Update on Clinical Trials in Alzheimer’s Disease

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Disclosure

In the last 12 months, I disclose the following relationships:

- UCSD service agreements for consulting with Arkuda, Axon Neuroscience, Genentech, Samus Pharma, Samumed, Tau Consortium

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  - QR Pharma (Posiphen), Toyama (T817), Biohaven (BH 4157), Probiodrug (PQ 912)

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Objectives

- To learn about progress in finding new and effective treatments for Alzheimer’s disease
- To be informed about the potential of multidomain lifestyle interventions for prevention of dementia
Therapy for AD: Licensed Pharmacologic Therapies

The cholinergic hypothesis

Memantine
NMDA Uncompetitive Receptor Antagonist

200 treatments reach phase II, none yet successful in phase III

Acetylcholinesterase inhibitors (AchEI),

Goal of NAPA to find an effective treatment or cure by 2025


Landscape of AD Drug Development

Fig. 1: Amyloid Therapies (45%), Other Therapies (47%), Tau Therapies (8%).

- **Amyloid Therapies:**
  - V950
  - MAD3293
  - ALZT-OP1
  - LDN-019120
  - BAN-2402
  - RG6162
  - BAN-2401
  - ADUC-001
  - Bexarotene
  - CAD-106
  - BAN-2401
  - LY3303560
  - D073
  - V950
  - Gantenerumab
  - BAN-2401

- **Phase 1:**
  - Memantine (patch)
  - VX-745
  - MK-7622
  - BI 409306
  - LY3202626
  - T-817MA
  - BPN14770
  - PF-05251749
  - PF-06648671

- **Phase 2:**
  - Bexarotene
  - CAD-106
  - BAN-2401
  - LY3002813
  - Gantenerumab
  - Solanezumab
  - Aducanumab
  - Nilvadipine
  - Sodium oligo-mannurarate
  - Solanezumab
  - Aducanumab
  - Gantenerumab
  - Solanezumab
  - Aducanumab
  - Nilvadipine
  - Sodium oligo-mannurarate

- **Phase 3:**
  - Memantine (patch)
  - VX-745
  - MK-7622
  - BI 409306
  - LY3202626
  - T-817MA
  - BPN14770
  - PF-05251749
  - PF-06648671

- **Others:**
  - Crenezumab
  - Gantenerumab
  - Aducanumab
  - BAN-2401
  - ACI-24
  - AGB-101
  - AZD-3480

- **Cholinergic drugs:**
  - Donepezil (patch)
  - Bisnorycmerine
  - Sodium oligo-mannurarate
  - Masitinib
  - Methylphenidate

- **Amyloid Therapies:**
  - ↓Aβ aggregation n=7
  - ↓Aβ production n=12
  - ↑Aβ clearance (immunotherapy) n=16

- **Tau Therapies:**
  - Active vaccine p-tau n=2
  - Passive immune n=4
  - Small molecules n=3

Figure adapted from Mangialasche F, et al. Lancet Neurol 2010; 9: 702–716
Enhancing Clearance of Aβ
AD Immunotherapy Lowers Aggregates Aβ

Active Vaccination
AN 1792

Passive Immunotherapy
Bapineuzumab

<table>
<thead>
<tr>
<th>MOUSE</th>
<th>MOUSE</th>
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<tbody>
<tr>
<td>UNVACCINATED</td>
<td>VACCINATED</td>
</tr>
<tr>
<td>HUMAN</td>
<td>HUMAN</td>
</tr>
<tr>
<td>UNTREATED</td>
<td>TREATED</td>
</tr>
<tr>
<td>MMSE 0</td>
<td></td>
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</tbody>
</table>


Holmes C et al Lancet 2008;

Post mortem AN 1792

- ↓ Mean Aβ in vaccinated
- Variation in Aβ load and SNP removal
- 7 subjects had severe dementia without improved survival or course
- ↑ Vascular amyloid and ↑ soluble species
- No change in synapses or activated microglia
- Tangles and neuropil threads remain
Amyloid Immunotherapy: Leading Candidates with POC

Aducanumab: currently Ph 3: RCTs complete 2020
- Dose response relationship
- Significant clinical effects at 12 months
- Converging evidence of clinical and PET response
- Caveats: Small samples, high drop out and ARIA at higher doses (30-40%)

BAN 2401
- PK dose relationships
- Removes Aβ on PET across doses
- High dose 30% slowing of composite (ADCOMS) at 18 months
- Correlation of amyloid removal and clinical outcomes
- Caveats: high dose stopped at regulatory request; missed primary endpoint at 12 months

