Current progress towards new treatments & preventions for dementia

Dementia 2020 Conference
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Some challenges to researching dementia

- Disorder of the brain – *complexity, inaccessibility*
- Not a single disease - *a syndrome with many possible causes*
- 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
- Long ‘preclinical’ phase – *significant damage before symptoms set in*
- Nomenclature: pathologies, diagnostic symptoms & criteria
- Relatively small pool of researchers;
  seen as an unattractive area – difficult, poorly-funded, few opportunities in academia and industry
  - Record levels of attention, interest, investment

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Different pathologies cause different types of dementia

- damage to and death of neurons in response to the build up of particular proteins (*neurodegeneration*)

Dementia subtype	Defining pathologies of misfolded, mislocated or aggregated proteins
Alzheimer's disease	Amyloid beta: soluble and insoluble (plaques) Tau: aggregated forms (tangles)
Parkinson's disease & Dementia with Lewy Bodies	Aggregated alpha synuclein (Lewy bodies)
Frontotemporal dementias	e.g. TDP43, FUS, tau
Prion disease	PrP variants

Vascular dementia

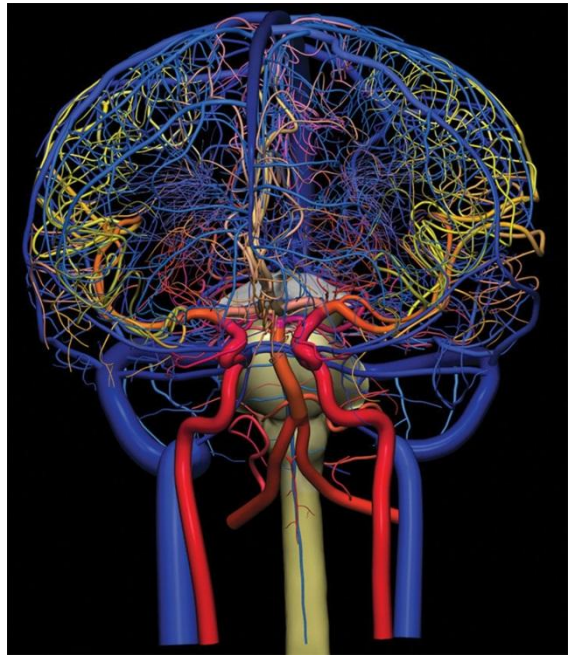
The human brain accounts for ~2.5 % body's weight but uses ~20 % of the body's oxygen and energy needs

Vascular dementia results from damage to and death of nerve cells in response to reduced blood supply

Subtypes and causes:

- Multi-infarct (cortical vascular) dementia
- Small vessel (subcortical vascular) dementia
- Strategic infarct dementia *(e.g. thalamus)*
- Hypoperfusion dementia
- Haemorrhagic dementia
- Hereditary vascular dementia (CADASIL)
- AD with cardiovascular disease

