Overview

- **AD**
  - The epidemic
  - Failed trials targeting amyloid
- **Tauopathies (clinical)**
  - Tau mutations and other primary tauopathies
  - Secondary tauopathies – CTE, AD
- **Getting rid of tau**
- **Future therapies against tau**

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**Alzheimer’s Disease (AD)**

- Described by Alois Alzheimer in 1906
- Presenile dementia with amnesia, psychosis
- Microscopic level
  - Amyloid plaque
  - Neurofibrillary tangle

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Alois Alzheimer, 1906

Original drawing of Alois Alzheimer (1864-1915)
Frontotemporal Dementia (FTD)

- In 1892, Arnold Pick describes a focal neurodegenerative condition
- Disease preferentially affects the frontal and temporal lobes
- Later pathologists require cellular inclusion (Pick body) to diagnose

FTD Versus AD Atrophy

Voxel-based morphometry FTD & AD versus controls

Alzheimer’s Drawings of Pick Bodies

AD Becomes an Epidemic: FTD Disappears

- Amyloid correlates with dementia in nursing facilities
- Alzheimer’s disease is epidemic and a public health threat

Dementia Dark Ages: Don't Pick Pick's Disease

- “Alzheimer’s” becomes equivalent to dementia & all of the rich complexity of dementia is ignored
- A simplified version of AD emerges requiring memory as the primary problem
- Pick’s disease (vascular dementia, Lewy body) disappear
- Misdiagnosis of non-AD dementias high
- Pharmaceutical industry focus on the AD-specific molecule Aβ-42
- Trials fail

Bapineuzumab Background

- Humanized N-terminus anti-A-β monoclonal for AD
- Phase 3 trials safety/efficacy potential disease modifier based on clinical and biomarker evidence
- Based on Phase 2 results, separate Phase 3 trials were designed for apolipoprotein E (apoE) ε4 allele carriers and non-carriers mild-moderate AD
- Primary efficacy, biomarker safety, both trials, pooled analysis across studies, pre-specified mild (MMSE ≥ 21) and moderate (MMSE ≤ 20) subgroup analyses

Current AD passive immunotherapy trials employ sequence-specific anti-Aβ antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Description</th>
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<tbody>
<tr>
<td>Bapineuzumab</td>
<td>Humanized mouse monoclonal, binds first 5 a.a. of N-terminus, clears plaques and vascular Aβ</td>
</tr>
<tr>
<td>LY2062430</td>
<td>Humanized mouse monoclonal, binds amino acids 14-26, clears soluble Aβ not deposits</td>
</tr>
<tr>
<td>PF-4360365</td>
<td>Binds to C-terminus, deglycosylated to decrease Fc effects, clears plaques, less microglial action</td>
</tr>
</tbody>
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Amyloid Related Imaging Abnormalities

- Multi-focal gray white matter edema (ARIA-E)
- Sulcal effusion (ARIA-E)
- Subtle leptomeningeal involve (ARIA-E)

Sperling et al. Alz & Dementia 2011
Trial Design

- Randomized double-blind, placebo-controlled, 18-month clinical trials in mild – moderate AD dementia (MMSE 16–26)
- APOE ε4 carriers: bapineuzumab 0.5 mg/kg or placebo (ratio 3:2)
- Non-carriers: bapi 0.5 mg/kg, 1.0 mg/kg or placebo (ratio 3:3:4)
- 2 mg/kg dose terminated early in Phase 3 due to ARIA
- Primary Clinical Endpoints: ADAS – Cog 11, DAD
- Key Biomarker Secondary Endpoints
  - Brain amyloid burden on PiB PET
  - CSF phospho-tau
  - MRI brain volume
- Schedule of Events
  - 6 infusions every 13 weeks
  - MRI monitoring for ARIA =6 weeks after each infusion

Analysis Populations

<table>
<thead>
<tr>
<th>Study 302 APOE ε4 Carriers</th>
<th>Total Randomized N = 1121</th>
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</thead>
<tbody>
<tr>
<td>Population</td>
<td>Placebo (%)</td>
</tr>
<tr>
<td>Randomized (Safety population)</td>
<td>448 (100.0)</td>
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<tr>
<td>πM1T</td>
<td>432 (94.4)</td>
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<tr>
<td>PiB PET</td>
<td>40 (8.9)</td>
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<tr>
<td>CSF</td>
<td>85 (15.0)</td>
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<tr>
<td>vMRI</td>
<td>238 (50.3)</td>
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<table>
<thead>
<tr>
<th>Study 301 Non-Carriers</th>
<th>Total Randomized N = 1331</th>
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<tbody>
<tr>
<td>Population</td>
<td>Placebo (%)</td>
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<tr>
<td>Randomized (Safety population)</td>
<td>524 (100.0)</td>
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<tr>
<td>mT1T</td>
<td>493 (94.3)</td>
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<tr>
<td>PiB PET</td>
<td>16 (3.0)</td>
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<tr>
<td>CSF</td>
<td>77 (14.7)</td>
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<tr>
<td>vMRI</td>
<td>244 (46.0)</td>
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</table>