Pathological Tau Aggregates as a Target in AD

- Spread of tau pathology from EC to HC and lateral temporal cortex correlates with
  - Clinical amnestic presentations of AD
  - Braak pathological stages III and IV

- Tau pathology correlates more strongly to
  - Clinical expression of disease
  - Markers of neurodegeneration

- Pathological spread of tau:
  - Tau oligomers from donor neurons act as efficient seeds for template induced growth and neuron to neuron spread
  - Experimental EC spread via HMW tau from AD brain

Approaches to Treating Tauopathy

C2N-8E12

BMS-986168
RG7345
RO 7105705
LY3303560
ACI-35
AADvac1
JNJ-63733657
UCB0107
BPN14770
MK 8719

Sodium selenate
Tideglsulib
Lithium chloride
Methylene blue/LMTX
Curcumin
Epithione D
XAP
TP1287
Salsalate

Kinase inhibitor or phosphatase activator
Aggregation inhibitor
Acetylation inhibitor
Microtubule stabilizer
Deglycosylation inhibitor
PDE4 inhibitor
Immunotherapy

Congdon EE and Sigurdsson Nature Rev Neurol 2018
# ADCS Pipeline: Focus on POC

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Phase</th>
<th>Duration of Intervention</th>
<th>Experimental Agent</th>
<th>PD Biomarker</th>
<th>Biological Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DISCOVER U19</strong></td>
<td>Early AD</td>
<td>1B MAD 4 weeks</td>
<td>Posiphen vs Placebo</td>
<td>Fractional Synthesis rate of Aβ</td>
<td>Other CSF biomarkers</td>
</tr>
<tr>
<td>PD Farlow/Galasko</td>
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<tr>
<td><strong>EXERT U19</strong></td>
<td>MCI</td>
<td>3 18 months</td>
<td>Exercise vs Stretching</td>
<td>rCBF ASL MRI</td>
<td>CSF Inflamm, Met BDNF,VEGF</td>
</tr>
<tr>
<td>PD/Baker</td>
<td></td>
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<tr>
<td><strong>PEACE-AD U19</strong></td>
<td>AD Disruptive Agitation</td>
<td>2B 14 weeks</td>
<td>Prazosin vs Placebo</td>
<td>CNS ↑ Noradrenergic Stimulation N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>PD Peskind/Raskind</td>
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<td></td>
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<tr>
<td><strong>AC Immune (R01)</strong></td>
<td>Down Syndrome</td>
<td>1B 24 months</td>
<td>ACI-24 vs Placebo</td>
<td>Anti-Aβ serum Ig</td>
<td>AD, Inflamm, vascular biomarkers</td>
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<tr>
<td>Rafii/Feldman</td>
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<tr>
<td><strong>NEAT (UC Cures)</strong></td>
<td>Early AD</td>
<td>2A 12-24 months</td>
<td>Nicotinamide vs Placebo</td>
<td>p-tau231</td>
<td>Other CSF biomarkers</td>
</tr>
<tr>
<td><strong>SAL-AD (UC Cures)</strong></td>
<td>Mild to Moderate AD</td>
<td>2A 12 months</td>
<td>Salsalate vs Placebo</td>
<td>Acetylated tau</td>
<td>Tau PET</td>
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<tr>
<td><strong>T2 PROTECT AD</strong></td>
<td>Mild to Moderate AD</td>
<td>2-3 12 months</td>
<td>Troriluzole vs Placebo</td>
<td>Glutamate Transport N/A</td>
<td>BDNF, other biomarkers</td>
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<tr>
<td>Biohaven</td>
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<tr>
<td><strong>Probiodrug (pending)</strong></td>
<td>Early AD</td>
<td>2A-2B 18 months</td>
<td>PQ 912 vs Placebo</td>
<td>Glutaminyl Cyclase Inhibition (TO)</td>
<td>CSF biomarkers Spectral EEG vMRI</td>
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<tr>
<td><strong>Vitamin D- RO1</strong></td>
<td>N , Dementia</td>
<td>2-4 42 months</td>
<td>4000 IU D3 vs 600 IU</td>
<td>25-OH Vit D levels</td>
<td>vMRI, biomarkers, inflamm, oxid stress</td>
</tr>
</tbody>
</table>
### To What Extent is Dementia Preventable?

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>PAR</th>
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<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>2.9%</td>
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<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.

