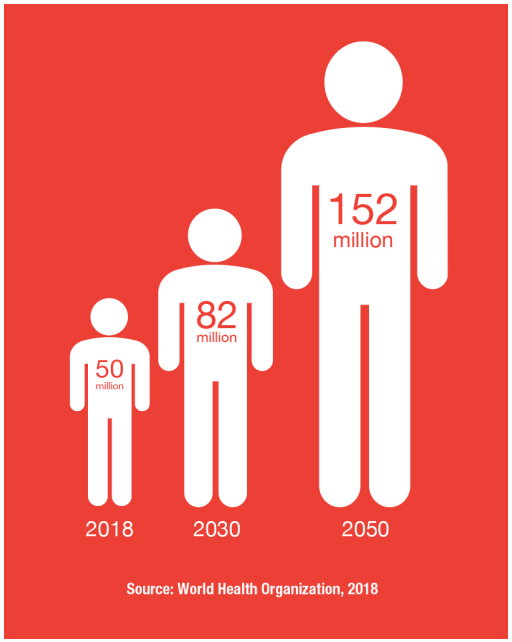
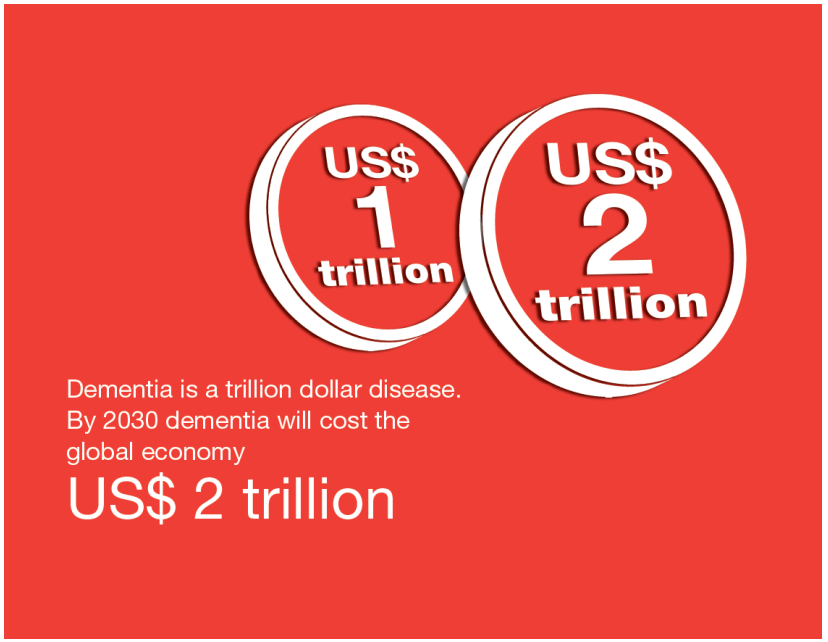
Alzheimer's disease - the prospects of preventing and slowing its progress

- More shots on goal
- Shooting earlier
- Shooting accurately

Simon Lovestone
Disease Area lead Janssen Pharmaceuticals
Professor of Translational Neuroscience, University of Oxford (part-time)