Change in ADAS-Cog 11 by Treatment Group Over 78 Weeks (mITT population)

<table>
<thead>
<tr>
<th>Study 302 (Carriers)</th>
<th>Study 301 (Non-Carriers)</th>
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<tbody>
<tr>
<td>Improvement</td>
<td>Improvement</td>
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<tr>
<td>ADAS-Cog</td>
<td>ADAS-Cog</td>
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<tr>
<td>Mean (n=432)</td>
<td>Mean (n=493)</td>
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<tr>
<td>Baseline</td>
<td>Baseline</td>
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<td>Change From</td>
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<td>Baseline</td>
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Placebo vs Bap 0.5 mg/kg p=0.798
Placebo vs Bap 0.5 mg/kg p=0.042
Placebo vs Bap 1.0 mg/kg p=0.620

Pooled 302/301: Change in Amyloid Burden as assessed by [11C] PiB-PET at Week 71 (PiB PET analysis population)

<table>
<thead>
<tr>
<th>All Subjects</th>
<th>Mild Subjects (MMSE&gt;21)</th>
</tr>
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<tbody>
<tr>
<td>Placebo (n=55)</td>
<td>Placebo (n=25)</td>
</tr>
<tr>
<td>Bap 0.5 mg/kg (n=57)</td>
<td>Bap 0.5 mg/kg (n=46)</td>
</tr>
<tr>
<td>Bap 1.0 mg/kg (n=12)</td>
<td>Bap 1.0 mg/kg (n=9)</td>
</tr>
</tbody>
</table>

Placebo vs Bap 0.5 mg/kg p=0.027
Placebo vs Bap 1.0 mg/kg p=0.028

No significant effect in moderate group
Biomarker Summary

- 36% non-apoE4 carriers normal amyloid
- Reduced amyloid burden PiB PET relative to placebo observed in carrier and pooled studies
- Reduced CSF p-tau relative to placebo observed in carrier, non-carrier and pooled studies
- Increased rate ventricular expansion relative to placebo in carrier, non-carrier and pooled analyses

Future of Amyloid Trials

- Crenezumab humanized monoclonal 1-40 and 1-42 Beta amyloid
- Trial of 300 subjects with PSEN1 mutation (5000 in Medellin, Columbia sick by 45 years)
- Asymptomatic over 30 (secondary prevention)
- DIAN (Dominantly Inherited Alzheimer Disease Network) study – 3 different amyloid lowering compounds in a US cohort with familial AD
- Solanezumab will probably be tried again in very mild cohort

Amyloid Deposition in Autosomal Dominant AD

Bateman et al., NEJM 2012
**Immunization Against Aβ-42**

- Meningoencephalitis 5%
- Subjects who mount antibody
  - Lower Abeta load, plaques removed
  - Reduced tau neuronal processes, not in cell bodies
  - No beneficial effect on synapses,
  - increased microglial activation & amyloid angiopathy
  - No slowing of clinical improvement

**Will Amyloid Trials Fail?**

- Misdiagnosis, co-morbid pathology?
- Do therapies hit right form of amyloid?
- Are therapies starting too late?
- Amyloid present in presymptomatic and peaking in MCI (early AD is really late)
- Can we realistically treat population before disease begins (primary prevention)?
- How about tau?

**Tau Stabilizes Microtubules**

**Pure Tauopathies**

- Tau mutations and susceptibility genes – bvFTD, nfvPPA, PSP, CBD
- Pick’s disease – bvFTD, nfvPPA
- Corticobasal degeneration (CBD) – bvFTD, nfvPPA, executive motor syndrome
- Progressive supranuclear palsy – falls, ophthalmoplegia, axial PD, dementia
- Argyrophilic grain disease – slow MCI, bvFTD associated with other tauopathy pathology
**Secondary Tauopathies**

- *AD
- *CTE
- Niemann-Pick-C
- Guam-ALS-PD-Dementia
- Aluminum Toxicity
- Post-encephalitic PD