O'Brien and Thomas (2015) Lancet 386, 1698-1706



Nita DA, Neurology 2012;79:e10

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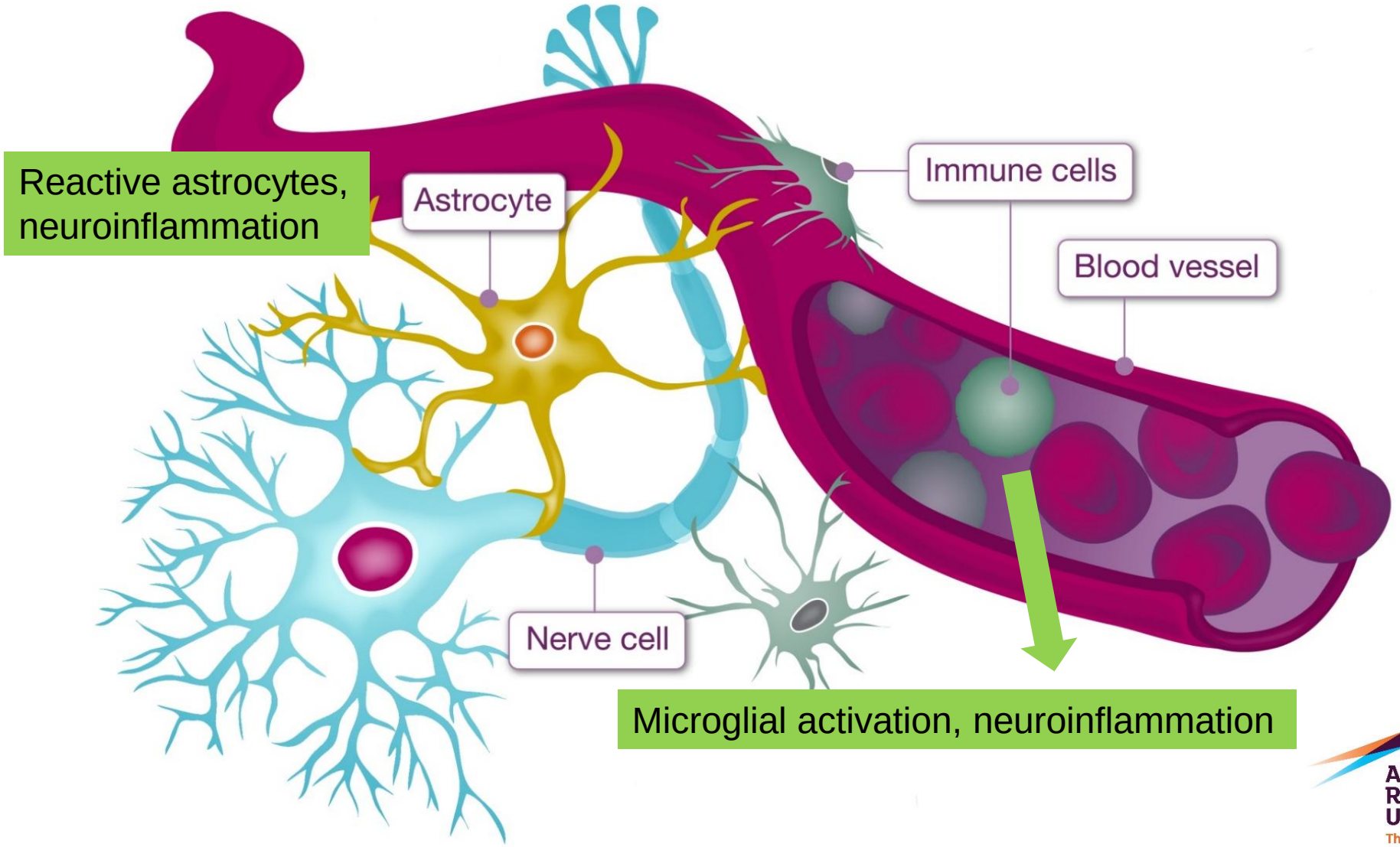
Dementia pathologies are not just about neurons and blood vessels