Dementia; an enormous, and growing unmet health need

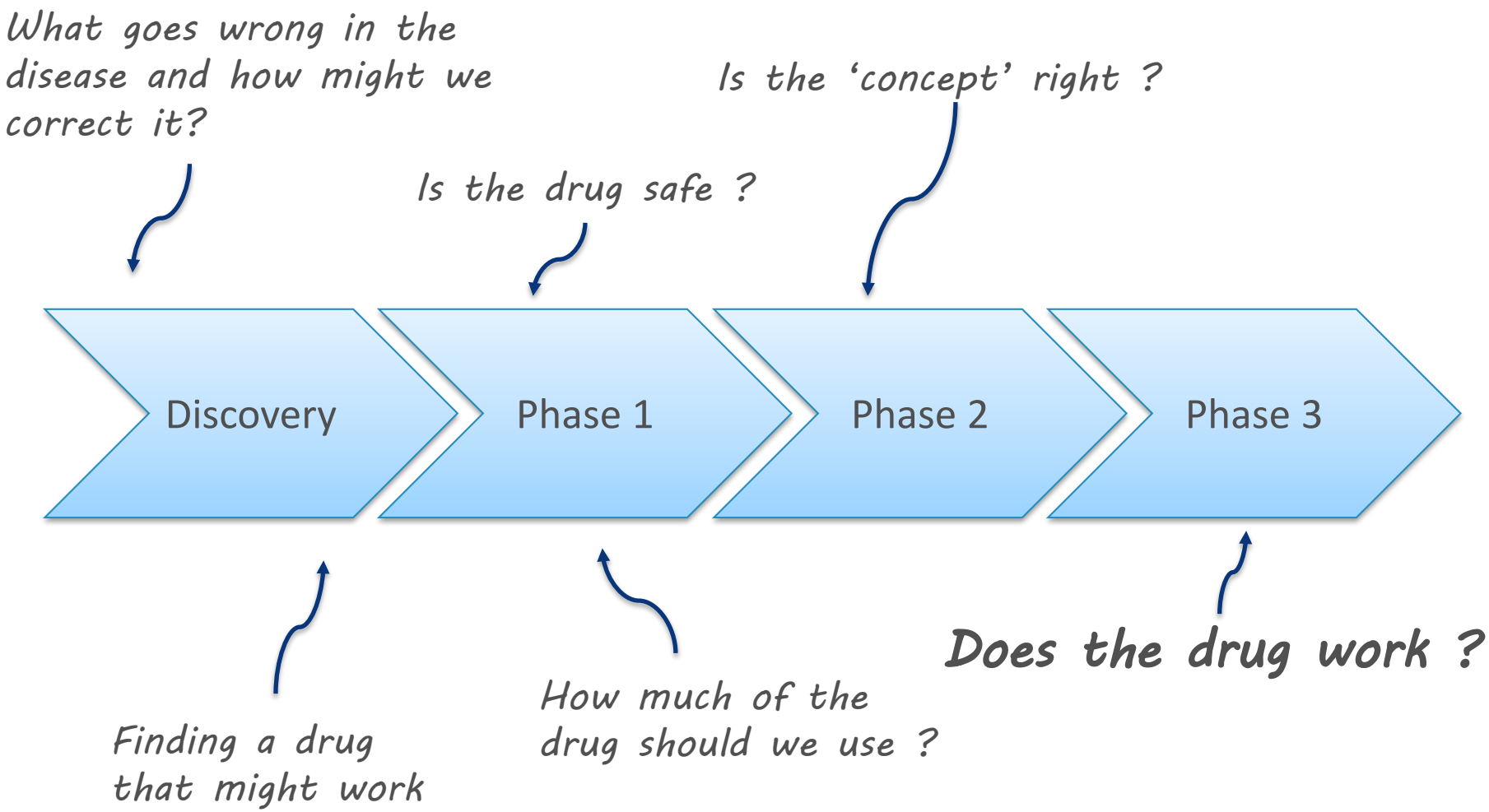




Alzheimer's Disease International
From Plan to Impact II; *The urgent need for action*
https://www.alz.co.uk/adi/pdf/from-plan-to-impact-2019.pdf

