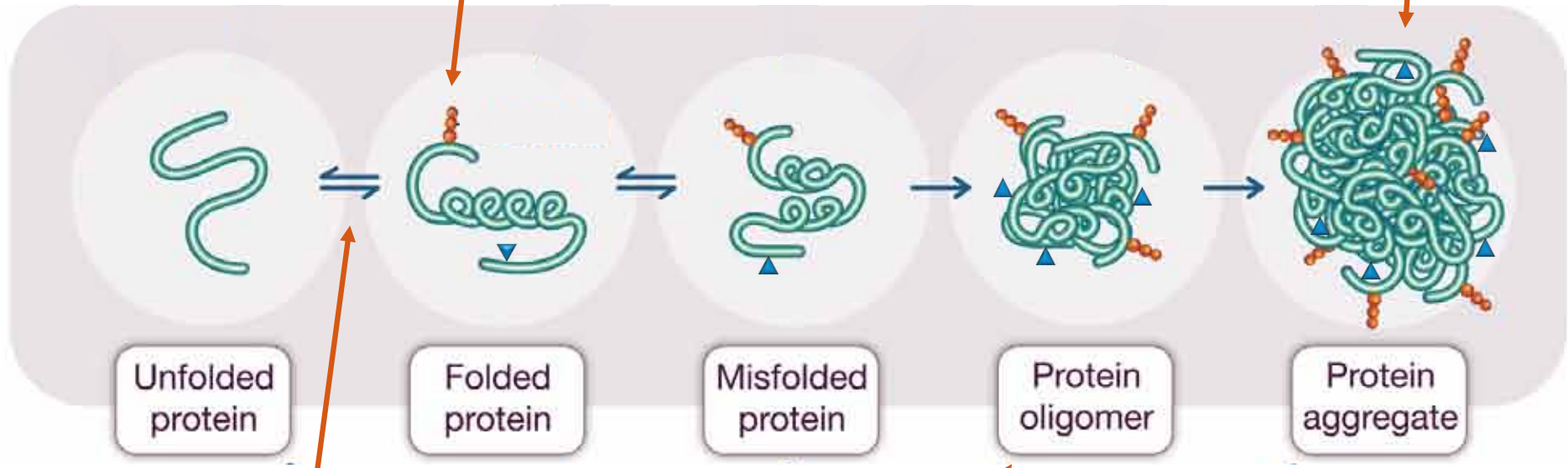
The misfolding process

Proteins are tagged with "**PTMs**" that affect their fate

These are the **plaques, tangles** or **Lewy bodies**



Chaperones help Correctly fold proteins and flag misfolded proteins for degradation