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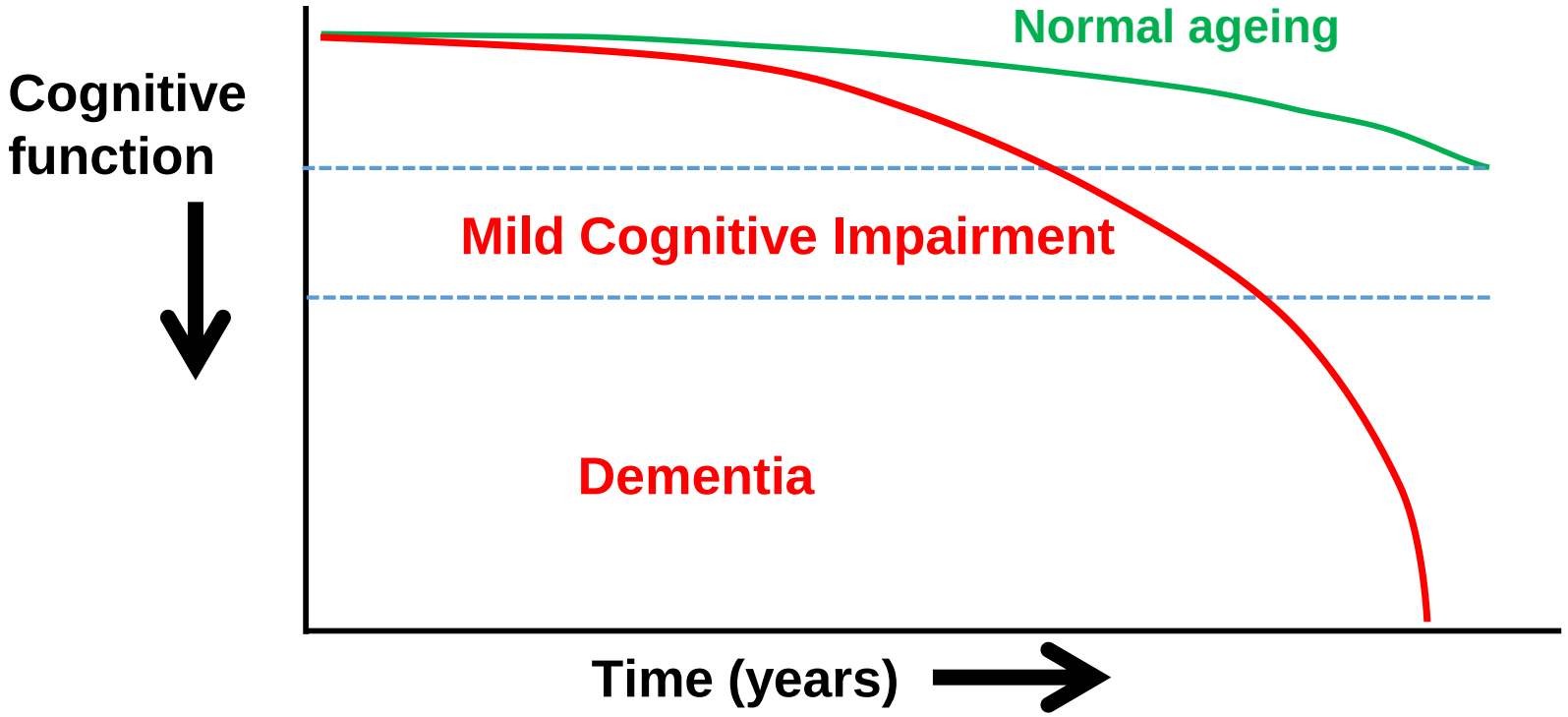
Different dementia pathologies and the diseases/symptoms they cause:

- Can often occur together
- Cause different dementia symptoms depending on the parts of the brain affected
- Are progressive and irreversible
- Are not yet fully understood
  - difficult to follow in people and to model experimentally

