STATE OF ALZHEIMER DISEASE RESEARCH

Serge Gauthier, C.M., MD, FRCPC
McGill University Research Center for Studies in Aging
Douglas Mental Health University Institute
Montréal, Canada
Conflict of interest

• Clinical trial support from Lilly and Roche in DIAN-TU, TauRx, Lundbeck
• DSMB member of ADCS, ATRI, API, Eisai
• Scientific advisor to Affiris, Boehringer-Ingelheim, Lilly, Servier, Sanofi, Schwabe, Takeda, TauRx, Roche
OUTLINE

• What is Alzheimer’s disease?
• What is new in the diagnosis?
• What is new in the treatment?
• What is coming next?
WHAT IS ALZHEIMER’S DISEASE?

A progressive neurodegenerative disease affecting initially the temporal areas of the brain [memory], then posterior associative areas [language, spatial orientation], then frontal lobes [personality & behavior]
PROGRESSION OF SYMPTOMS IN ALZHEIMER’S DISEASE

Lovestone & Gauthier 2000
STAGES OF ALZHEIMER’S DISEASE

- No symptoms
- Mild cognitive symptoms
- Dementia

Increasing Alzheimer’s pathology

Time
PATHOLOGIES ASSOCIATED WITH AD

AGE

β-amyloid Deposition (plaques)

Microglial Activation (inflammation)

NFTs (tangles)

Neuronal Loss (atrophy)

Symptoms
Increased tissue concentrations of amyloid in preclinical Alzheimer's disease will activate microglia.

We hypothesize that the interaction between regional amyloid, local NFT and levels of microglial activation will drive propagation of NFT and cognitive decline (see statistical methods).
WHAT IS ALZHEIMER’S DISEASE?

PATHOLOGY

• Classic pathology includes amyloid plaques and neurofibrillary tangles
• Neuroinflammation is a key factor at some stage of the disease
• Most older patients also have small strokes
• Many older patients also have Lewy Bodies
WHAT IS ALZHEIMER’S DISEASE?

BIOMARKERS

• *Pathophysiology markers* include amyloid deposition seen on PET scans and lower CSF levels of β42

• *Neurodegeneration markers* include brain atrophy on MRI, hypometabolism on PET-FDG, higher CSF levels of phospho-tau, spread of tau pathology on PET
AD PROGRESSION USING BIOMARKERS

Figure 1 - Summary of the imaging agents and PET outcomes proposed

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Image (min, max)</th>
<th>Interpreted Tissue Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid imaging</td>
<td><img src="image" alt="Amyloid imaging image" /></td>
<td>Tissue availability of Fibrillary amyloid</td>
</tr>
<tr>
<td>[¹¹C]PIB SUVR</td>
<td><img src="image" alt="SUVR amyloid image" /></td>
<td><img src="image" alt="SUVR amyloid image" /></td>
</tr>
<tr>
<td>Tau imaging</td>
<td><img src="image" alt="Tau imaging image" /></td>
<td>Tissue availability of Paired Helical Filaments</td>
</tr>
<tr>
<td>[¹⁸F]THK5351 SUVR</td>
<td><img src="image" alt="SUVR tau image" /></td>
<td><img src="image" alt="SUVR tau image" /></td>
</tr>
<tr>
<td>TSPO imaging</td>
<td><img src="image" alt="TSPO imaging image" /></td>
<td>Tissue availability of TSPO expression</td>
</tr>
<tr>
<td>[¹¹C]PBR28 SUVR</td>
<td><img src="image" alt="SUVR TSPO image" /></td>
<td><img src="image" alt="SUVR TSPO image" /></td>
</tr>
</tbody>
</table>

**Interpretation**

- **Amyloid plaques**
- **Neurofibrillary tangles**
- **Microglia**
  - Resting
  - Activated