These are what most people think are the **toxic species**

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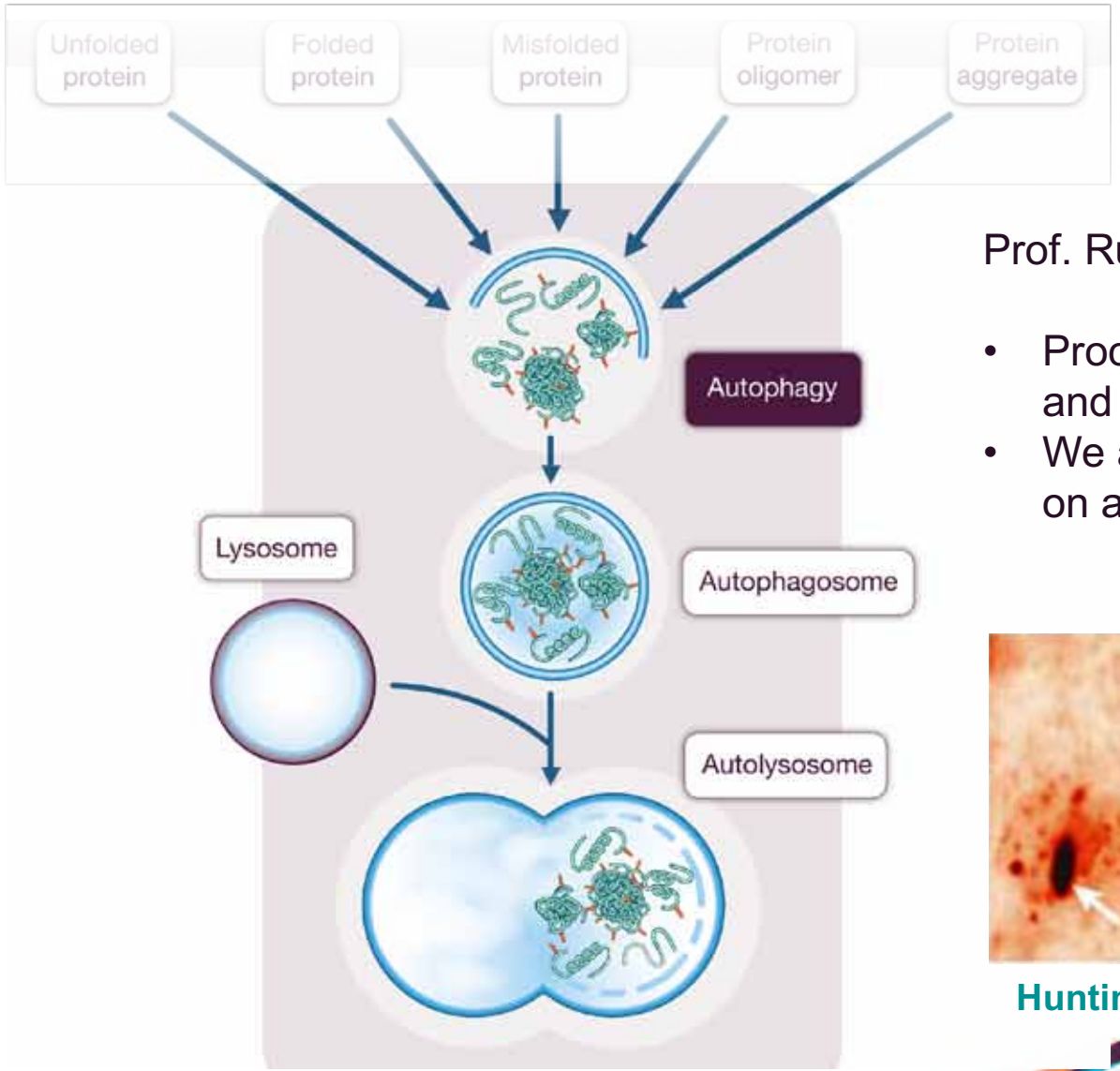
Autophagy… taking out the trash

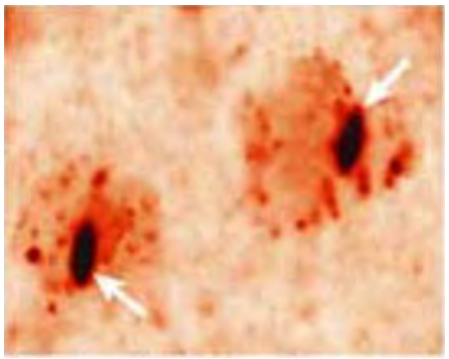
Prof. David Rubinsztein

University of Cambridge

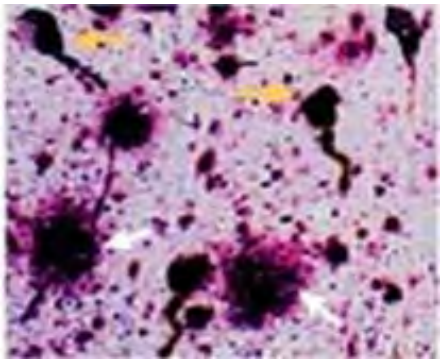


Prof. Rubinsztein is studying **autophagy**

- Process by which the brain can destroy and recycle of the misfolded proteins
- We are searching for drugs that will turn on autophagy



Huntington's Disease



Alzheimer's Disease

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Questions?

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