*Tau is a good target

**MAPT**

- Gene: Microtubule associated protein tau, Chrom 17, most cases, intron mutation, splice in exon 10, or mutations in exons 9–13
- Epi: 3–14% all FTD, 17% familial FTD (UCSF)
- Syndrome: usually bvFTD, PSP preceded by depression, addiction, bipolar, poor judgment
- Path: Unclassifiable tauopathy
- MRI: Symmetric, anteromedial temporal lobes, anterior insula, OFC, fornix

Rohrer 2009 & 2011

**CTE: Amygdala/Tau**

**Pick’s Disease**

- Mean age 68 range 49 to 96)
- bvFTD (20% UCSF cases) or nfvPPA (12% UCSF)
- Rarely familial
- Massive frontotemporal atrophy
- Can spare movement till very late
- 3R tau aggregates in granule cells of dentate gyrus
- Spares substantia nigra

**Tau Mutations**

**Clinical History & Exam**

- 62 year old right-handed male
- First symptoms 60 years, grandson fell off high-chair. Didn’t move, wouldn’t let daughter use his napkin to help child’s bleeding
- Computer all day, bought $7,000 book on internet. Compulsively watches “Mary Poppins” and “Grease”
- For wife’s 60th birthday bought a battery
- Craves candies/cookies 30 lb wt gain 15 mos

**International Research Criteria**

- Early (2-3 yrs) behavioral disinhibition
- Early (2-3 yrs) apathy or inertia
- Early (2-3 yrs) loss of emotional reactivity/sympathy and empathy
- Perseverative, stereotyped or compulsive/ritualistic behavior
- Hyperorality and dietary changes
- FTD neuropsychological profile
- Frontal and/or anterior temporal atrophy on MRI
- Presence of known mutation
Clinical History

- Very slow progression
- Nursing home after 2 years
- Movement stayed good till near end
- Death aspiration

At Autopsy

Pick Bodies
VBM results scans Year 1, Year 4, Year 5 compared to controls

PIB+ nfvPPA

Co-pathology in PIB+ nfvPPA

- Aβ IHC (mid frontal gyrus)
- 3R Tau IHC (dentate gyrus)
- High likelihood AD
  - CERAD frequent; Braak V
  - Moderate amyloid angiopathy
- Pick's disease
  - FTLD-Tau
UCSF Path Proven CBD

- 18 cases: Avg age at presentation 67 years
  - bvFTD: 5
  - PNFA: 5
  - Executive Motor: 7
  - Posterior Cortical Atrophy: 1
- Only 7 movement changes first 4 years
- 13 executive or language deficits vs. 4 early parietal deficits
- Alien foot more common than limb apraxia

Clinical syndrome:
- bvFTD
- Exec-Motor
- PNFA

Astrocytic Plaque

PSP

- Frontal executive disorder (dementia)
- Axial rigidity
- Falls
- Ophthalmoplegia
- Behavioral disorder or non-fluent aphasia

Steele, Richardson Olszewski (1963)
**Dorsal midbrain connectivity in healthy young and older controls**

Young controls (HC1)

Older controls (HC2)

Overlap

Seed

(Gardner et al, Ann Neurol 2013, In Press)

**Reductions in dorsal midbrain connectivity in PSP compared to matched controls**

(Gardner et al, Ann Neurol 2013, In Press)
Dorsal midbrain connectivity within the PSP network correlates with functional status

(Gardner et al, Ann Neurol 2013, In Press)

Globose Tangles

Thorny Astrocyte

Argyrophilic Grain Disease
**Tau**

- Clinical syndromes bvFTD, nfvPPA, PSP
- Tau therapies emerging
  - Decrease production
  - Decrease production of toxic forms
    - Prevent Acetylation,
    - Decrease phosphorylation
  - Increase clearance
    - Antibodies
    - Stimulate Autophagy
    - Stimulate degradation in proteosome

**Tau Spreads Like a Prion**

- Spreads from one cell to next (heparin receptor)
- Moves along specific circuits
- Can be removed by monoclonal antibodies
- Trauma, genetic mutations, polymorphisms aging all predispose to tauopathies
- Strains of tau?

**Tau Clearance by Proteolytic Pathways**

**Acetylation Slows Tau Turnover by Inhibiting Its Ubiquitination**

-Min et al. Neuron 2010
Tau Therapies Are Coming

- PSP, Tau mutations carriers easy to recognize (good clinical target)
- AD, CTE also good targets
- Need tau imaging agent (like PIB) or blood/CSF biomarker
- Antibody studies very appealing
- Learn from AD failures to treat FTD and AD
- Non-amyloid approaches needed