More people dying from Alzheimer's disease than from COVID19

Drug development pipeline

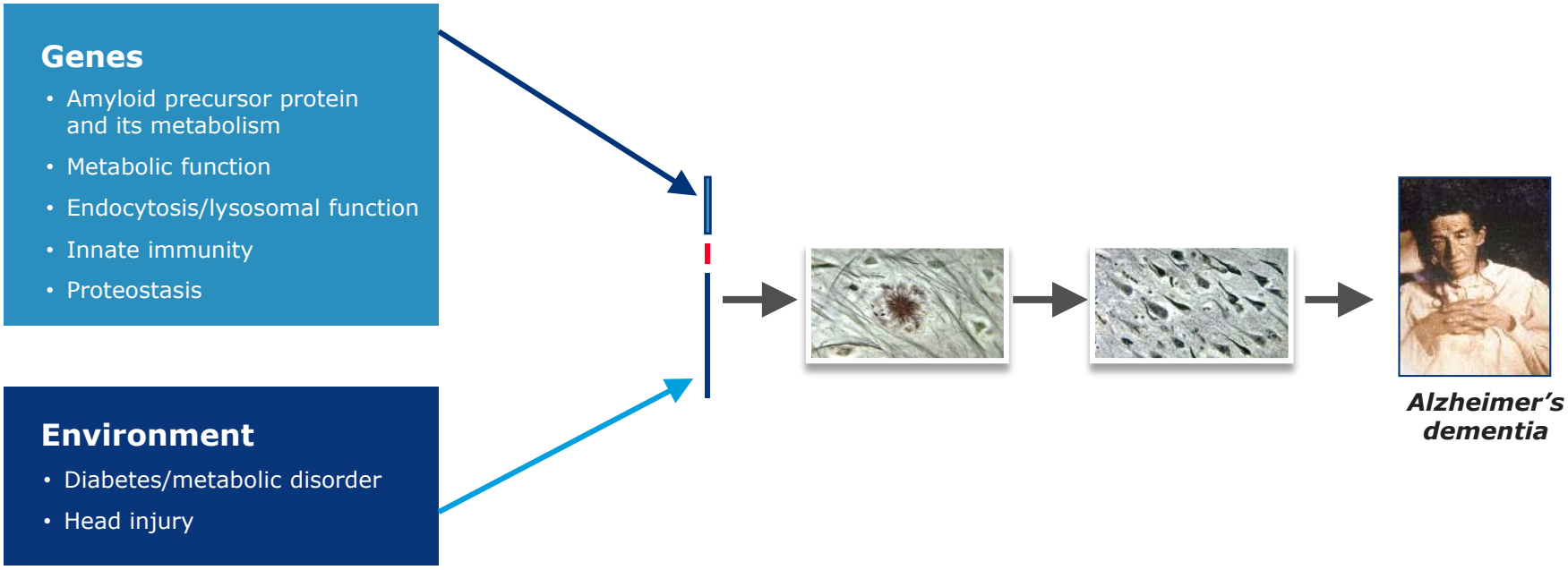


Costs of the Alzheimer's Disease development pipeline

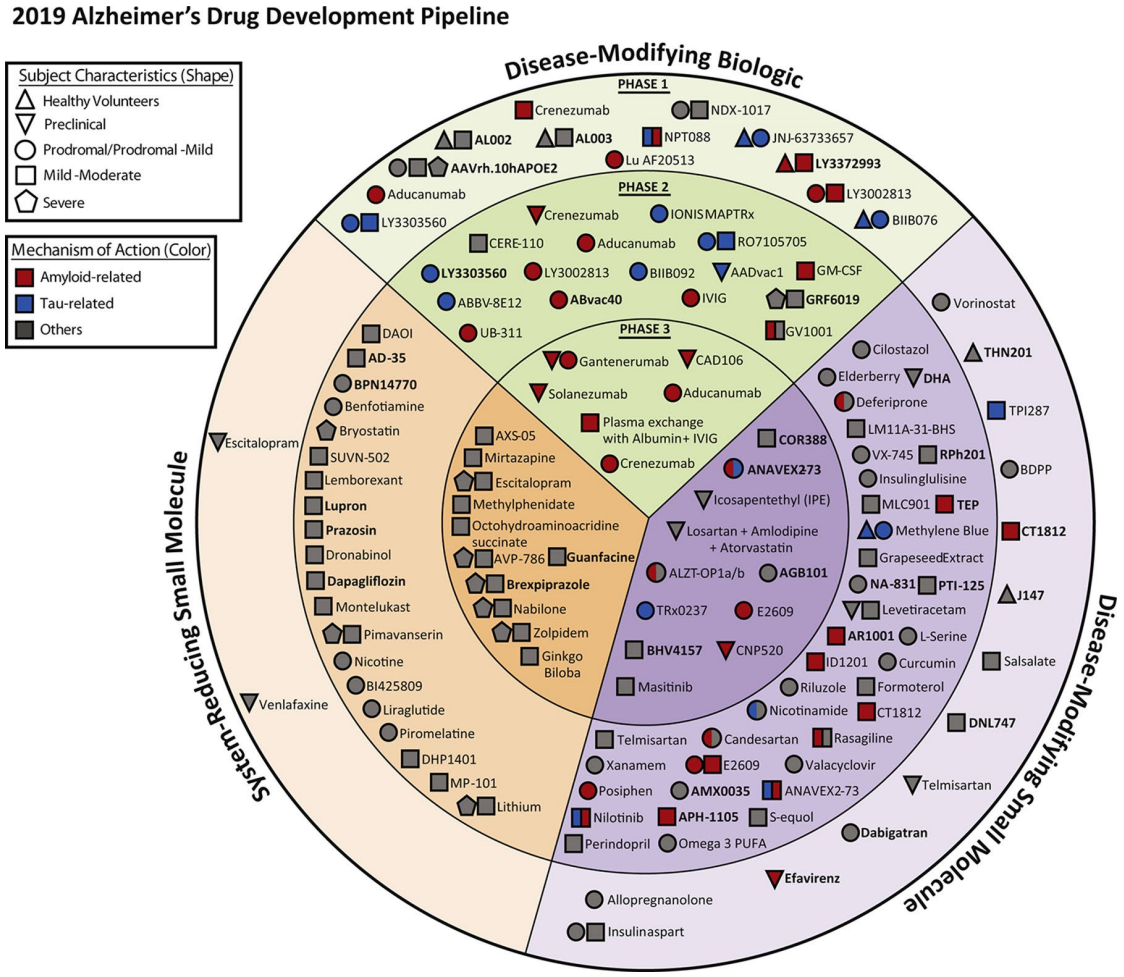
Stage of process	Duration (months)	Cost (billions)* ($)	Cumulative out-of- pocket costs (at end of each stage) (millions) ($)
Preclinical	50.1	1.65	
Phase I	12.8	1.19	71
Phase II	27.7	1.04	126
Phase III	50.9	1.79	413
FDA	18	0.02	
Total	13.3 years	5.69	

Cummings J, Reiber C, Kumar P: **The price of progress: Funding and financing Alzheimer's disease drug development**. *Alzheimers Dement (N Y)* 2018, **4**:330-343

The growing understanding of Alzheimer's disease



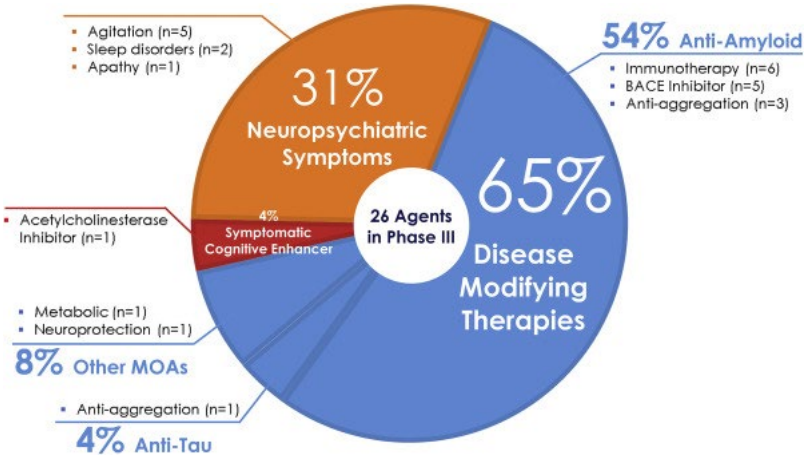
Lots of drugs in development for Alzheimer's disease



Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K: **Alzheimer's disease drug development pipeline: 2019**. *Alzheimers Dement (N Y)* 2019, **5**:272-293.

