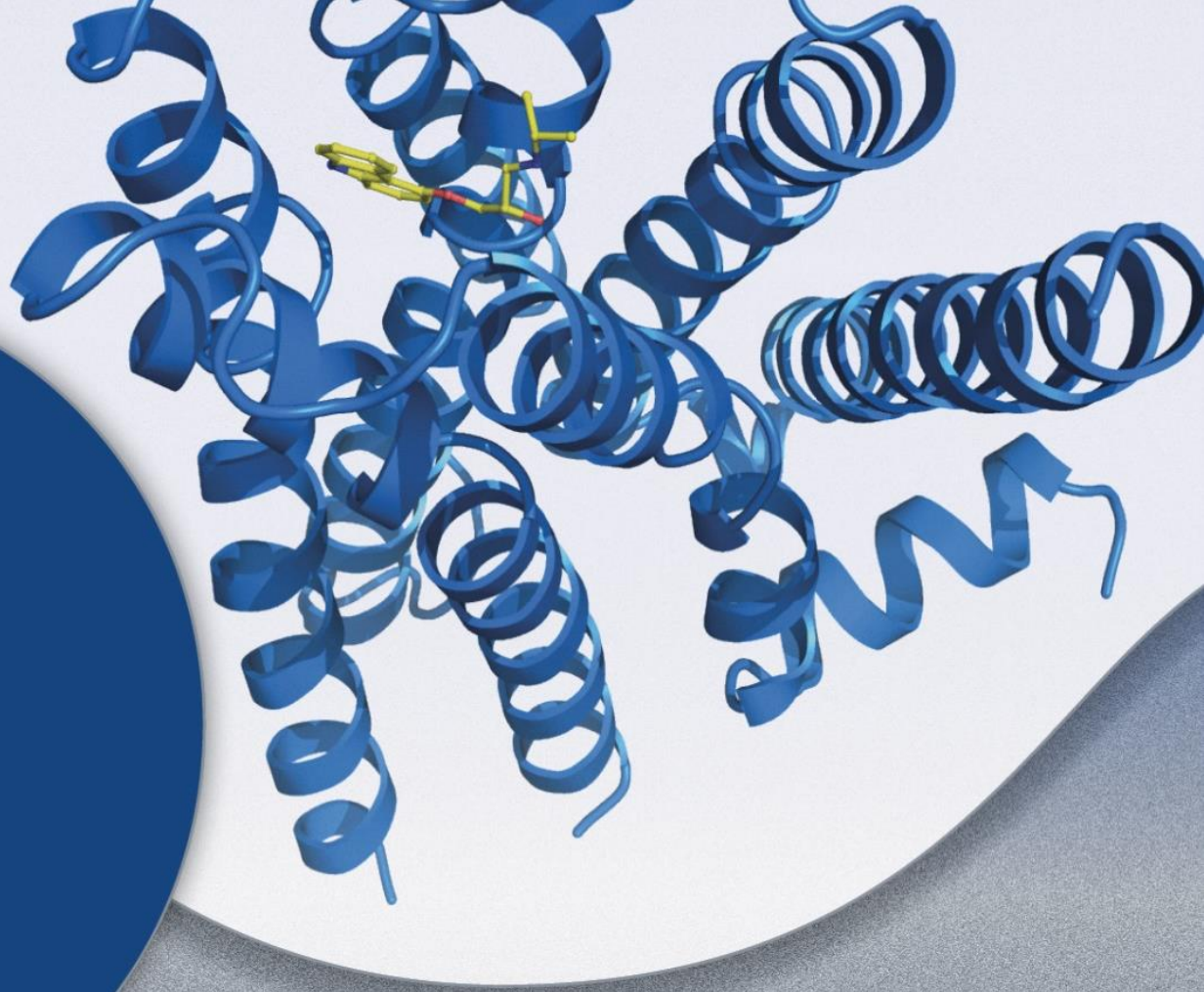
Sosei Group Corporation

HTL0018318 for Dementia with Lewy Bodies (Japan)

Dr Tim Tasker, Chief Medical Officer

2018 Investor Day
New Otani Hotel, Tokyo



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HTL0018318 Muscarinic M_1 Agonist

Novel approach for symptomatic treatment of DLB

Denotes:
Covered in this presentation

Emerging wholly-owned GPCR portfolio

Three Lead Programs

M_1

Phase 2 ready 2018
HTL0018318
Dementia with Lewy Bodies (Japan)

CGRP

Phase 1 ready 2018
HTL0022562
Migraine & Other Severe Headache

$mGlu_5$

Phase 1 ready 2018
Code: Not disclosed
Example indications: ALS or Dystonia

Plus Examples of Selected Preclinical Pipeline Programs Including…

SSTR

Preclinical
Code: Not disclosed
Example indication: Cushing's disease

GLP1

Preclinical
Code: Not disclosed
Example indication: Hypoglycaemia

GLP2

Preclinical
Code: Not disclosed
Example indication: PN Short Bowel Syndrome

Partnered GPCR portfolio

Two Key Products Marketed

NOVARTIS
Ultibro® Breezhaler®
COPD

NOVARTIS
Seebri® Breezhaler®
COPD

Three Novel Phase 1 Candidates

AstraZeneca
A2a
Phase 1b
AZD4635
Immuno-oncology

Allergan
M_1
Phase 1b
HTL0018318
Alzheimer's Disease (AD)

Allergan
M_4
Phase 1
HTL0016878
Neurobehavioral Sx of AD

Discovery and Preclinical Collaboration Partnerships

Pfizer · Daiichi-Sankyo · morphosys · PeptiDream · kymab

Subject to approval, we are aiming for our lead M_1 program for DLB to enter into a Phase 2 PoC study in Japan in 2018

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Agenda

1. Introduction to DLB
2. Diagnosis/Treatment Approach for DLB
3. HTL0018318 M_1 Agonist for DLB in Japan

Introduction to DLB
What is dementia?

- Dementia - **a collection of symptoms** including
  - Memory loss
  - Difficulties with thinking, problem-solving or language
- No specific disease called dementia
- **Several diseases cause dementia**

- 認知症は大脳の疾患の症状（群）をいう
- 認知症という病気があるのではない
- 多くの認知症を起こす病気がある

Alzheimer's disease

Dementia with Lewy bodies (DLB)

Parkinson's disease dementia (PDD)

Vascular dementia

Frontotemporal dementia (Pick's disease)