Cognitive decline: treatments and cures



Adapted from Sperling et al (2011) Alzheimer's & Dementia 280-292

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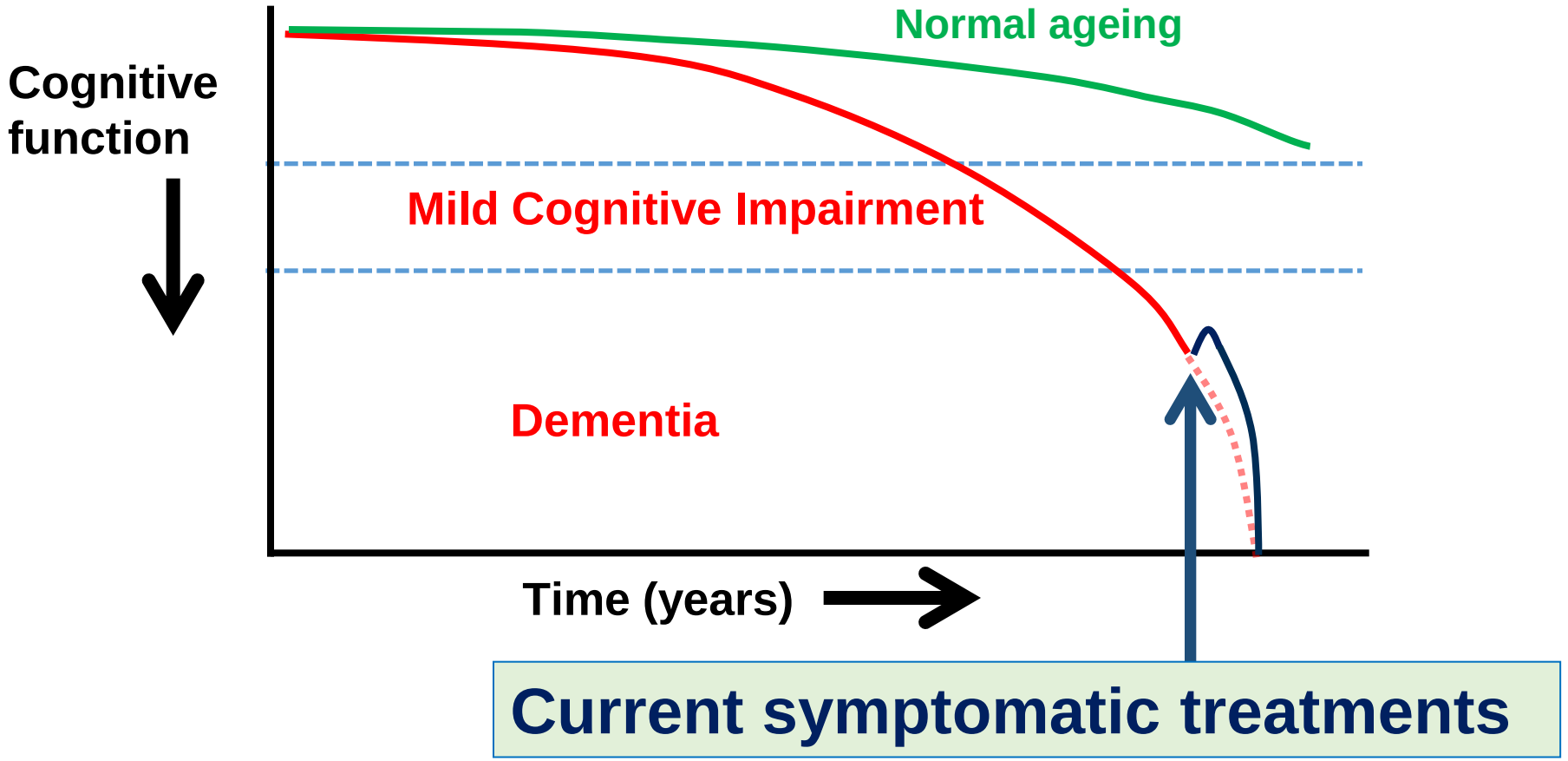
Cognitive decline: treatments and cures



