

GSK-3 In Alzheimer's Disease

pathogenic kinase, biomarker and therapeutic target

- bench to bedside in action



Urgent need for translational success

700,000 people with dementia in the UK

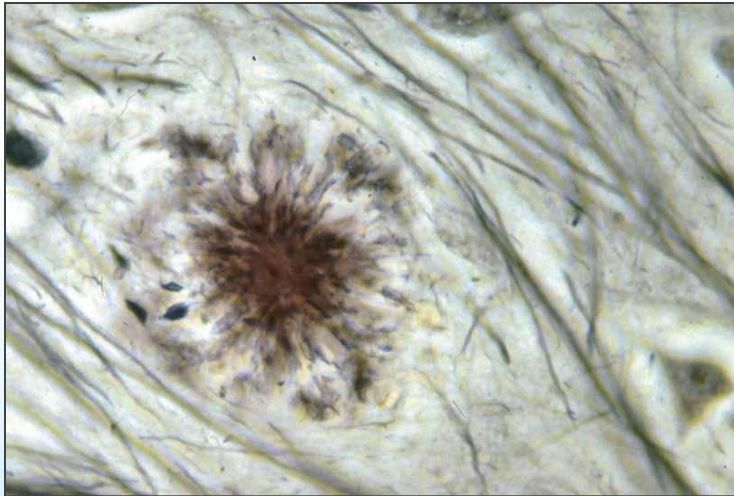
over a million with dementia by 2025

financial cost of dementia to the UK is over £17 billion a year

Accelerating translation through an AHSC

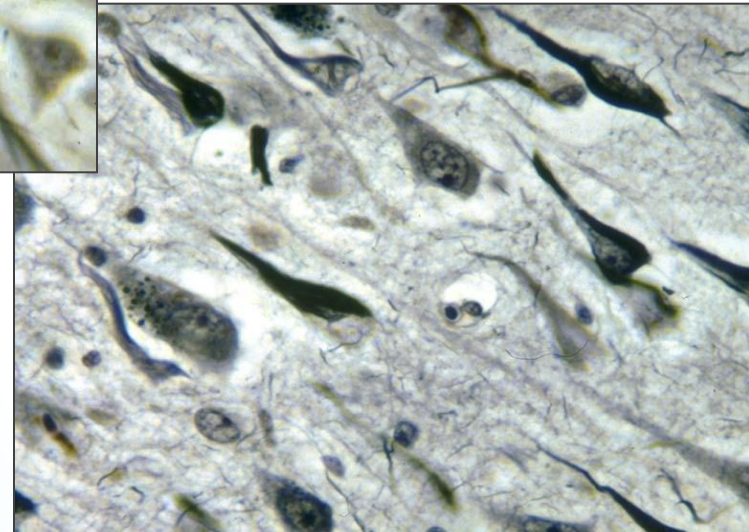
- **An example of bench to bedside translation**
 - GSK-3 as a biomarker and a therapeutic target in AD
 - in vitro, cellular models, animal models
 - biomarker discovery and early clinical trials
- **Translation in the context of collaborative organisations**
 - three Trusts, one university; many collaborations, numerous disconnects
- **Accelerated translation**
 - facilitating research
 - incentivising rapid translation

Alzheimer's pathology



Amyloid plaques composed of a core of aggregated A β derived from APP

Neurofibrillary tangles composed of aggregated, phosphorylated tau

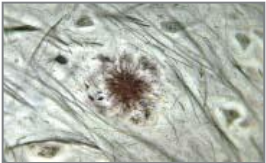


Amyloid cascade hypothesis

Environment



Genes



GSK-3 alters tau phosphorylation

In vitro

Hanger *et al Neurosci. Lett.* (1992) **147**, 58-62

In non-neuronal cells and neurons

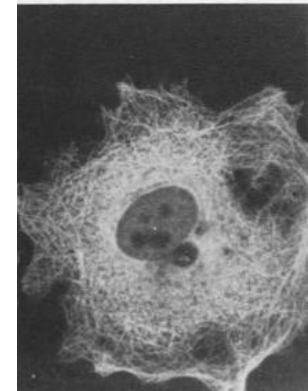
Lovestone *et al Curr Biol* (1994); **4**:1077-1086