Creutzfeldt-Jakob disease

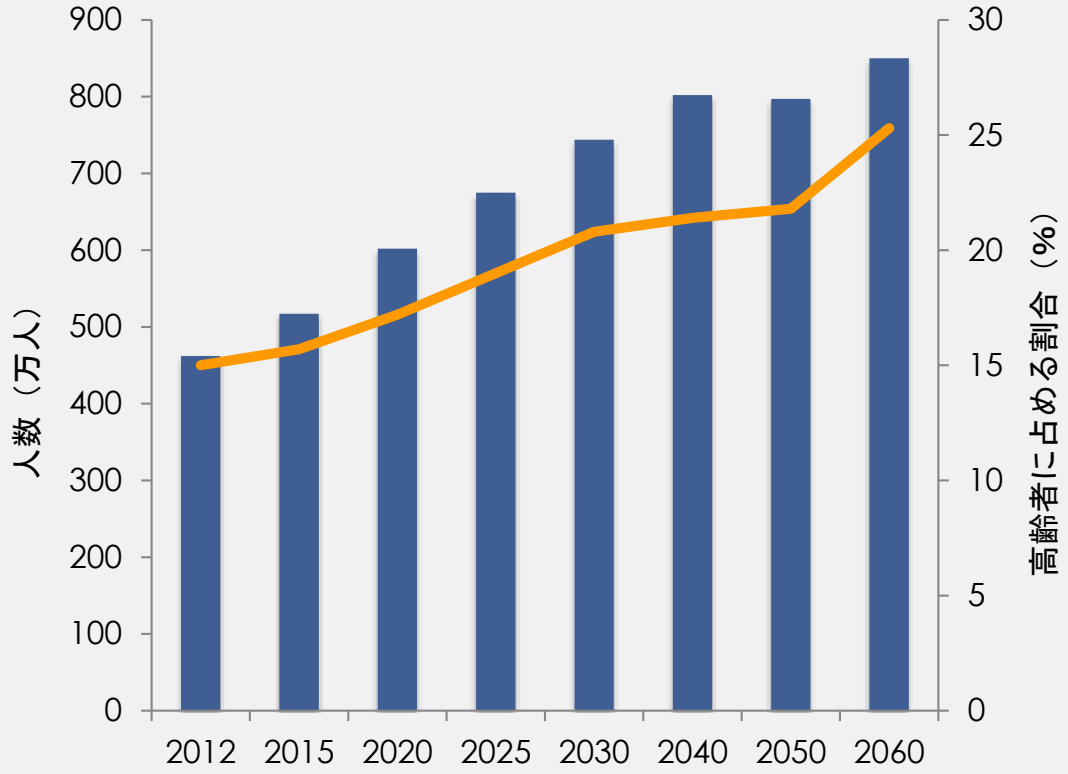
Introduction to DLB

Steady increase in dementia patients expected in Japan

- Approximately **5 million patients** with dementia **in Japan today**
- **Increased number of dementia patients expected** with rapidly ageing population
- **Real patient need**
- **Huge social and economical impact**

- 現在の認知症の数
  - 約500万人

認知症患者は45年後まで増え続ける

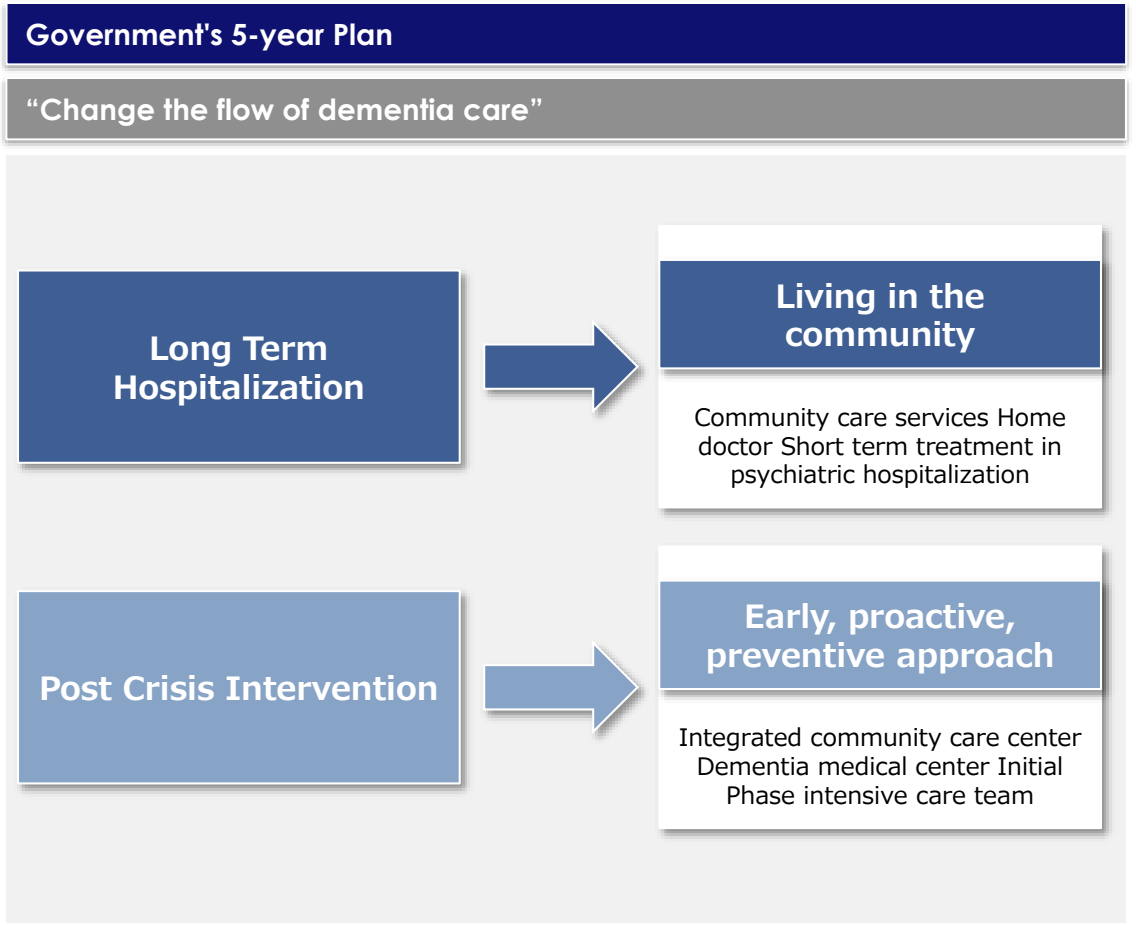


Dementia has a physical, psychological, social, and economical impact, not only on people with dementia, but also on their carers, families and society at large

Introduction to DLB

Dementia is a social and political priority

- Dementia is a **political priority in Japan,**
- **Government policies to 'change the flow of dementia care'**
  - Early detection
  - More doctors and primary care givers
  - SOS networks' to help find missing people and 'dementia supporters' to help within the community
- **Pioneering approach to dementia care in Japan**
- **Could potentially facilitate the entry of new drugs**



Japan is leading the global fight in treating dementias like DLB

Source: Alzheimer's Disease International Presentation, 2014

Introduction to DLB

Second most common type of progressive dementia

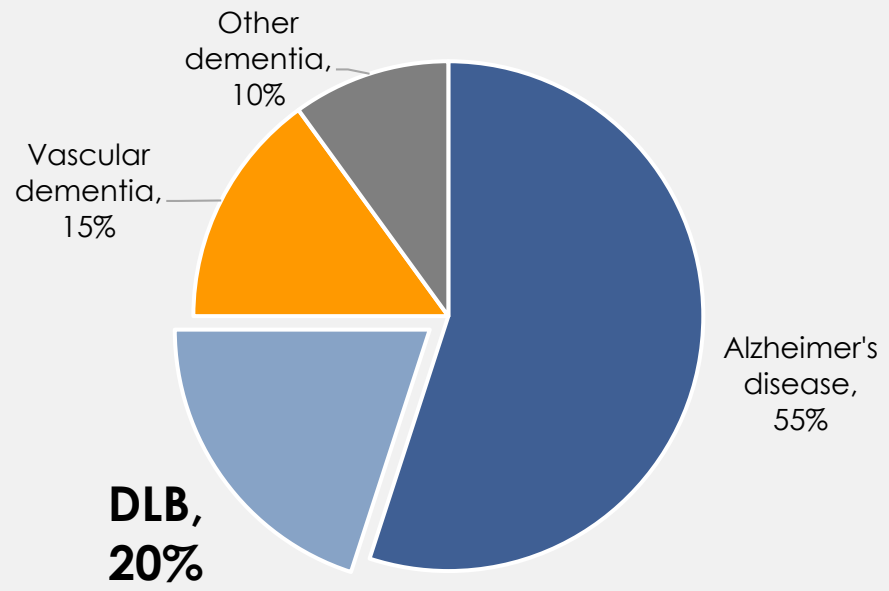
- Dementia with Lewy Bodies (DLB)
  - **Dr. Kenji Kosaka of Japan instrumental in defining DLB**
- **Second most common type of progressive dementia** after Alzheimer's disease
- DLB estimated to cause 10-20% of dementias
- **Low level of recognition**
- **Difficult to diagnose** due to **complicated symptoms**
- Central feature is progressive cognitive decline
  - Pronounced **fluctuations in cognition**
  - Recurrent **visual hallucinations**
  - **Parkinsonism**
  - **REM sleep behaviour disorder** (RBD)

- 84歳の女性
- 主訴：ぼけてきた
- １年前から部屋の中に「大勢の子どもが見える」，「犬や猿がいる」と訴える(幻視)．テレビの中の登場人物が実際に自分の家にいるように行動したり，災害が自分のまわりで起こったように言う(誤認妄想)．とりつかれたようになって，理解力が全くなくなってしまうことがよくある(認知機能の変動)．数年前から夜間睡眠中突然大声で叫ぶ(レム睡眠関連行動異常)．歩行が遅く，転倒しやすい(パーキンソニズム)．