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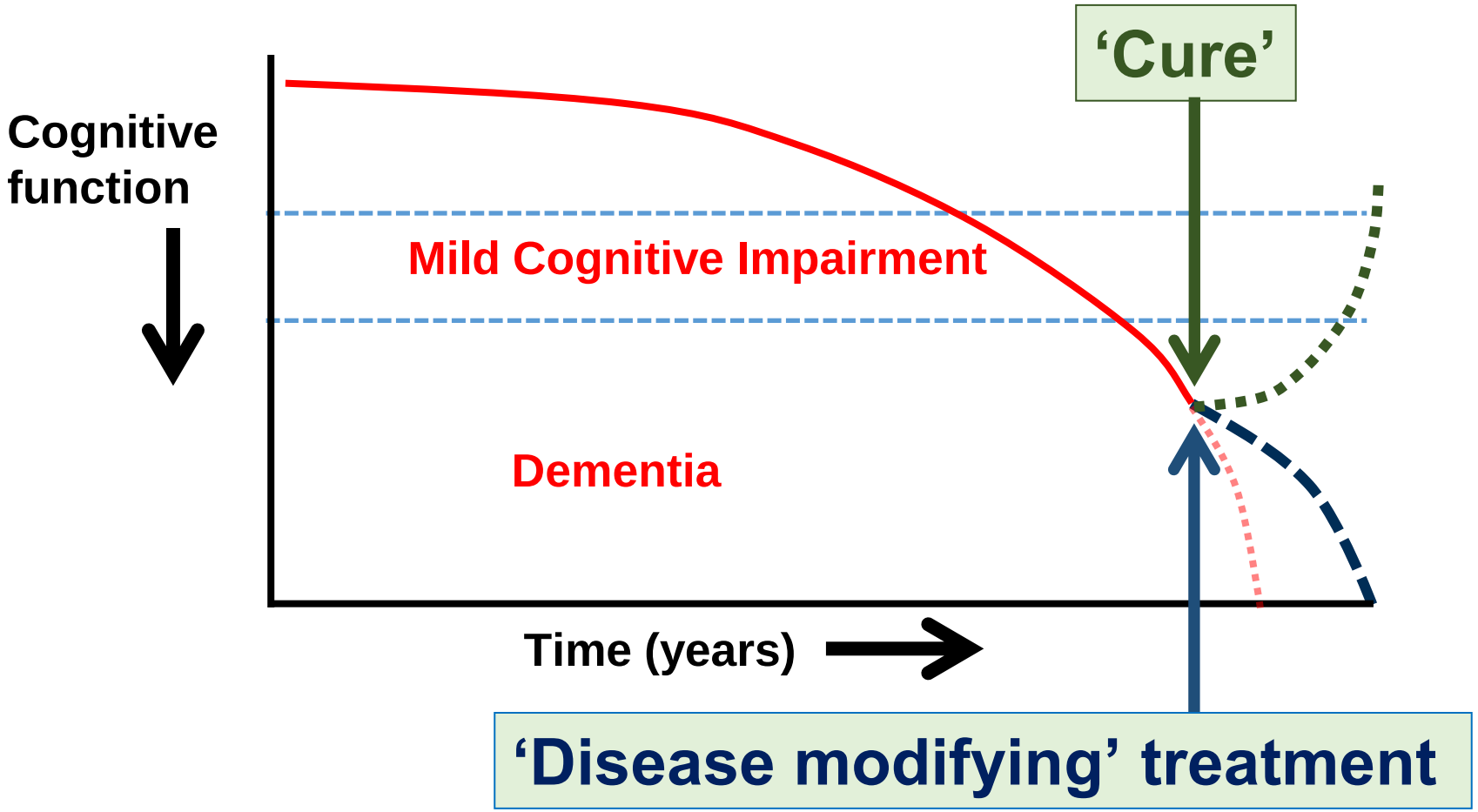
Cognitive decline: treatments and cures