Lovestone *et al Neuroscience* (1996) **73** 1145-1157

In transgenic mice

Brownlees *et al. Neuroreport* (1997) **8**, 3251-3255

Tau – no GSK3



Tau – with GSK3

Amyloid cascade hypothesis

Environment

Genes



A β increases GSK-3 activity in neurons

Takashima, A. *et al. Neurosci. Res.* **31**, 317-323 (1998)

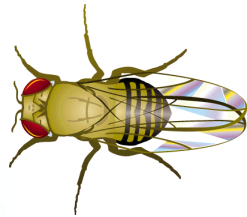
A β neurotoxicity is decreased by GSK-3 inhibition

Alvarez, G. *et al. FEBS Lett.* **453**, 260-264 (1999)

Tau over-expression phenotype is GSK-3 dependent

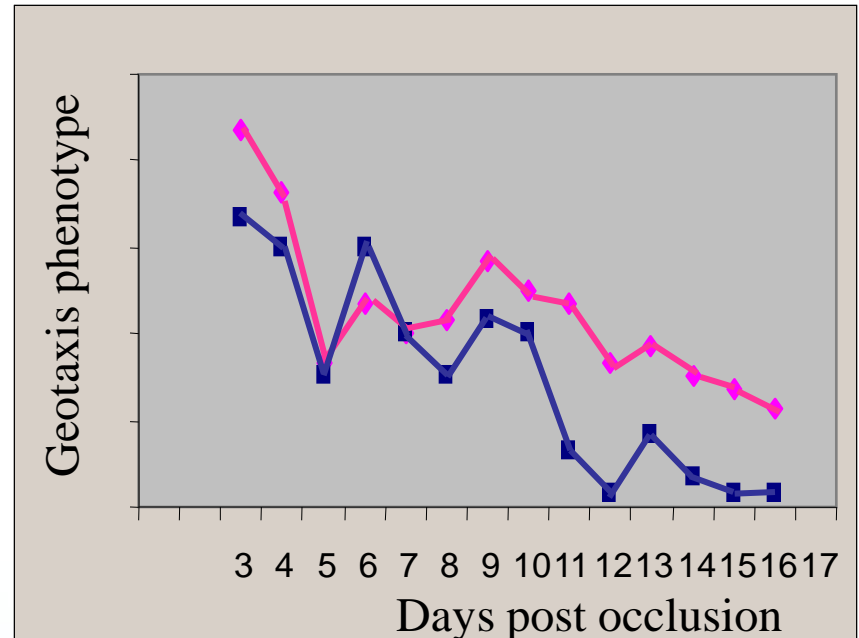
Motor neuron expression of

- Tau
- Tau + GSK-3 β

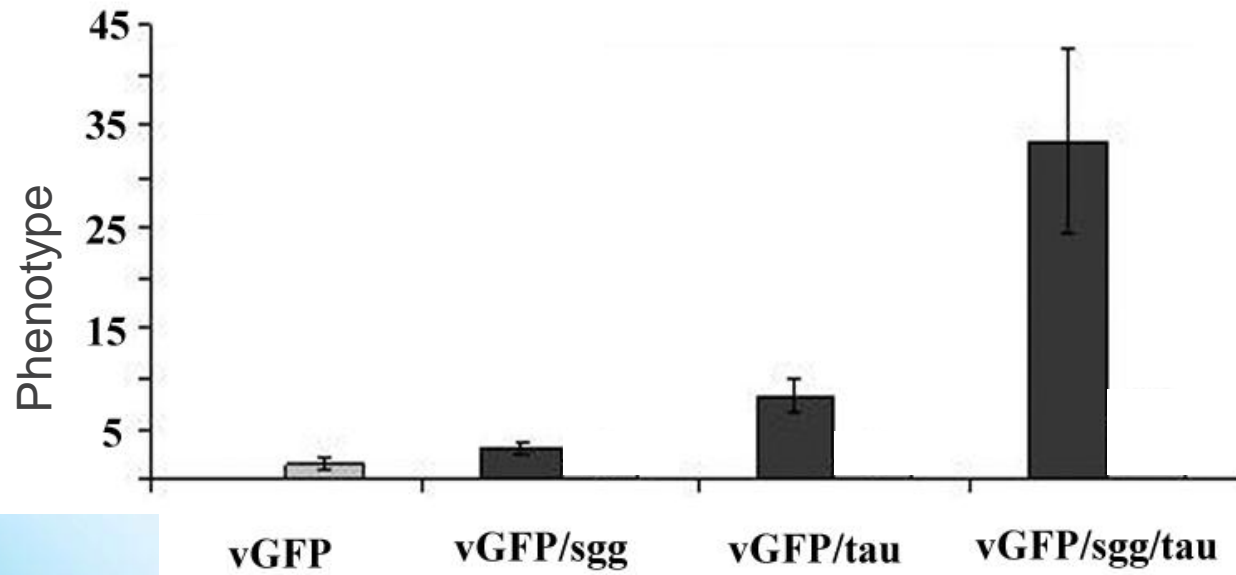


Mudher et al
(2004) **9**, 522–530

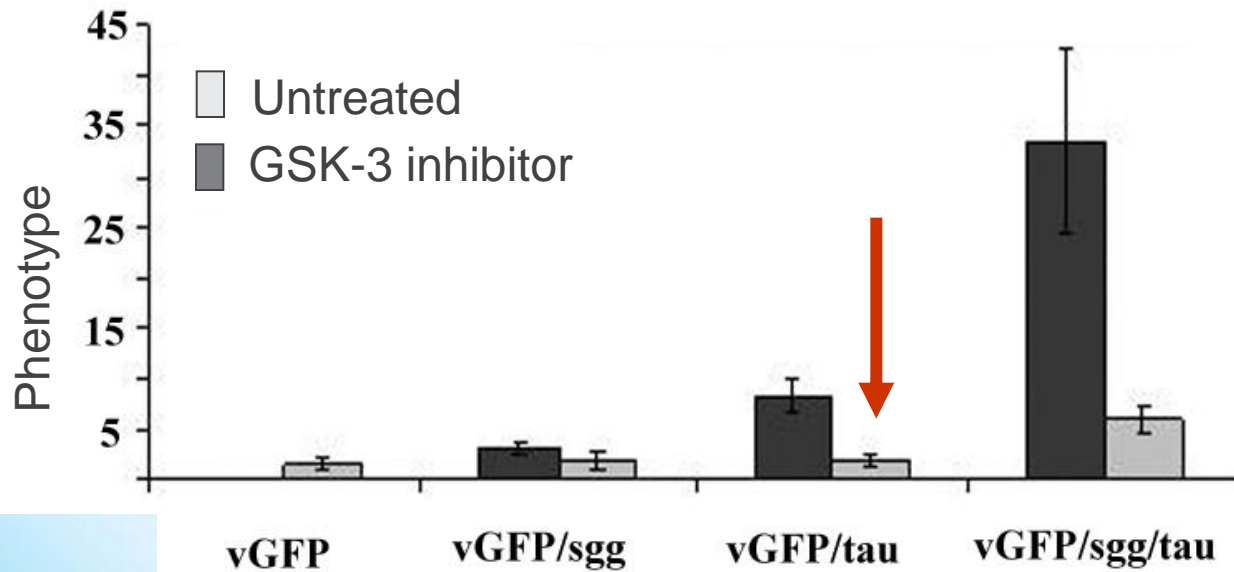
— Wild-type
— Tau transgenic



GSK-3 inhibition rescues phenotype



GSK-3 inhibition rescues phenotype



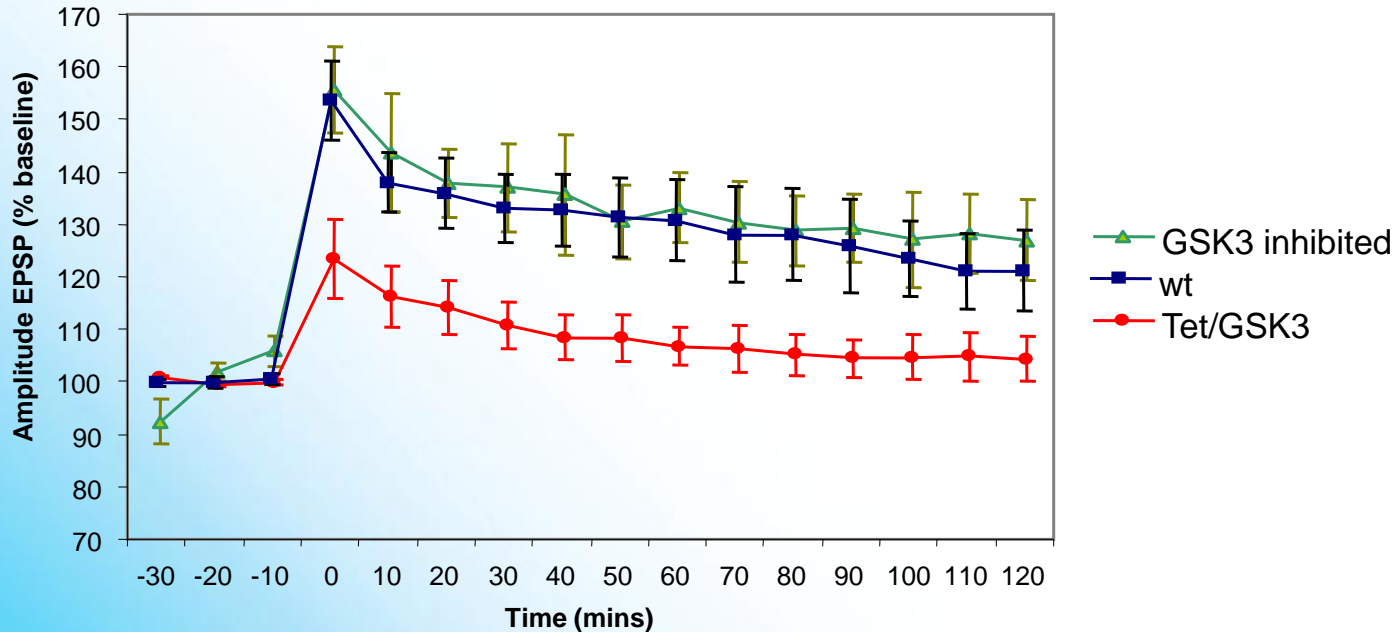