Introduction to DLB

DLB is estimated to cause up to 20% of all dementias…

…however may be underestimated due to ageing population, increased awareness and improvements in diagnosis

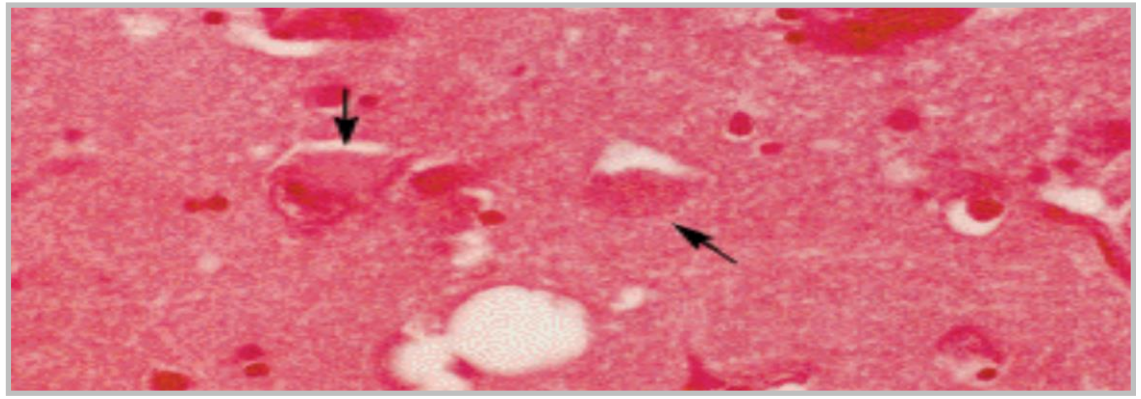


Up to 20% of dementia diagnosed as DLB, which represents a significant potential market for drug development activities

Source: Management estimates; Eisai Press Release, April 2015

Introduction to DLB
Pathology of DLB

- Lewy body dementia (LBD) includes:
  - DLB – Dementia with minimal Parkinson's
  - Parkinson's disease dementia (PDD) – Parkinson's disease with dementia
- LBD pathology includes Lewy bodies (abnormal deposits of a protein called alpha-synuclein) build up in areas of the brain that regulate behavior, cognition, and movement



- 広範かつ多数のレビー小体の中枢神経系への出現を特徴とする変性性認知症疾患
- DLBの臨床診断基準（1996）
- 認知症/認知障害の存在
- パーキンソニズム発症から１年以内
- ３主徴のうち２つ
- 特発性のパーキンソニズム
- 繰り返す構築され具体的な内容の幻視体験
- 注意や明晰さの著明な変化を伴う認知機能の変動
- 示唆的特徴（2005改訂版）
- RBD，抗精神病薬に対する過敏性，DATスキャン

Introduction to DLB

Clinical features of DLB compared to AD

- **Different disturbance of cognition with marked fluctuations in severity day to day ,hour to hour**
- **Faster progression**
- **Potentially associated with higher mortality rates**
- **Distressing Behavior and Psychotic Symptoms of Dementia (BPSD)**
  - Hallucinations, delusions, REM sleep disorder, confusion, depression, anxiety
- BPSD affecting caregivers' Quality of Life (QOL)
- Faster nursing home admission
- Frequent falls and fall-related injuries
- Dysautonomia
- Hypersensitivity to antipsychotics and anticholinergics prevents use of other drugs to control hallucinations

- 重症化が早い
- 死亡率が高い
- 精神症状・行動異常（BPSD）が特異的
  - 幻視，誤認妄想，RBD，意識・認知の変動
- BPSDが介護者QOLを決める
- 患者・介護者のQOLが低く，入所が早い
- パーキンソニズムによる運動障害が問題
- 抗精神病薬でパーキンソニズムが生じる（過敏性）
- 転倒事故が多い
- 自律神経障害が強い

Donepezil (AChE inhibitor) has provisional approval for DLB in Japan; no approved treatment worldwide

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Introduction to DLB

Features of Behavior and Psychotic Symptoms of Dementia (BPSD)

BPSD

- **Visual hallucinations**
  - Recurrent well-formed visual hallucinations
    - People, children, animals, bugs
  - Memory +/-, insight+/-
- **Passage hallucinations**, sense of presence, visual illusions
- **Delusional misidentifications**
- **Persecutory delusions**
- **Depression, anxiety**

pareidolia=para（疑似の,異常な）+ eidolon/eidos（像）

心霊写真

パレイドリア
知覚対象を他のものとして知覚する

座敷わらし

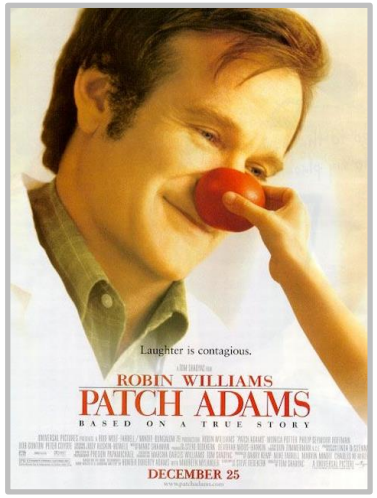
幻視
現実には存在しないものを視覚的に知覚する

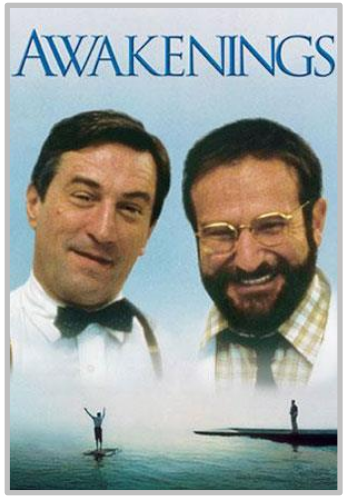
Introduction to DLB

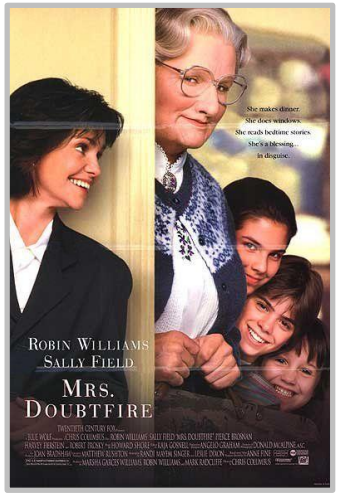
Robin Williams' Lewy body disease

- American actor and comedian Robin Williams died by suicide on August 11, 2014
- **Upon autopsy, he was found to have diffuse Lewy Body disease**
- **He had been diagnosed with Parkinson's disease** prior to his death
- **He also had depression, anxiety, and increasing paranoia**

- 自宅で首つり自殺しているところを発見された．63歳だった．うつ，不安，妄想，初期のパーキンソン病に苦しんでいた(CNN 2014/8/11)
- レビー小体型認知症が自殺のキーファクターだった (CNN 2014/11/10)







Agenda

1 Introduction to DLB

2 Diagnosis/Treatment Approach for DLB

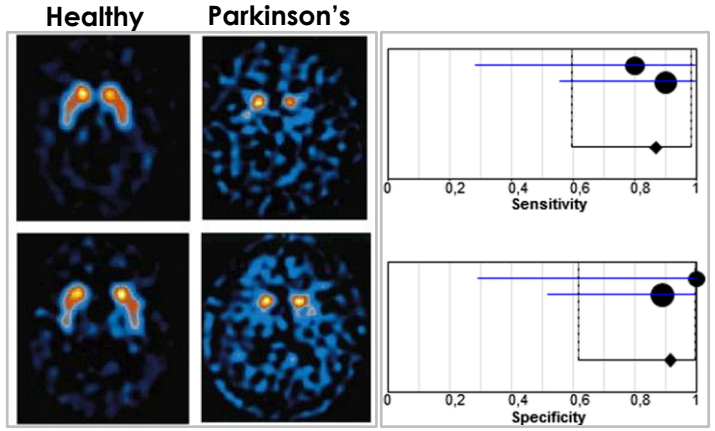
3 HTL0018318 M_1 Agonist for DLB in Japan