More shots on goal; the need for diversity in development

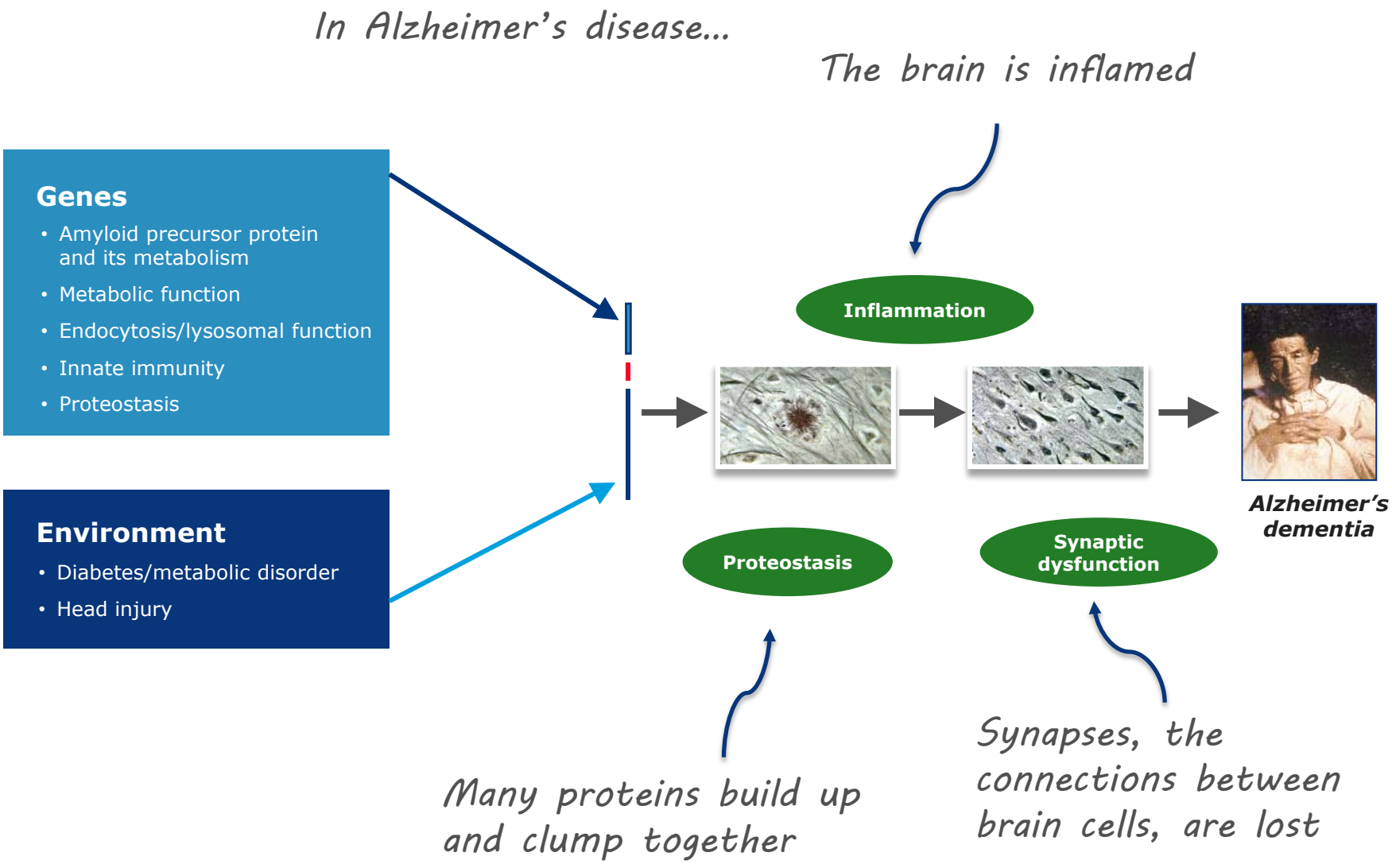
2018



Even in 2018 over half of all drugs in late phase trials in Alzheimer's disease were targeting one disease process (and it was worse before that)

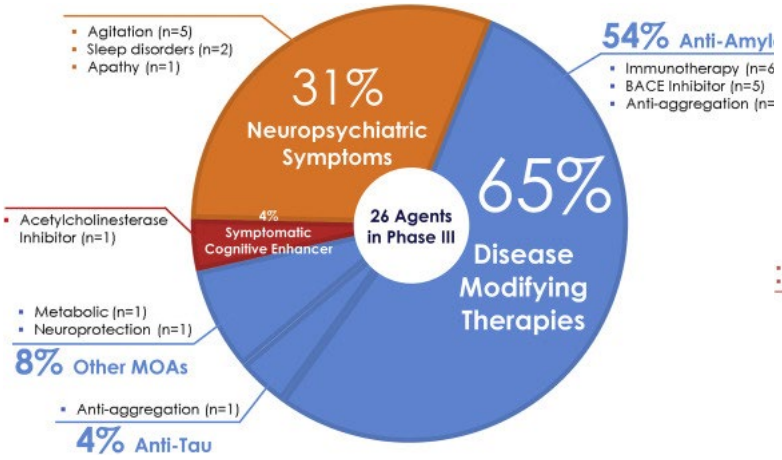
Cummings J, Lee G, Ritter A, Zhong K: **Alzheimer's disease drug development pipeline: 2018**. *Alzheimers Dement (N Y)* 2018, **4**:195-214.