GSK-3 dependent, tau induced phenotype

GSK-3 regulates memory and plasticity

Increased expression of GSK3 in mouse brain:

- Increased tau phosphorylation
- Deficits in learning and memory

– Lucas et al, *EMBO J.* 2001;20:27-39



Hooper et al *Eur J Neurosci* (2007); **25**: 81-86.

GSK3 cascade hypothesis

GSK3 regulation
ie diabetes



GSK-3

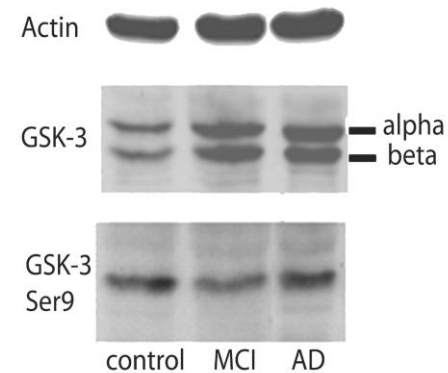
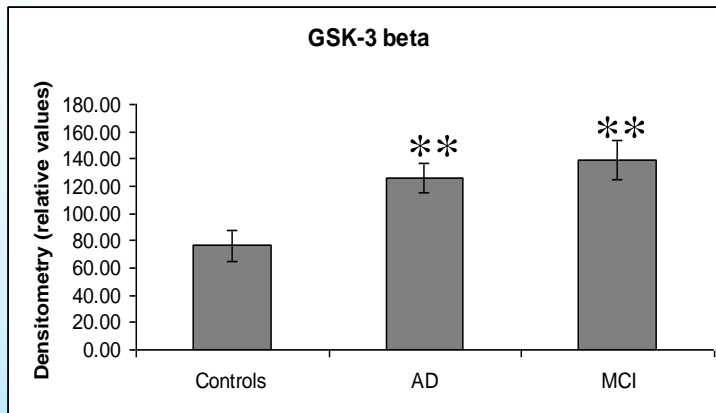