Diagnosis/Treatment Approach for DLB

Core features and indicative biomarkers exist for DLB – Japan the world leader

- **Essential: dementia**
  - **Memory impairment may not be prominent**
  - Deficits of attention, executive function and visuoperceptual ability may be prominent
- **Core clinical features**
  - Fluctuating cognition
  - Recurrent visual hallucinations
  - **REM sleep behaviour disorder (RBD)**
  - Parkinsonism
- **Indicative biomarkers**
  - **DaTSCAN**
  - **MIBG** myocardial scintigraphy
  - **PSG confirmation of REM sleep w/out atonia**

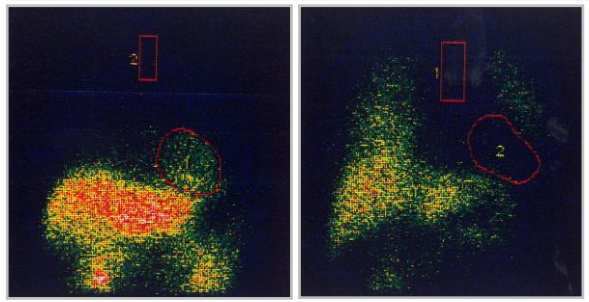
DaTSCAN



- Meta-analysis
- 対AD (病理):
  - 感度=87%
  - 特異度=92%

Brigo F, et al. J Neurol Sci 2015

MIBG Myocardial Scintigraphy



- Multicenter clinical study
  - 対AD:
    - 感度=68.9%（早期/遅延）
    - 特異度=89.1%（早期/遅延）

  Yoshita M, et al. PLoS One 2015
- Multicenter pathology study
  - 感度: 90.9%(早期)，95.7%(遅延)

Takahashi M, et al. JNNP 2015

Improves ability to enroll homogenous clinical trial population

Diagnosis/Treatment Approach for DLB

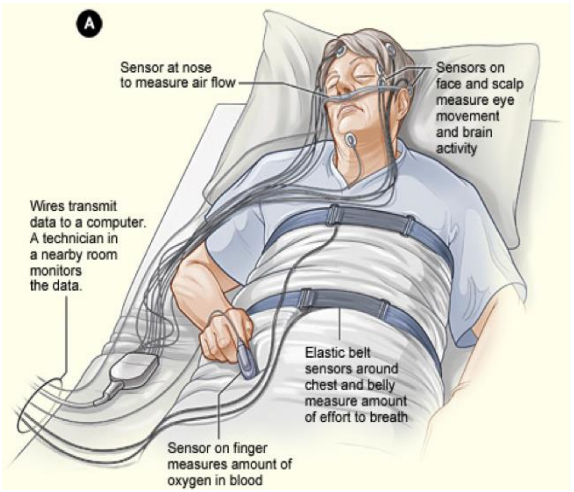
Core features and indicative biomarkers exist for DLB

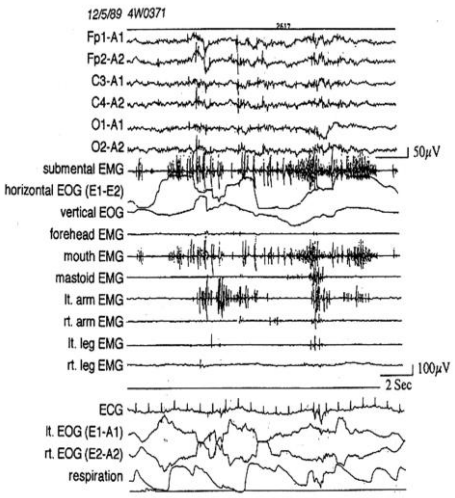
REM sleep behavior disorder (RBD)

- RBD is a parasomnia manifested by vivid, often frightening dreams
- Patients act out their dreams with simple or complex motor behavior during REM sleep
- Loss of atonia during REM sleep
- Patient or bed partner have sustained injuries from limb movements
- Sleep EEG features characteristic

Polysomnography (PSG)

- PSG confirmation of REM sleep without atonia
- PSGはRBDの確診に必須
- PSGは認知症患者，メモリークリニックでは困難





Japan arguably leads the world in the differential diagnosis of DLB

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Diagnosis/Treatment Approach for DLB

Global regulators recognise the real patient need for new treatments

Several dementia drug failures over the past five years…

- Axovant Sciences (DLB) - nelotanserin ✗
- Merck (AD) - verubecestat ✗
- Lundbeck (AD) - idalopirdine ✗
- Axovant Sciences (AD) - interpirdine ✗
- Eli Lilly (AD) - solanezumab ✗
- Prana Biotech (AD) - hydroxyquinoline ✗
- Pfizer (AD) – bapineuzumab ✗

Regulatory environment is adapting quickly to the high unmet need for new treatment…

FDA

- *"U.S. regulators have proposed lowering the bar for clinical trial success for experimental Alzheimer's drugs" - Reuters, 15 Feb 2018*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- *"European regulators are following in the footsteps of the U.S. FDA with plans to help pharmaceutical companies win approval for novel Alzheimer's drugs" - Reuters, 28 Feb 2018*

With no new dementia treatments in 15 years, globally regulators are looking at ways to fast track and/or improve the chances of success for new drugs

Source: Alzheimer's Disease International Presentation, 2014

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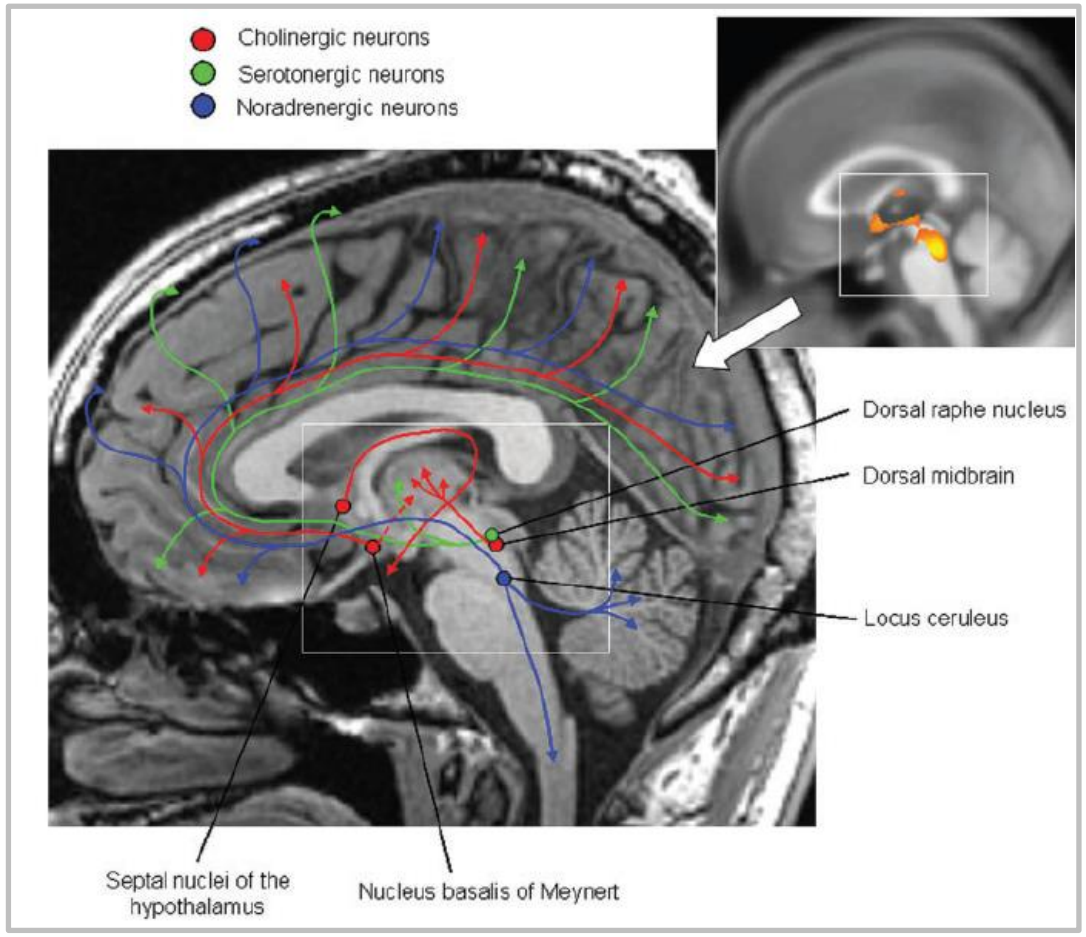
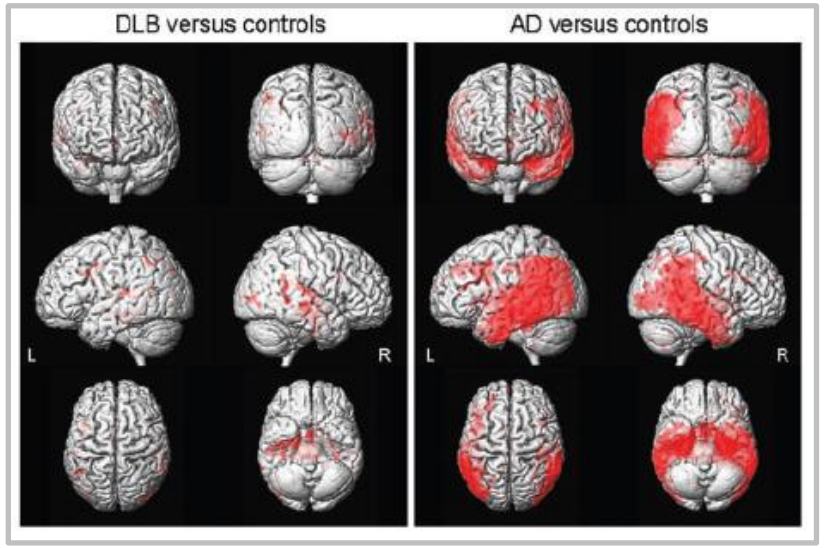
Diagnosis/Treatment Approach for DLB