The growing understanding of Alzheimer's disease



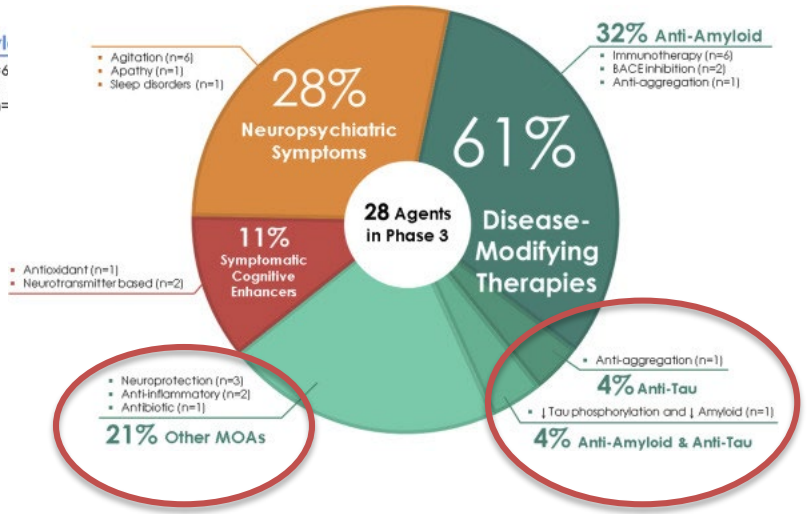
Growing diversity of drug development

2018



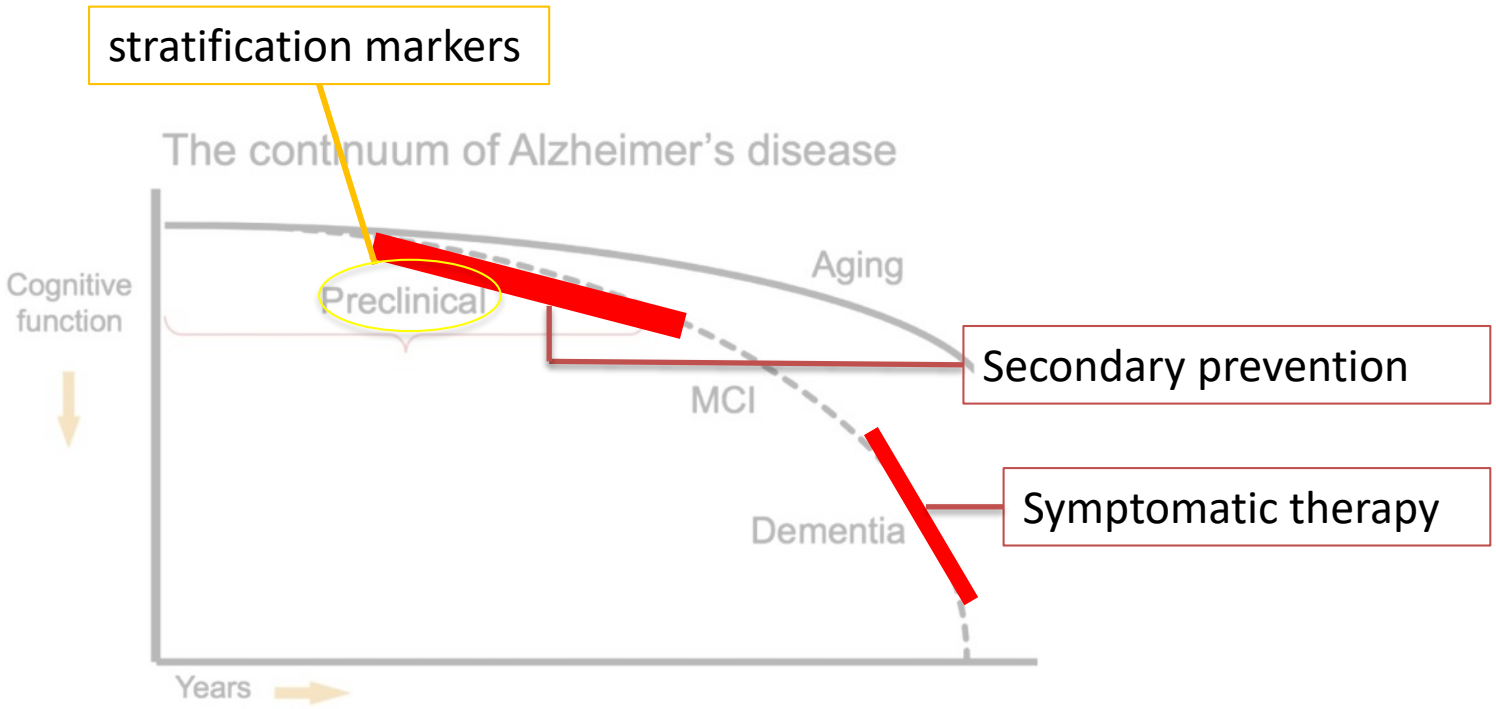
Cummings J, Lee G, Ritter A, Zhong K: **Alzheimer's disease drug development pipeline: 2018**. *Alzheimers Dement (N Y)* 2018, **4**:195-214.

2019

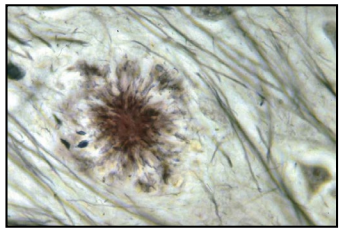


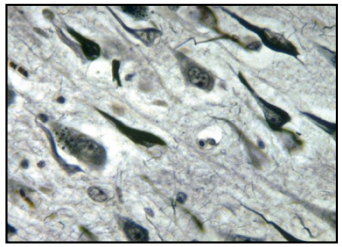
Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K: **Alzheimer's disease drug development pipeline: 2019**. *Alzheimers Dement (N Y)* 2019, **5**:272-293.

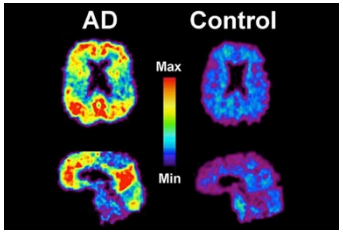
Shooting earlier; the need for trials early in the disease process