**TSPO = Translocator protein (18kDa) - mitochondrial cholesterol transporter**
AMYLOID PET IN MUTATION CARRIERS

 Courtesy of Mark Mintun and Randy Bateman
Figure 1: Cortical patterns of 18F T807 binding. Coronal 18F T807 positron emission tomographic (PET) images (top row) and whole-brain surface renderings of standardized uptake value ratio (SUVR; cerebellar reference; second row) from 3 clinically normal (CN) and 4 impaired (2 mild cognitive impairment [MCI] and 2 mild Alzheimer dementia [AD] dementia) participants. Top: (A) A 71-year-old CN subject with low amyloid b (Ab) by Pittsburgh compound B (PiB) PET (mean cortical distribution volume ratio [DVR] 5 1.0) had low, nonspecific 18F T807 binding in cortex, consistent with a Braak stage less than III/IV. (B) A 74-year-old CN subject with high Ab (DVR 5 1.2) with 18F T807 binding in inferior temporal cortex, left>right, consistent with Braak stage III/IV. (C) A 79-year-old CN subject with high Ab (DVR 5 1.8) had binding in inferior temporal neocortex, consistent with Braak stage III/IV. B and C show focally intense subcortical uptake that is likely due to off-target binding (see Discussion). (D–G) Cognitively impaired participants all with high Ab and with successively greater levels of cortical 18F T807 binding successively involving temporal, parietal, frontal, and occipital cortices. Bottom: 18F T807 SUVR calculated at vertices (see Subjects and Methods) indicating the extent of cortical binding, with left hemisphere views (lateral, inferior, superior, medial) at left. The 52-year-old AD dementia patient (G) showed confluent 18F T807 binding that is nearly pancortical, sparing only portions of primary cortex and consistent with Braak stage V/VI. Dx5classification; MMSE5Mini-Mental State Examination; PET Braak 5 estimate of Braak stages based on the anatomic pattern of T807 binding assessed visually and quantitatively in regions and full volume data.
WHAT IS ALZHEIMER’S DISEASE?

GENETIC FACTORS

• Autosomal dominant early onset (<65) infrequent but important as involving only amyloid mutations (PS1, PS2, APP)

• ApoE4 genotype frequent (15%) and is the major genetic risk factor in late-onset AD

• Genes effects can be additive or protective
WHAT IS ALZHEIMER’S DISEASE?
RISK AND PROTECTIVE FACTORS

RISK FACTORS

- Alcohol misuse
- Hypertension
- Obesity
- Dyslipidemia
- Diabetes
- Vascular insults
- Neuronal damage

PROTECTIVE FACTORS

- Physical activity
- Cognitive and social activity
- Education
- Brain reserve

APOE, Other genes

Mangialasche, Kivipelto et al., 2012
OUTLINE

• What is Alzheimer’s disease?
• What is new in the diagnosis?
• What is new in the treatment?
• What is coming next?
WHAT IS NEW IN THE DIAGNOSIS?

• Validation of new diagnostic criteria proposed by the IWG and the NIA-AA workgroups.
• There has to be a balance between sensitivity, specificity and affordability
• Sharing of data from large observational studies (ADNI, AIBL, CCNA, DIAN)
### Diagnostic Criteria for Dementia Probably Due to AD Using Biomarkers

(Modified from McKhann et al, 2011)

<table>
<thead>
<tr>
<th></th>
<th>Aβ</th>
<th>Neuronal injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD with high likelihood</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Probable AD with intermediate likelihood</td>
<td>+ or untested</td>
<td>untested or +</td>
</tr>
<tr>
<td>Probable AD dementia</td>
<td></td>
<td>untested or conflicting results</td>
</tr>
<tr>
<td>Possible AD dementia (atypical clinical presentation)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>* Unlikely AD dementia</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
WHAT IS NEW IN THE DIAGNOSIS?

• Interest in ‘asymptomatic AD’ for preventive studies, e.g. biomarker or ApoE4 positivity and no symptoms

• Ethical issues in disclosing results of biomarkers and genetic testing for is a “risk state”, not a clinical disease

• Special case of mutations causing familial early onset AD
Comparison of Clinical, Cognitive, Structural, Metabolic, and Biochemical Changes as a Function of Estimated Years from Expected Symptom Onset.

OUTLINE

• What is Alzheimer’s disease?
• What is new in the diagnosis?
• What is new in the treatment?
• What is coming next?
To what extent can Alzheimer dementia be prevented?

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>PAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>2.9%</td>
</tr>
<tr>
<td>Midlife hypertension</td>
<td>5.1%</td>
</tr>
<tr>
<td>Midlife obesity</td>
<td>2.0%</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>12.7%</td>
</tr>
<tr>
<td>Depression</td>
<td>7.9%</td>
</tr>
<tr>
<td>Smoking</td>
<td>13.9%</td>
</tr>
<tr>
<td>Low education</td>
<td>19.1%</td>
</tr>
<tr>
<td>Combined PAR*</td>
<td>28.2%</td>
</tr>
</tbody>
</table>

PAR=population-attributable risk.
*Adjusting for non-independence of the risk factors.

Graph showing the difference in Alzheimer dementia prevalence from 2010 to 2050 with 10% and 20% reduction per decade. The combined PAR* indicates a significant reduction in dementia risk.