A muscarinic M_1 agonists is likely to have a superior profile – Lewy Body disease affects the origin of the cholinergic fibres – different from Alzheimer's disease



- MRI of 72 DLB patients with 72 age matched AD and 72 controls
- Marked loss of cortical GM in AD (red)
- Loss in dorsal midbrain, SI and hypothalamus in DLB
- Loss in cortex in AD



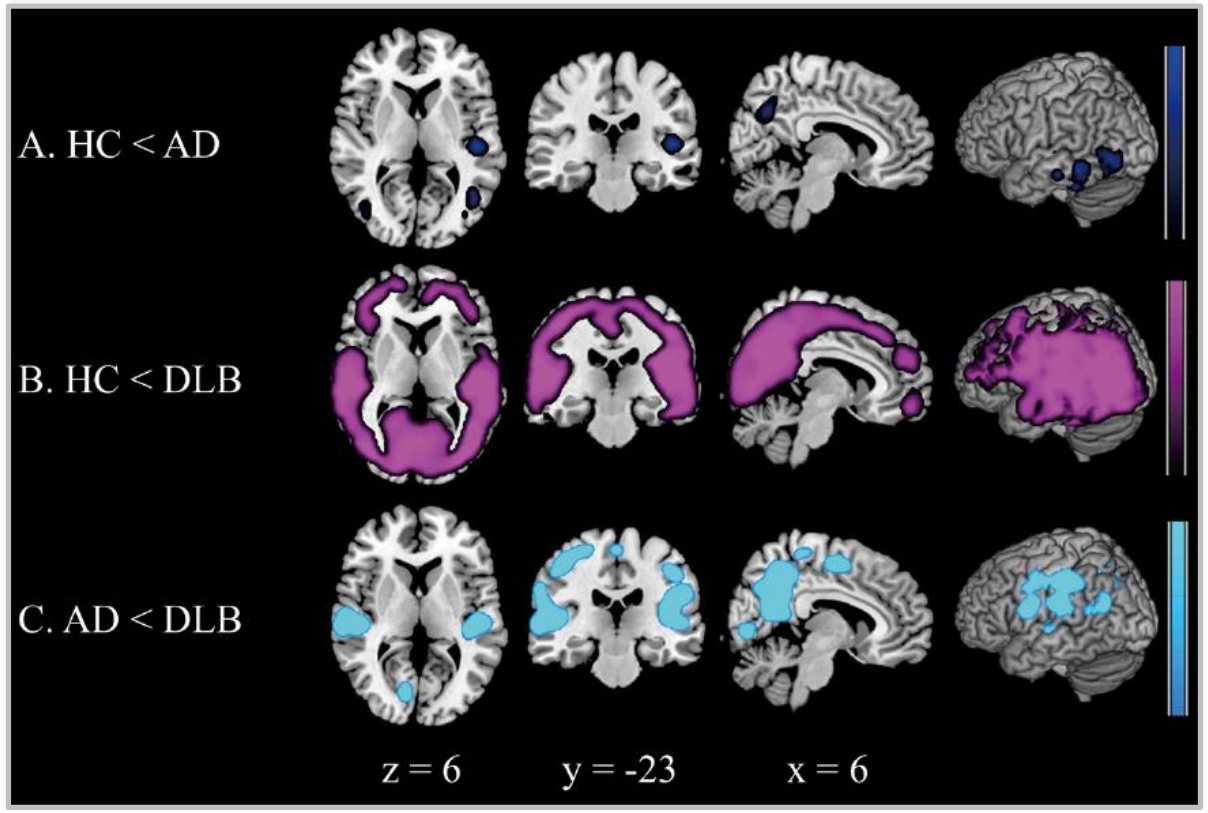
Brain atrophy in DLB is different to that in AD and is more centred on cholinergic system

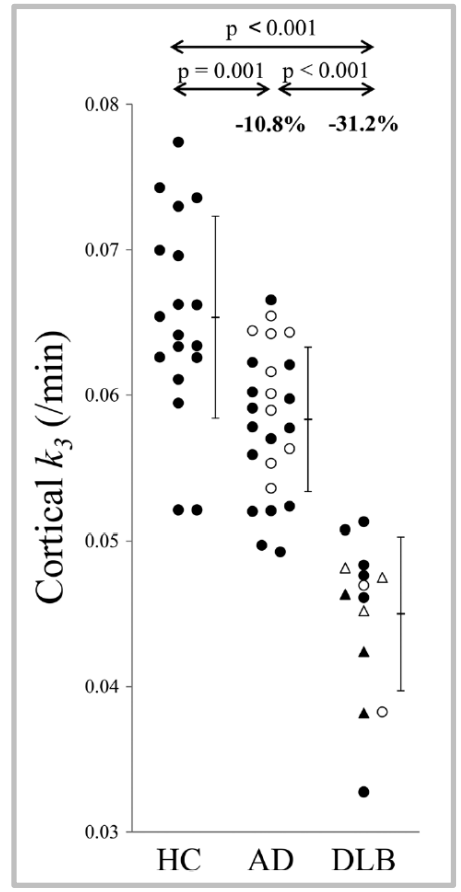
Source: Whitwell et al ,Brain 2007 Focal atrophy in DLB differs from AD

Diagnosis/Treatment Approach for DLB

A muscarinic M_1 agonist is likely to have a superior profile – much greater reduction in cholinergic system in DLB than in Alzheimer's disease

N-[^{11}C]-methyl-4-piperidyl acetate (MP4A) PET





Greater reduction of AChE activity in DLB patients relative to AD patients

Source: Shimada H, et al. Int J Geriatr Psychiatry (2015)