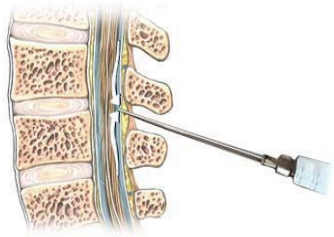


Shooting accurately;
biomarkers for the disease processes

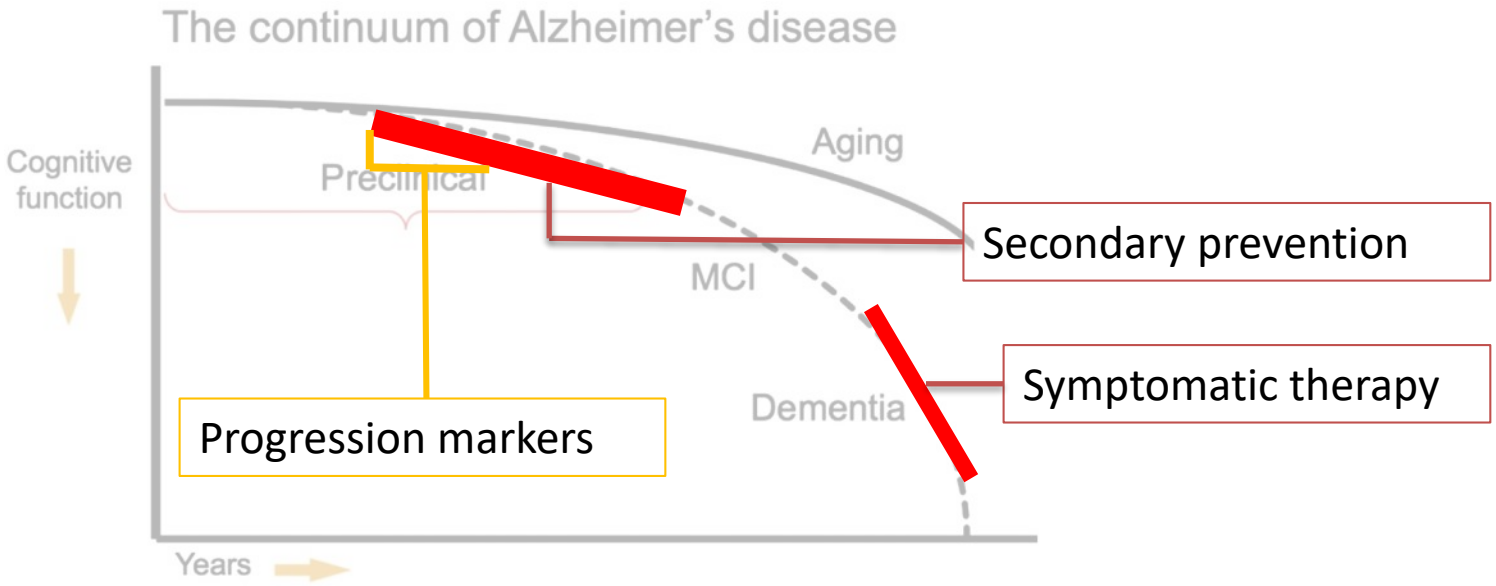








Trials are too long, too costly and too risky; We need to do better



Using biomarkers to make faster decisions, reduce the length and the cost of clinical trials and make finding a therapy more likely

Biomarkers enabling early disease trials

Deep and Frequent Phenotyping study

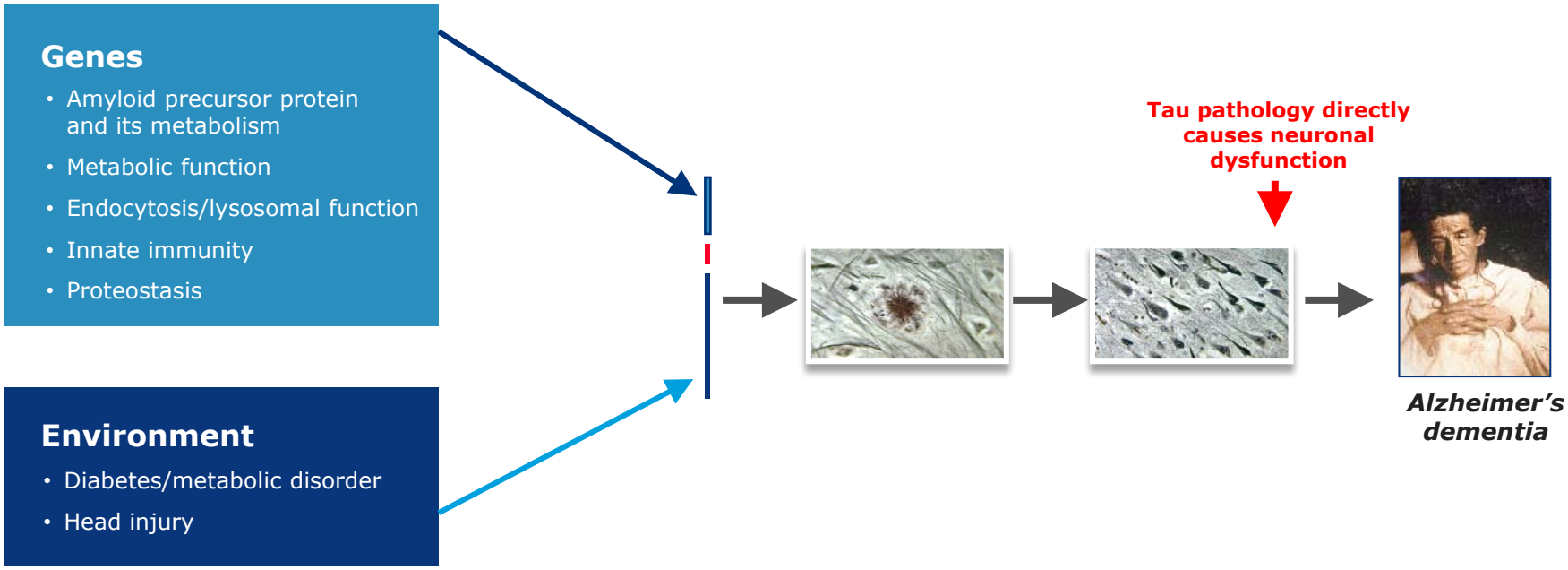
Aims to identify optimal set of markers for :

- patient stratification and selection for pre-clinical secondary prevention trials
- Markers of change for target engagement and early proof of concept trials