Genes associated with
GSK3 regulation

GSK-3 as a biomarker for AD

Increase in GSK-3 protein in AD and in MCI in white blood cells

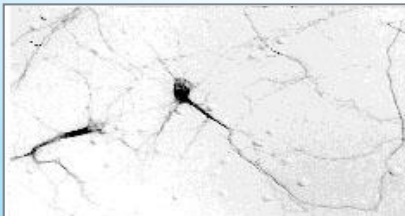
Hye,A. *et al. Neurosci. Lett.* **373**, 1-4 (2005)



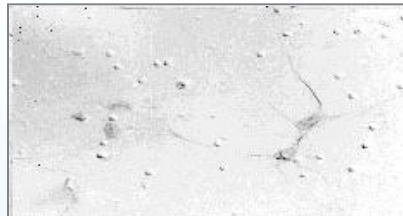
GSK-3 inhibition as a therapeutic strategy

- Lithium is an inhibitor of GSK-3
- In neurons and at therapeutic doses

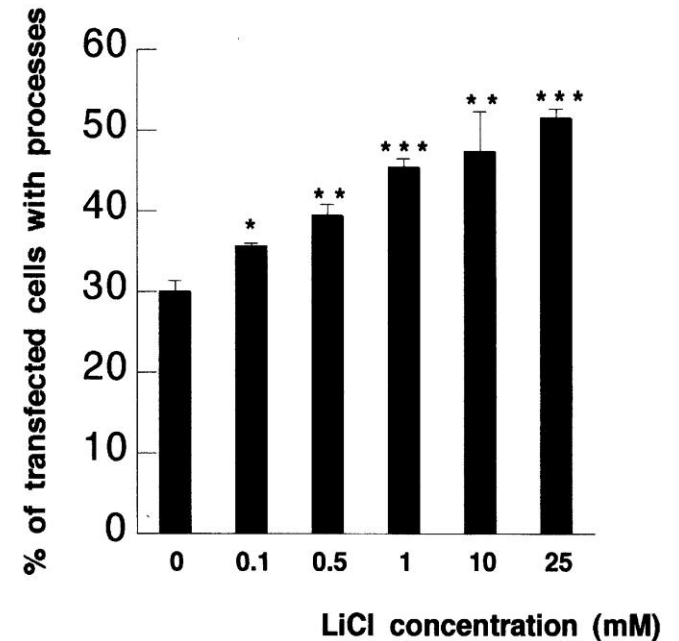
Phosphorylated tau
(ie AD like)



Non-phosphorylated tau
(ie normal)



Lovestone et al *Biol Psychiatry* 1999; 45:995-1003



Leroy et al. *FEBS Lett* 2000; 465:34-38

GSK-3 inhibition as a therapeutic strategy

- **Lithium is a safe and feasible treatment in AD**
 - One year, MRC sponsored trial
 - Macdonald et al. *Int J Geriatr Psychiatry* 2008; 23:704-711.
- **Lithium trials underway in multiple neurodegenerative diseases**
- **Specific GSK3 inhibitors in Phase II clinical trials in AD**

Conclusions

Therapeutic target

Tau kinase induced by A β

Mice and Drosophila models show reversible AD-relevant phenotypes

Environmental and genetic evidence aetiologies involving dysregulation of GSK3 in AD