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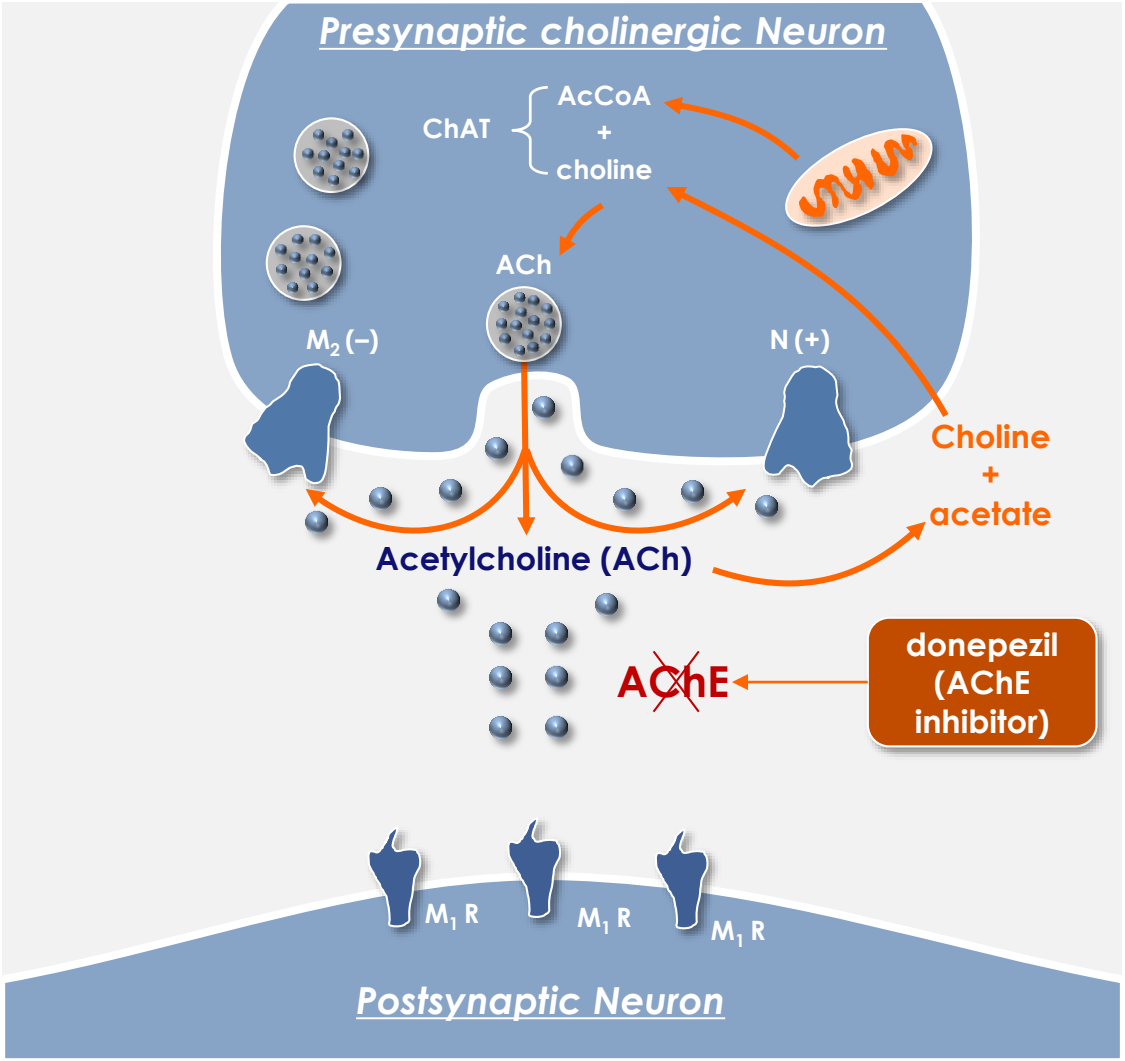
Diagnosis/Treatment Approach for DLB

Donepezil (AChE inhibitor) is the Standard of Care for DLB in Japan

Donepezil is the standard of care for DLB patients in Japan… but clinical efficacy limited

- Donepezil (AChE inhibitor) inhibits cholinesterase enzymes (AChE) that break down acetylcholine (ACh)
- ACh is the neurochemical that stimulates the M_1 receptor, which in turn mediates cognition
- Enhancement of ACh by donepezil provides benefit in patients
- Benefits limited due to low/declining levels of ACh as disease progresses, plus adverse side-effects[1]

Donepezil in DLB patients provides some benefit – however effects are limited



[1] Adverse side-effects of AChE inhibitors could be mediated at other sub-types of muscarinic receptors (M_2, M_3, M_4), some located peripherally, at which enhanced ACh activity does not differentiate

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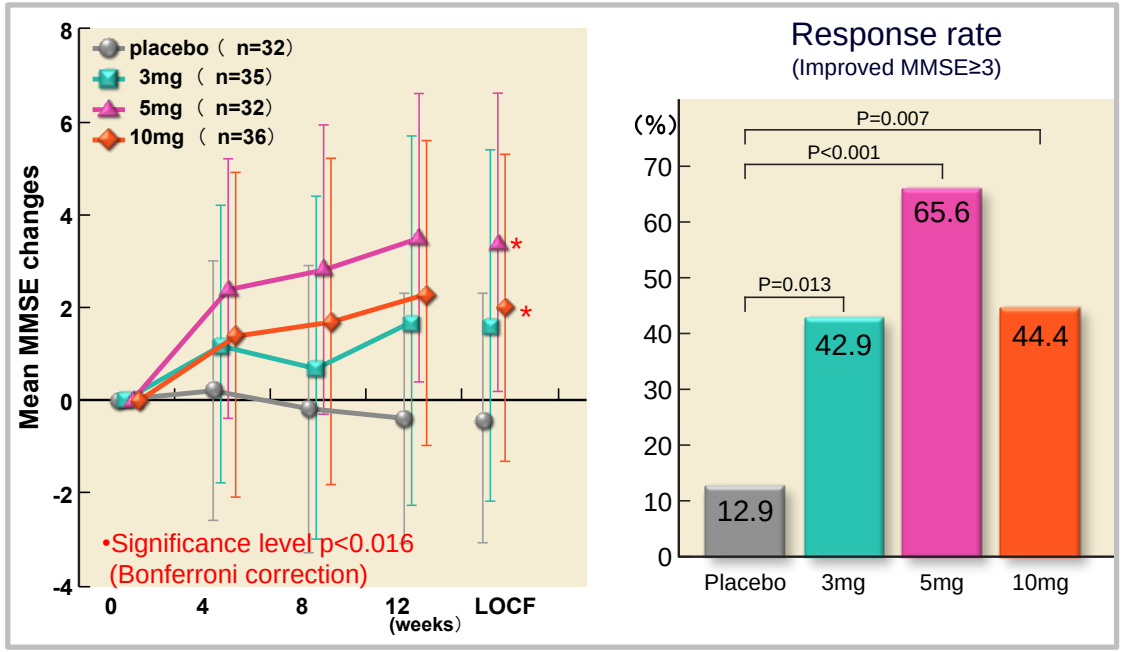
Diagnosis/Treatment Approach for DLB

Donepezil (AChE inhibitor) the SoC for DLB in Japan – shows the type of benefits that cholinergic enhancement by M_1 agonists may produce

- Clinical studies of DLB patients receiving donepezil demonstrated improvements in several neuropsychiatric domains affected by DLB
- Delusions, hallucinations and cognitive fluctuations
- **Patients receiving 5 or 10 mg donepezil showed greatest improvement**
- **MMSE score improved by 2.0 to 3.8 points in those receiving donepezil over placebo**
- **Larger difference than that reported in other studies of ChEIs** in DLB, Alzheimer's and Parkinson's disease dementia
- Shown in 12 week studies shorter than 6 months needed in Alzheimer's disease



ChEIs improve cognition and show a greater degree of efficacy in DLB than in Alzheimer's disease

Source: Mori E, et al. Ann Neurol, 2012

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Treatment Approach for DLB – a disease affecting the cholinergic system