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial


The Lancet, 2015

(Published online March 12 2015)
INTERVENTION SCHEDULE

INTENSIVE MULTIDOMAIN INTERVENTION

NUTRITION:
7 group sessions, 3 individual sessions

EXERCISE:
- 1-2x/wk muscle
- 2-4x/wk aerobic
- 2x/wk muscle
- 4-5x/wk aerobic
- 2x/wk muscle strength training
- 5-6x/wk aerobic training

COGNITIVE TRAINING:
- 9 group sessions
- Independent training

EXERCISE:
- 2 group sessions
- Independent training

MONITORING AND MANAGEMENT OF METABOLIC AND VASCULAR RISK FACTORS
- Nurse: Visit every 3 months
- Physician: 3 additional visits

REGULAR HEALTH ADVICE

Kivipelto et al., Alzheimer & Dementia 2013
Primary efficacy outcome: overall cognition (NTB composite Z score)

Difference between intervention and control groups per year:
Estimate (95% CI) = 0.022 (0.002-0.042)
p=0.03

Lines = estimates for cognitive change from baseline to 12 and 24 months
Higher scores = better performance
Error bars = standard errors.
P-values = difference in trajectories over time between groups

Kivipelto et al, Lancet 2015
Intervention effects on main cognitive secondary outcomes

Difference between intervention and control groups per year:

Estimate (95% CI), p-value

Executive functioning

0.027 (0.001-0.052)  p=0.04

Processing speed

0.030 (0.003-0.057)  p=0.03

Memory

0.015 (-0.017-0.048)  p=0.36

Kivipelto et al, Lancet 2015
WHAT IS NEW IN TREATMENT?
PHARMACOLOGIC STUDIES

• Decrease beta-amyloid deposition or break up amyloid plaques
• Decrease Tau hyperphosphorylation with LMTM or antibodies
β-Amyloid treatment strategies under study

- APP gene
  - Production
    - APP
  - Antisense
  - Secretase inhibitors & modulators

- Aβ Monomer
  - Aggregation
    - Fibrillogenesis modulators
    - Aβ Oligomer
  - Immunotherapy

- Aβ Fibril
  - Deposition
    - Diffuse Plaque
    - Anti-inflammatory
    - Senile Plaque
Amyloid Plaque Reduction with Aducanumab

Analyses based on observed data. PD analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.

- Placebo (n=34, 34, 21)
- Aducanumab 1 mg/kg (n=26, 26, 21)
- Aducanumab 3 mg/kg (n=29, 27, 26)
- Aducanumab 6 mg/kg (n=23, 23, NA)
- Aducanumab 10 mg/kg (n=28, 27, 21)

SUVR cut-point for florbetapir = 1.13

Analyses based on observed data. PD analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.


Aducanumab is an investigational drug and not approved in Canada.
Aducanumab Effect on CDR-sb

CDR-sb is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-sb. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment.

Aducanumab is an investigational drug and not approved in Canada.
LMTM (leuco methylthioninium dihydro-mesylate) inhibits aggregation of Tau protein

Molecule is distinct from methylene blue (where nitrogen groups are planar)

Wischik et al. (1996) PNAS 92, 11213-11218
Harrington et al., J Biol Chem, 2015, 290 10862-10875
Summary of TauRx Clinical Development Program

TRx-237-005 (in competent imaging centres)
- 18-month study in 700 (800) patients with mild Alzheimer’s disease
- LMTM 200 mg/day versus placebo (8 mg/day)
- Primary endpoints: ADAS-cog and ADCS-CGIC (US) / ADCS-ADL (EU)
- Secondary endpoints: Volumetric MRI, FDG-PET

TRx-237-015 (diagnostic imaging only, broader recruitment base)
- 15-month study in 833 (890) subjects with mild-moderate Alzheimer’s disease
- LMTM 150 mg/day versus LMTM 250 mg/day versus placebo (8 mg/day)
- Primary endpoints: ADAS-cog and ADCS-CGIC (US) / ADCS-ADL (EU)
- Secondary endpoints: Volumetric MRI, FDG-PET (150 subset)

TRx-237-007
- 12-month study in 180 (220) patients with bvFTD
- LMTM 200 mg/day versus placebo (8 mg/day)
- Primary endpoints: ACE-R and ADCS-CGIC
- Secondary endpoints: Volumetric MRI, ACE-III, FTD-FRS, FAQ, UPDRS
OUTLINE

• What is Alzheimer’s disease?
• What is new in the diagnosis?
• What is new in the treatment?
• What is coming next?
• Learn from observations in people with recurrent head injuries, Down’s syndrome
• Share “big” data, e.g. pool information from around the world
• PET-tau brain scanning may be closer to the pathology causing symptoms
WHAT IS COMING NEXT? - 2

• National policies to support education and maintain healthy life-styles
• Patients and asymptomatic « trial ready» volunteer registries
• Anti-inflammatory drugs may get a second chance!
WHAT IS COMING NEXT? - 3

• Clinical trials combining anti-tau and anti-amyloid drugs, or drugs acting on different components of the amyloid pathway

• Learn from other fields such as cancer and infectious disease where such combinations are standard treatment and affordable