Potential biomarker

Altered in blood cells in AD

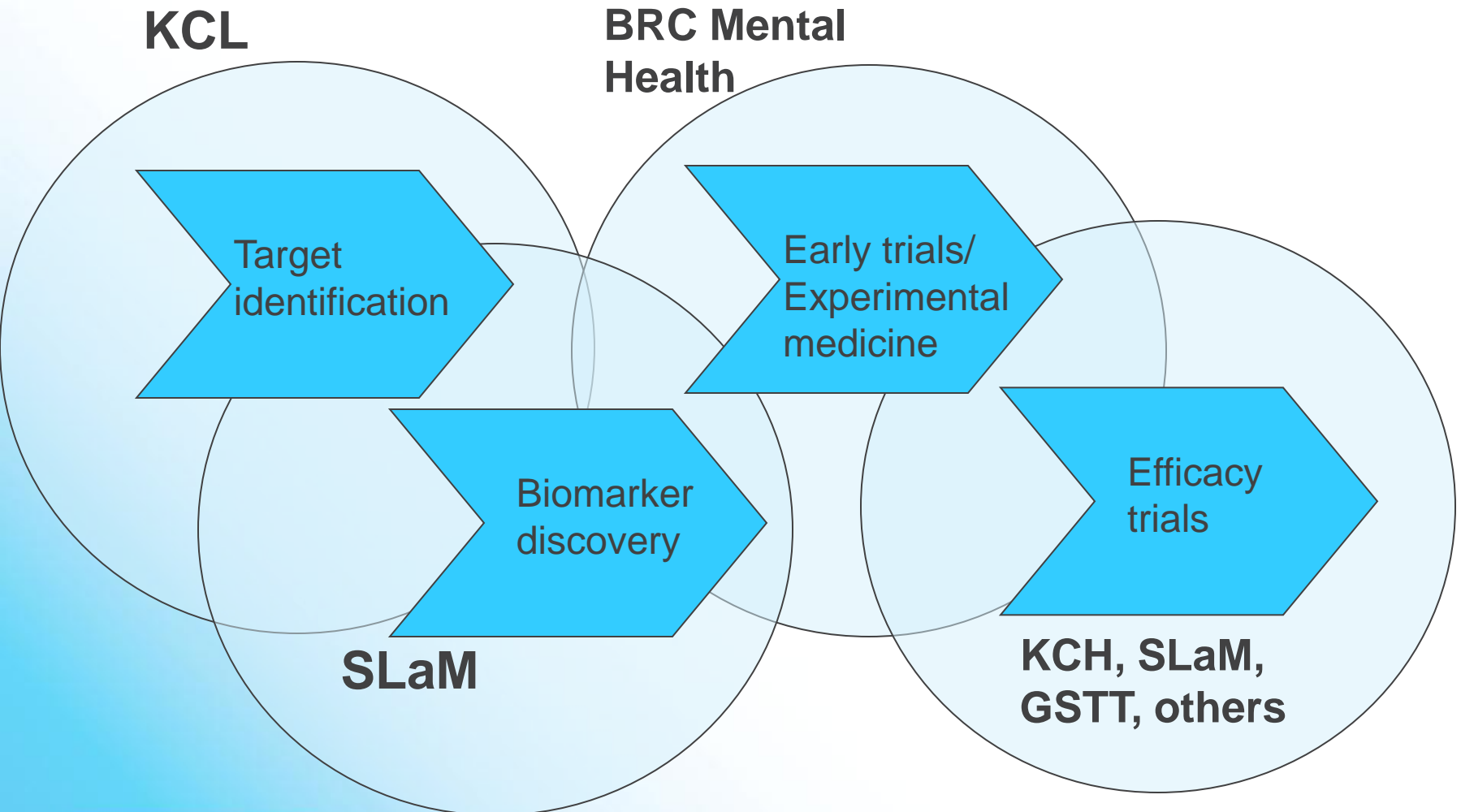
IP retained by KHP and exploitation plans underway