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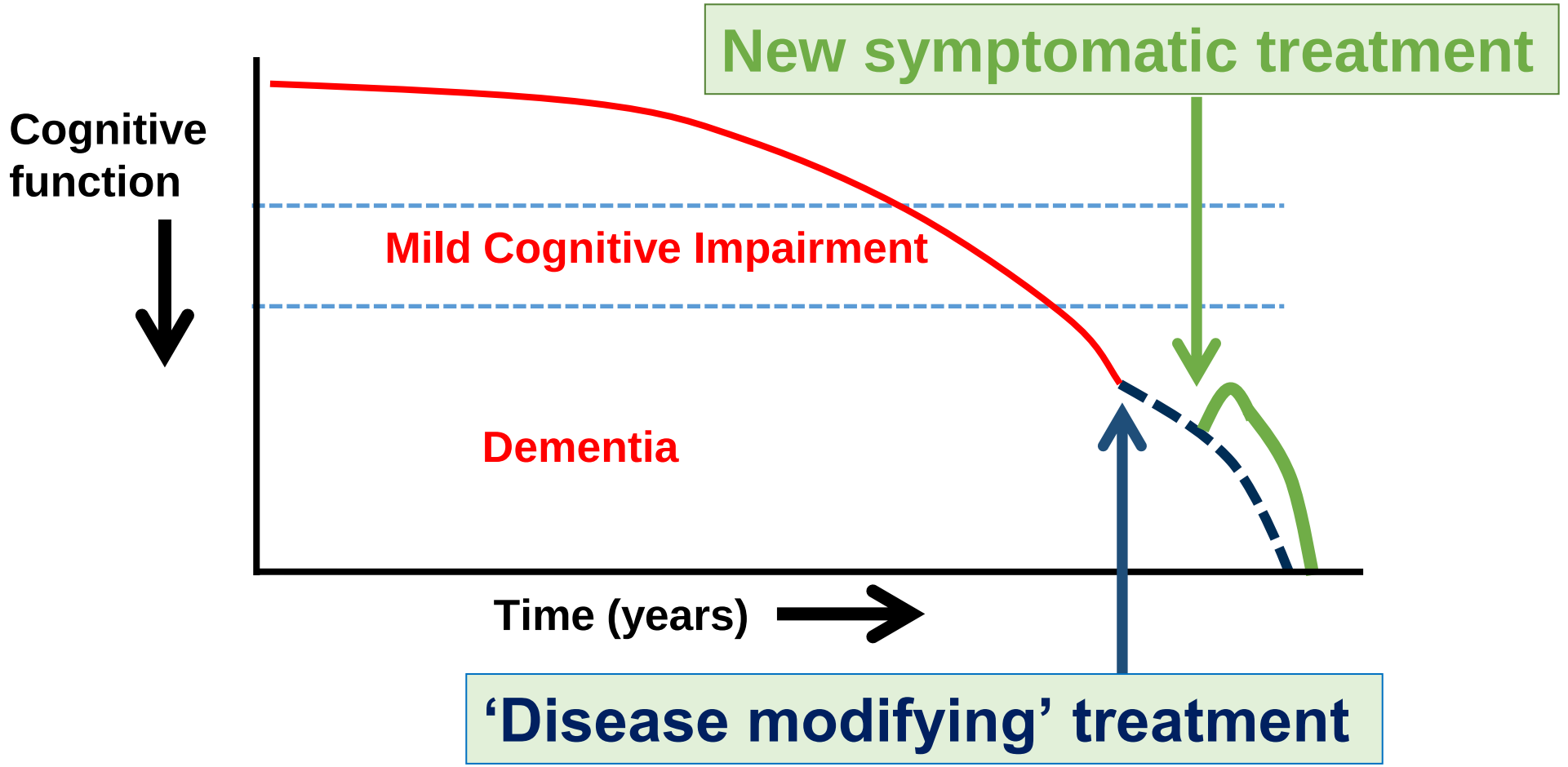
Cognitive decline: treatments and cures



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Approaches to develop disease-modifying dementia treatments

- Directly target the build-up of proteins which may cause dementia pathologies: *decrease production, boost clearance*
- Target the downstream events which result in nerve cells, blood vessels becoming damaged / lost
- Target other processes which contribute to the pathology, such as inflammation

So far, all clinical trials of disease modifying treatments have failed to meet their primary endpoints, apart from a few positive signs

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Why we should not give up hope of better treatments