- Cognition
- Location
- Movement
- Digital activity

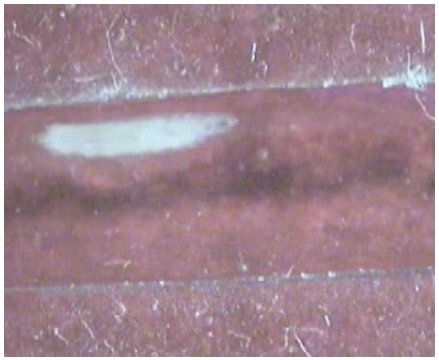
- **Deep phenotyping**
  - Amyloid and tau PET
  - Blood, CSF, MRI, MEG, EEG, retinal, cognition, gait,
  - connected devices for activity, cognition and function
- **Frequent phenotyping**
  - ~2-3 month repeat measures
  - Near continuous measures possible
- **Open science**
  - data sharing planned from outset

Choosing the right target: tau as a primary therapeutic opportunity



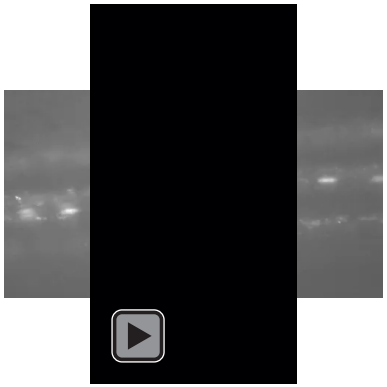
Tau as a choice of target; preclinical models

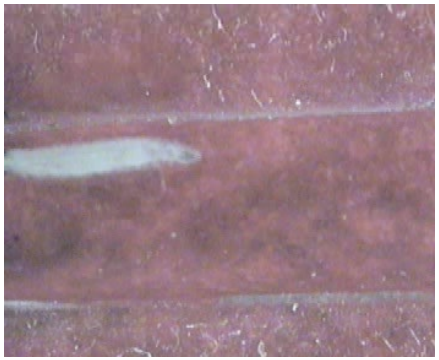
- Tau pathology results in neuronal dysfunction
- Multiple lines of evidence from in vivo and many in vitro models



Normal tau

- Microtubules intact
- Axonal transport active
- Normal neuronal function





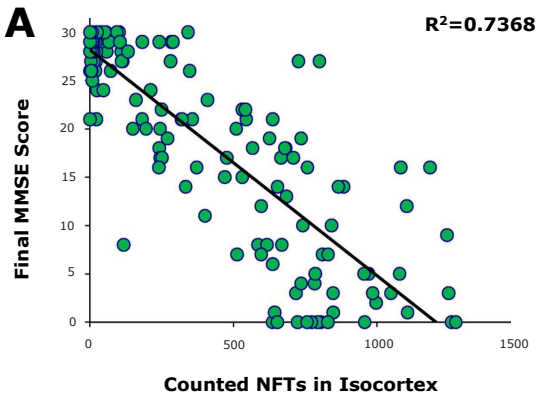
Altered tau expression or phosphorylation

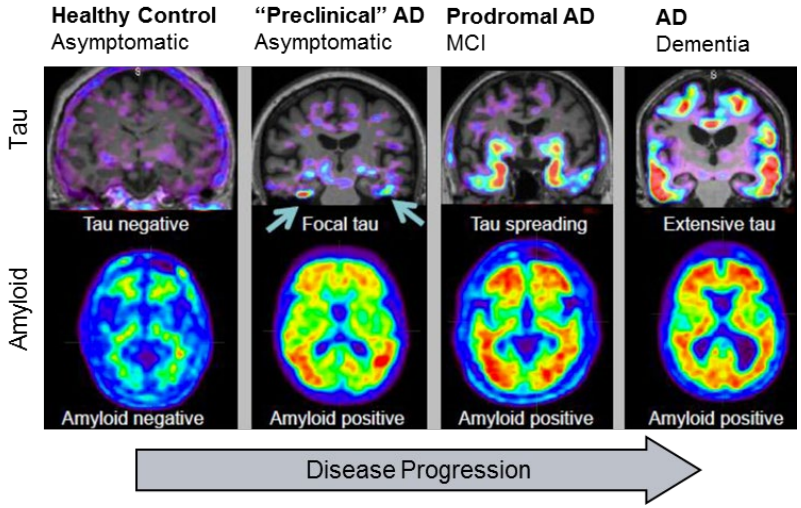
- Microtubules dysfunctional
- Axonal transport reduced
- Neuronal dysfunction

Lovestone, S., et al., *Lithium reduces tau phosphorylation: effects in living cells and in neurons at therapeutic concentrations.* Biol Psychiatry, 1999. **45**(8): p. 995-1003.

Tau as a choice of target; timing of intervention

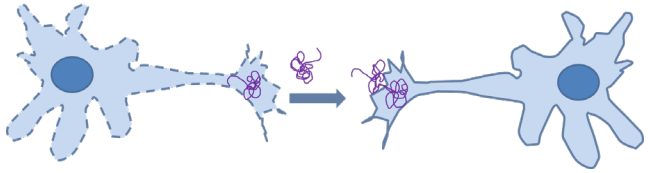
- Tau pathology correlates with symptoms
- Onset of tau pathology is proximate to onset of symptoms
- Tau pathology spreads between neurons





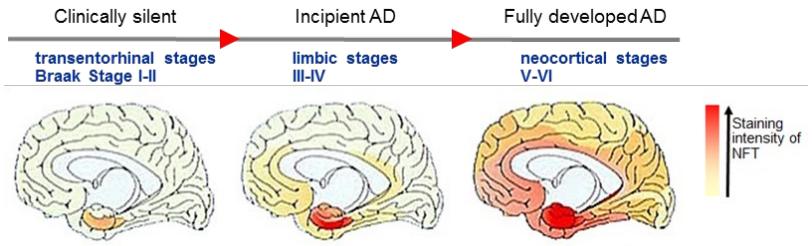
1. Nelson *PT J Neuropathol Exp Neurol.* 2012; 71(5):362–381