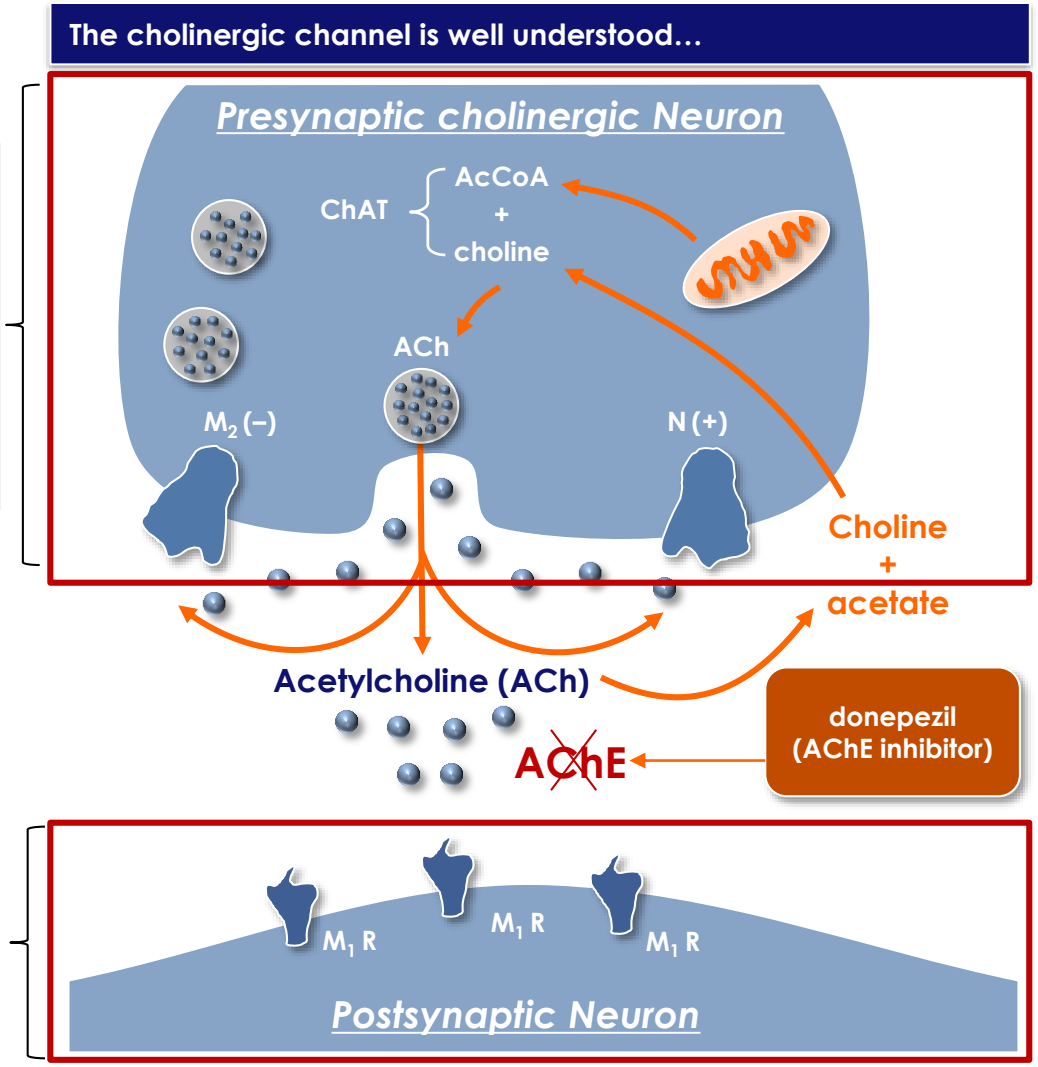
A muscarinic M_1 agonist is likely to have a superior profile

- **Greater cholinergic deficit in DLB patients** relative to Alzheimer's disease (AD) patients
- Loss of presynaptic cholinergic system reduces treatment potential of AChE inhibitors
- Post synaptic receptors more intact in DLB patients, potential for greater response to muscarinic M_1 agonists

Real opportunity for M_1 agonist to have superior profile relative to donepezil in DLB patients

***DLB patients**: presynaptic cholinergic system **less preserved** than AD patients*

***DLB patients**: postsynaptic neuron **more preserved** than AD patients* ✓



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Agenda

1 Introduction to DLB

2 Diagnosis/Treatment Approach for DLB

3 HTL0018318 M_1 Agonist for DLB in Japan

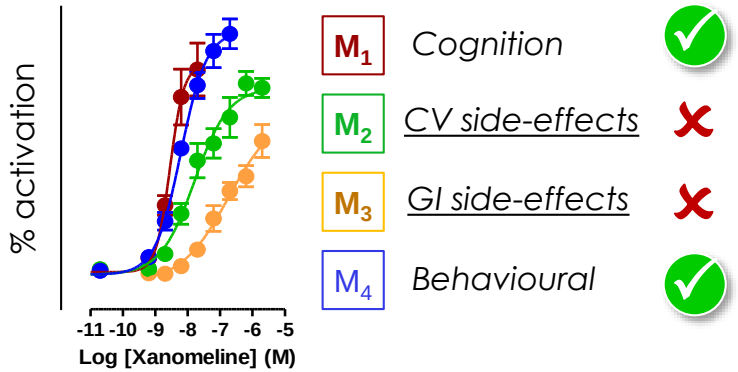
HTL0018318 is a potential first-in-class therapy for DLB

Highly selective M_1 receptor agonist derived from StaR® & SBDD

Rationale Behind Muscarinic M_1 Agonism

- **Cognitive benefits of M_1 receptor agonism supported by** Lilly's clinical studies of **Xanomeline**[1]
- Xanomeline's development stopped due to unacceptable CV and GI side effects linked to stimulation of M_2 & M_3
- **HTL0018318 – a potent** muscarinic M_1 agonist **with negligible M_2/M_3 agonism**
- StaR® & SBDD "designed out" unwanted selectivity over the M_2 & M_3 receptors

Xanomeline[1]



M_1 *Cognition*

HTL0018318 is a selective M_1 receptor agonist with potential to benefit cognition and neuropsychiatric symptoms with negligible agonist activity at M_2 or M_3 receptors

Selectivity is crucial. HTL0018318 has a differentiated mechanism with the potential to optimise symptomatic benefits in DLB patients

Source: Internal analysis

[1] Bodick et. al. "Effects of Xanomeline, a Selective Muscarinic Receptor Agonist, on Cognitive Function and Behavioural Symptoms in Alzheimer's Disease" Arch Neurol. 1997;54@465-473

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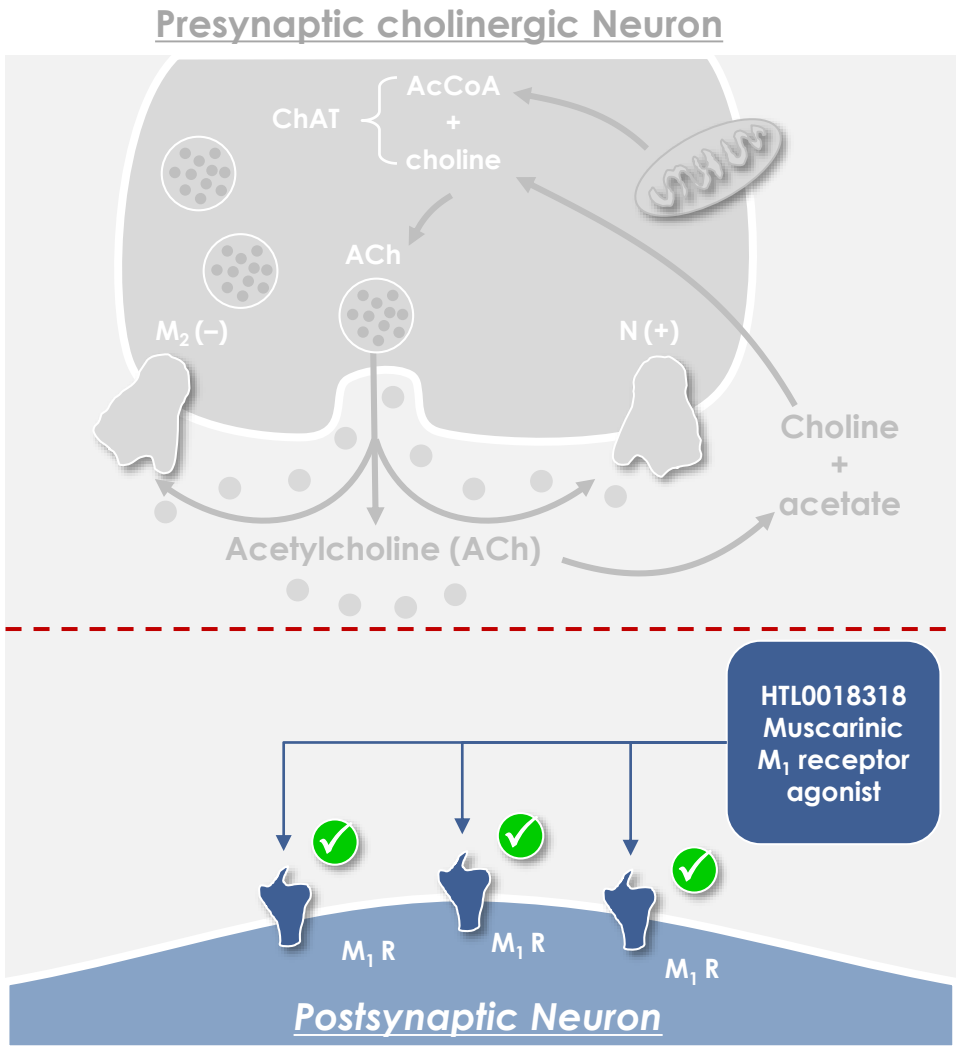
HTL0018318 is a potential first-in-class therapy for DLB