- Lessons from Phase III trials of anti-amyloid treatments:
  - Some PIII trials were not always well supported by Phase II or preclinical data
  - Many trial participants didn't have amyloid in their brains
  - Amyloid deposition may trigger further AD pathology 20 years before any symptoms appear.
    Giving anti-amyloid drugs to people who already have symptoms may be too little, too late
  - Solanezumab showed some promise in mild AD; Expedition-3 trial ongoing
  - *The amyloid cascade hypothesis has still not been properly tested in the clinic*

- Most of the failed trials were targeting amyloid in Alzheimer's disease – not many other approaches have been tried properly yet
- As we learn more about other disease processes in AD and other dementias, new drug targets will be found

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Diagnosis, detection, treatment and prevention

Primary Prevention	Secondary Prevention	Tertiary Prevention
No disease	***Asymptomatic disease***	***Clinical disease: dementia***
Reducing risk across the life course	**Onset of pathologies**	**Reducing impact & complications**
10-30% dementia cases preventable? Better evidence base Awareness	*Where/when possible*: Detection & targeting of pathologies for *'disease modification'* Currently at research level, not routine clinical practice: - Insufficiently validated tools - No proven drugs yet - Insufficient risk/cost/benefit	Early/timely diagnosis Alleviation of symptoms

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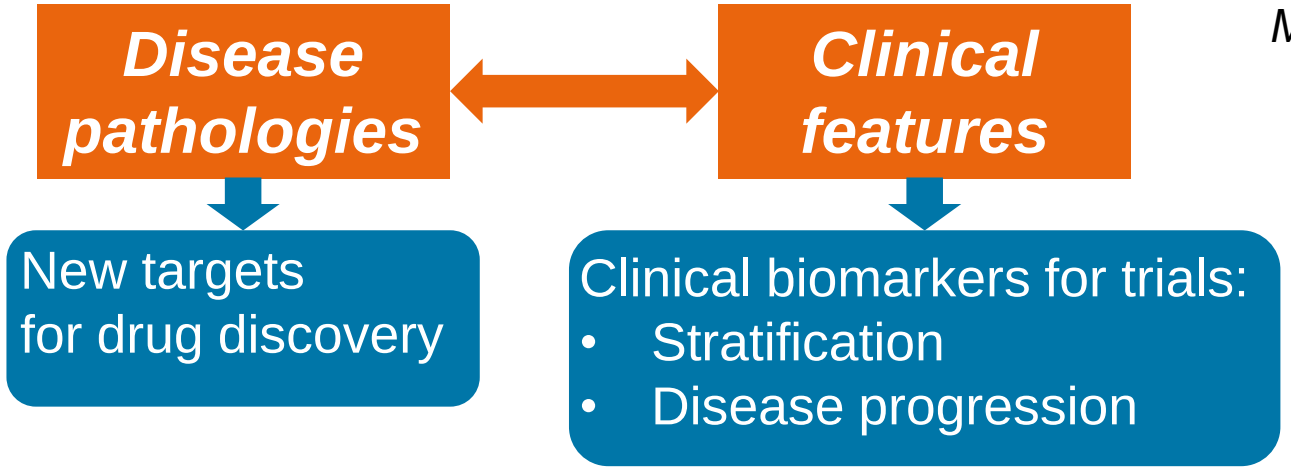
What is needed for new dementia treatments?

1. New scientific knowledge from general and targeted investments



MRC: Dementia Research Institute
Dementias Platform UK

NIHR: Biomedical Research Units in Dementia

EU Joint Programming in Neurodegenerative Diseases, IMI

Charity research grants

2. …and the means to translate it – investment, mechanisms, partnerships

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DRUG DISCOVERY ALLIANCE

DEMENTIA Consortium
abbvie | Alzheimer's Research UK | astex pharmaceuticals | Eisai | Lilly | MSD | MRC

Dementia Discovery Fund

3. Pharma interest and investment

4. Support and infrastructure for clinical trials

Join dementia research

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Thank you

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