Therapeutic trials underway

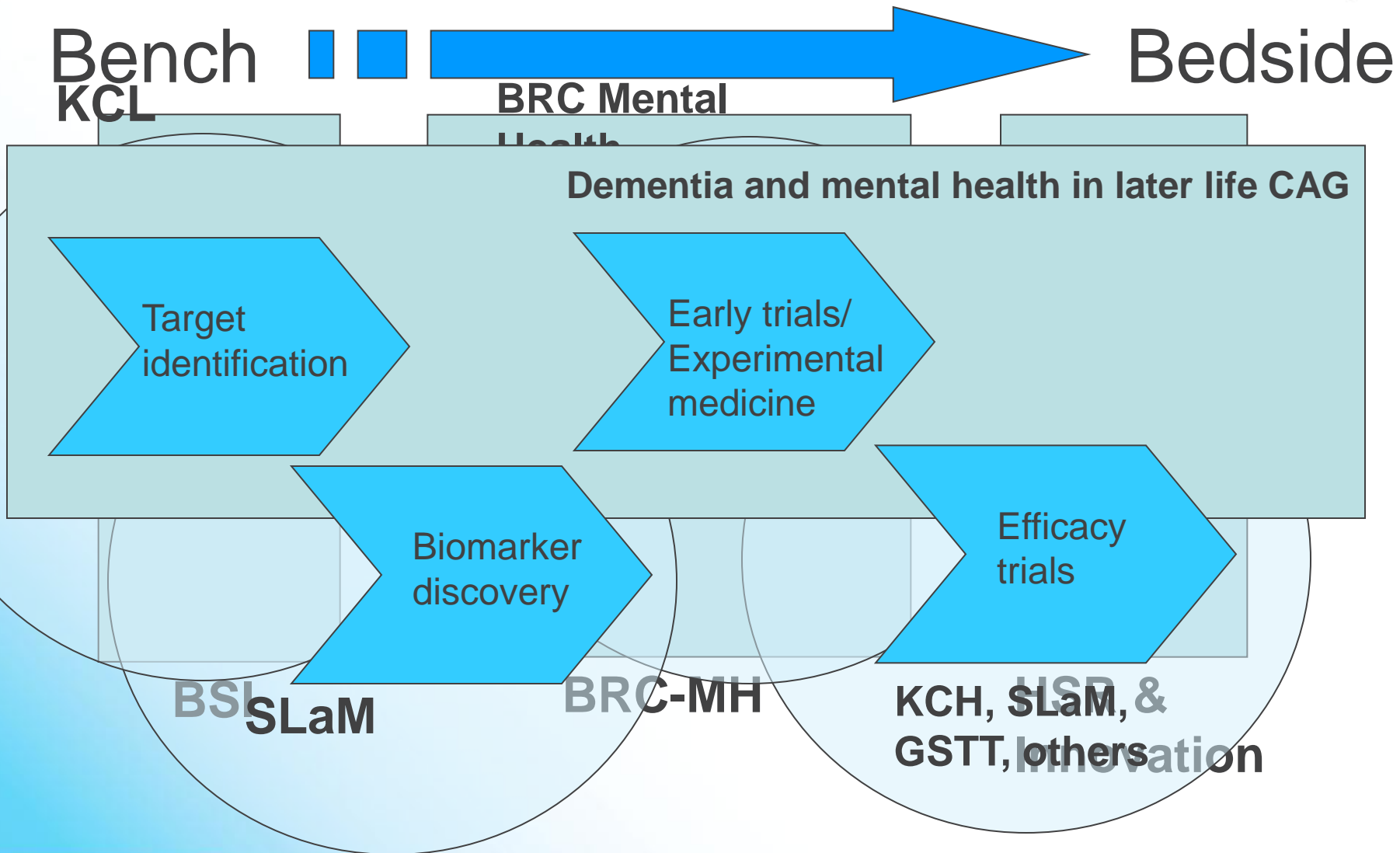
Lithium in AD and other neurodegenerative diseases

Specific GSK3 inhibitors in AD trials

Translational pathway – GSK3 and AD



Translational pathway – GSK3 and AD



Accelerating translation in the context of the AHSC

- **Closer collaboration between basic and clinical sciences**
 - CAG structure enables and incentivises collaboration
 - e.g. *lithium clinics and biomarkers of GSK3 activity via BRC-MH*
- **Closer collaboration between basic sciences**
 - basic science technologies ‘disease blind’
 - e.g. *GSK3 signalling in development and in differentiation in the BSI*
- **Enhanced recruitment to clinical studies**
 - use of IT based recruitment ; research as a mission within the NHS
 - e.g. *3000 referrals to MHOA / year accessed through CRIS and BRC-MH*
- **More effective experimental medicine**
 - complex interventions
 - e.g. *bed stays, EEG, lumbar puncture via the CRF and BRC-MH*
- **Rapid translation of research advances**
 - CAG structure enables and incentivises translation
 - e.g. *early detection, early intervention through memory services*

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