H.C. Kolb, M. Mintun ADPD 2013



Multiple tau therapeutic efforts in development

- Small molecules targeting tau modification (eg phosphorylation)
- Small molecule and other approaches targeting tau expression
- Recognition of disease spread through tau seeds opens new opportunities including tau monoclonal antibodies and vaccines
- Tau vaccination in clinical development



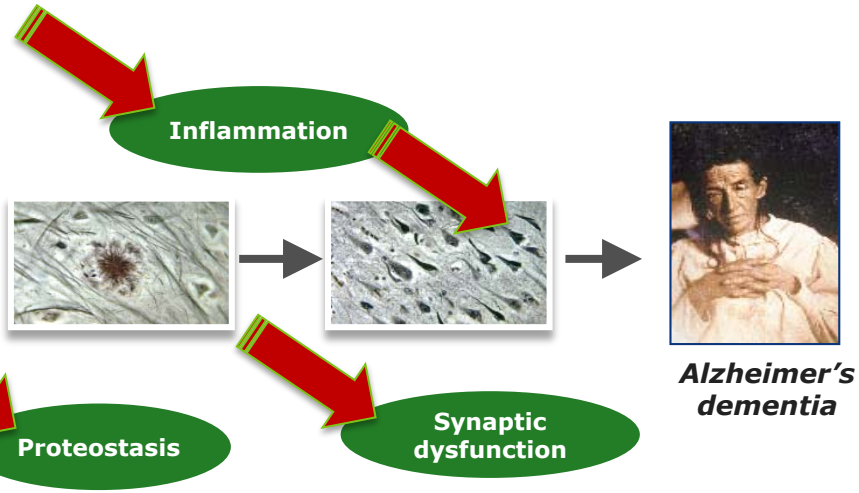
Multiple targets; multiple development programmes

Genes

- Amyloid precursor protein and its metabolism
- Metabolic function
- Endocytosis/lysosomal function
- Innate immunity
- Proteostasis

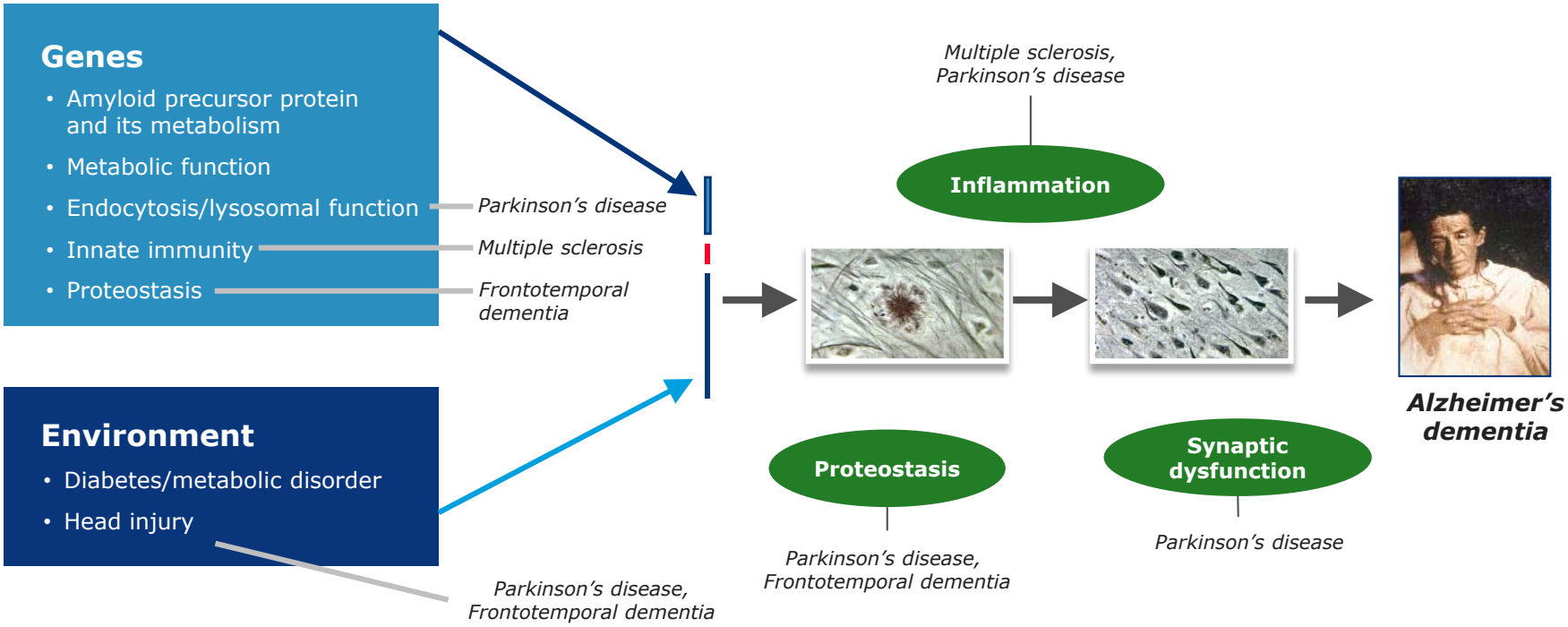
Environment

- Diabetes/metabolic disorder
- Head injury



opportunity for combination therapies

The growing understanding of Alzheimer's disease *and other neurodegenerative disorders*



Images provided by Lovestone, S., University of Oxford

Alzheimer's disease – slowing or prevention

- Diversification of drug development
- Early phase clinical trials
- Biomarkers for secondary prevention

- Alzheimer's disease – an end in sight?

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Will We Have a Drug for Alzheimer's Disease by 2030? The View From Pharma

Simon Lovestone ✉, Husseini K. Manji