Novel approach for symptomatic treatment

HTL0018318 represents a novel approach to stimulation of the M_1 receptor

- Same thesis as donepezil – **stimulate the M_1 receptor, mediate cognition and neuropsychiatric effects**
- HTL0018318 bypasses presynaptic activity, and does not rely on ACh levels in the brain
- **Acts directly to stimulate the M_1 receptor as an analogue of ACh** post the synapse
- **Designed to replace the underlying neurochemical deficit** in DLB patients
- HTL0018318 **offers first-in-class therapy**

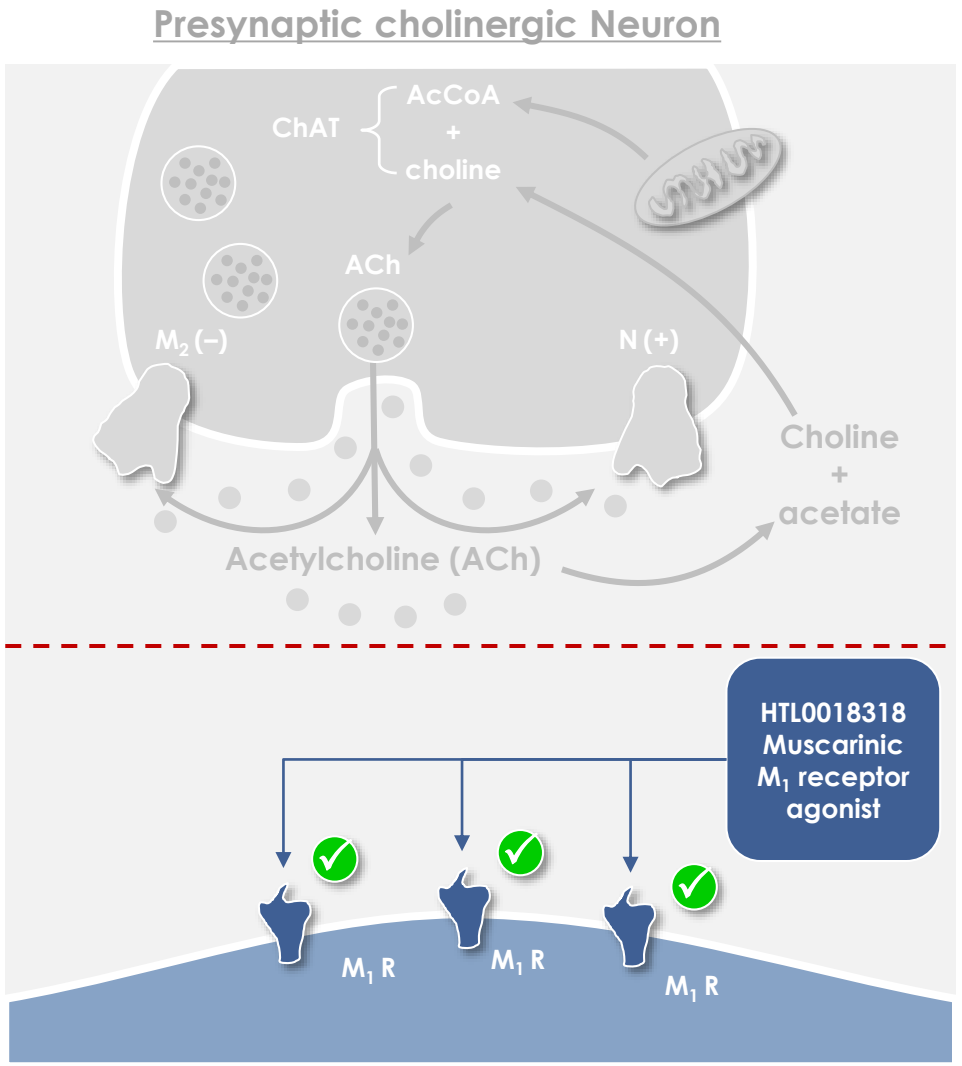
Selective muscarinic M_1 receptor agonism offers first-in-class therapy for DLB patients



HTL0018318 for DLB in Japan

Great potential for M_1 agonist treatment for DLB in Japan

- DLB is the second most common form of dementia and **highly relevant in Japan**
- **Real patient need in Japan** – ageing population
- **Recognition and diagnosis** of DLB symptoms significantly **more advanced in Japan**
- **M_1 agonist will show activity more rapidly and easily in DLB** than in Alzheimer's due greater cholinergic defect
- **Potential to have a superior profile to donepezil** as HTL0018318 acts independently of presynaptic system
- **Potentially favourable environment** – regulators in US/EU adapting dementia guidelines to meet increased disease understanding
- HTL0018318 represents a new treatment approach with **potential to show meaningful patient benefits**



HTL0018318 for DLB in Japan

Summary of clinical program to date

- HTL0018318 derived from Heptares' StaR® technology and SBDD
- **HTL0018318 - same compound being investigated in AD trials with our partner Allergan**
  - Allergan paid $125 million upfront for a portfolio of muscarinic compounds, including HTL0018318
- In Phase 1a studies, **HTL0018318 demonstrated** to be **safe and well tolerated, including in elderly people**
- **Ethnic bridging studies were completed by Heptares - safe and well tolerated in Japanese subjects**
- HTL0018318 currently in a Phase 1b trial in patients with AD in Europe[1]
- Agreed with Allergan that **Sosei has rights for approval and commercialization of HTL0018318 for DLB in Japan**

Clinical progress to date encouraging.
Subject to approval, we hope to move into a Phase 2 PoC study in DLB in Japan in 2018

[1] EU study of HTL0018318 in AD https://www.clinicaltrials.gov/ct2/show/NCT03456349

HTL0018318 for DLB in Japan

Target Product Profile for a Muscarinic M_1 agonist to treat DLB

Base Case	Best Case
➢ Monotherapy Treatment of DLB ➢ **Enhances cognitive function** • Particularly executive dysfunction and visuospatial impairment (early MAD data supports this) ➢ **Reduced frequency of cognitive fluctuations** ➢ **Reduced visual hallucinations** in DLB ➢ **Better tolerated than donepezil with less side effects** on gut (GI) and postural hypotension (cardiac) ➢ **Reduced caregiver burden from the DLB patient with economic benefits on cost of care**	➢ **Greater magnitude of cognitive enhancement and effects upon hallucination and delusions than donepezil** ➢ Reduced autonomic disturbance and reduced postural hypotension

Working towards a novel drug for DLB in Japan with the potential to significantly improve symptomatic treatment for patients, and ease the burden on Japanese society

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Thank you!