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**Risk Factors along the life course**

- **Early Life**
  - Less education: 8%
  - ApoE ε4: 7%

- **Midlife**
  - Hearing loss: 9%
  - Hypertension: 2%
  - Obesity: 1%

- **Late Life**
  - Smoking: 5%
  - Depression: 4%
  - Physical inactivity: 3%
  - Social isolation: 2%
  - Diabetes: 1%

**Delaying the onset of dementia by:**
- 1 year: ↓ 10%
- 5 years: ↓ 50%
Risk and Resilience for AD Dementia:

Adapted from Kivipelto, Mangialasche et al., Oxford Ger Text Medicine 2015,
Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia
A Randomized Clinical Trial

**POPULATION**

6029 Men
3332 Women

Adults aged ≥50 years with hypertension and without diabetes or stroke
Mean age: 68 years

**LOCATIONS**

102 US sites (including Puerto Rico)

**INTERVENTIONS**

9361 Patients randomized
8563 Patients analyzed

4278 Intensive control
(Target SBP <120 mm Hg)

4285 Standard control
(Target SBP <140 mm Hg)

Median treatment period, 3.3 years

**FINDINGS**

**PRIMARY OUTCOME:** Adjudicated probable dementia

- **Intensive control**
  - 149 patients
    - (7.2 cases/1000 person-years)
- **Standard control**
  - 176 patients
    - (8.6 cases/1000 person-years)

**Hazard ratio:** 0.83 (95% CI, 0.67-1.04)

**SECONDARY OUTCOME:** Adjudicated MCI

- **Intensive control**
  - 287 patients
    - (14.6 cases/1000 person-years)
- **Standard control**
  - 353 patients
    - (18.3 cases/1000 person-years)

**Hazard ratio:** 0.81 (95% CI, 0.69-0.95)

**SECONDARY OUTCOME:** Composite outcome

- **Intensive control**
  - 402 patients
    - (20.2 cases/1000 person-years)
- **Standard control**
  - 469 patients
    - (24.1 cases/1000 person-years)

**Hazard ratio:** 0.85 (95% CI, 0.74-0.97)

Occurrence of adjudicated probable dementia

Adjudicated mild cognitive impairment (MCI)

Composite outcome of MCI or probable dementia
### Finnish Geriatric Intervention Study To Prevent CI and Disability (FINGER)

<table>
<thead>
<tr>
<th>Study Design Multidomain</th>
<th>At-risk population</th>
<th>Primary outcome</th>
<th>Secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dbl blind RCT</td>
<td>n=1,260, Age 60-77, CAIDE Risk Score ≥ 6, NPS ≤ mean for age, CERAD Word Lists &lt;19, MMSE 20-26</td>
<td>2-year cognitive performance on NP test battery composite Z-score</td>
<td>Executive functioning, processing speed, and memory; Incidence of dementia and AD; Vascular RF, dietary intake and markers; Inflammation and oxidative stress, lipid and glucose metabolism, disability, etc.</td>
</tr>
</tbody>
</table>

**Control**
- regular health advice
- Population based

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**NGANDU T et al Lancet 2015**

- **NTB Score Primary**
  - *p=0.03*

- **Executive**
  - *p=0.04*

- **Processing Speed**
  - *p=0.03*

- **Memory**
  - *p=0.36*
Considerations for Multidomain Interventions

- **Dietary**
  - MIND diet or Mediterranean diet.
  - Ketogenic diet or supplements,

- **Stress control**
  - Mindfulness, meditation, yoga

- **Neuromodulation** with TMS, TCD

- **Medications**
  - Micro-dose lithium, Metformin,
  - Anti-oxidant supplements, Anti-inflammatory Cox-1 inhibitors (ibuprofen),

- **Sleep therapies**
  - Non REM sleep correlates with tau and Aβ[^1][^2]
  - Apnea treatment
  - Orexin analogues for sleep fragmentation,
  - Grehlin agonists

- **Targets will not be unitary or necessarily well defined**

- **Doses may not be easy to define or refine for target engagement**

- **Durations of intervention are likely to be long to achieve significant endpoints**

- **Trial design: preferences, compliance and community implementation**

Conclusions

- Pharmacological approaches
  - Amyloidopathy necessary but not sufficient to cause disease
  - Interaction with ↑ tau pathology associates with symptoms
  - Monotherapy approaches with amyloid lowering have not been successful
    - Readouts still forthcoming on aducanumab and BAN 2401

- Tau therapies
  - are in active development

- ADCS trials at UCSD:
  - provide community opportunity with 5 active trials to potentially participate in

- Multidomain interventions for prevention

- Personalized medicine approaches with molecular fingerprinting
Acknowledgements!

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Committee Selection and Program Evaluation

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“Skate where the puck is going to be……..”

- The Canadian Philosopher
Wayne Gretzky