Alzheimer's Disease Drug Development Pipeline: Innovations and New Directions
Disclosures

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Alzheimer’s Disease Drug Development Pipeline: Innovations and New Directions

- Drug development
- Pipeline overview
- Target categories
- Monoclonal antibodies
- Aducanumab Appropriate Use Recommendations
Drug Development Overview (with Biomarkers)

Nonclinical Discovery and Animal Testing

- Candidate Treatments; Efficacy (Biological, Behavioral) and Safety/Toxicity
- Measurable Biological Changes in Assays and Animals

Phase 1

- Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) Studies in Healthy Volunteers
- Safety Biomarkers; ECG, Liver Functions, Etc

Phase 2

- Proof-of-Concept and Dose-Finding Studies in AD Patients (400-800)
- Diagnosis; Target Engagement; Dose Response; Safety

Phase 3

- Confirmatory Trials with Clinical Benefit Shown (Accelerated Approval Require Biomarker Effect); 600-1200 Patients
- Diagnosis; Support for Disease Modification; Safety

FDA Review

- Comprehensive Review of Efficacy and Safety
- Clinical Pharmacology Section of Label (not the Indication); Accelerated Approval
Rights of Drug Development

- Precision neurology/medicine requires precision drug development
- Each “right” improves the probability of success of advancing the agents to the next level of development
- Phase 3 is the most expensive phase of drug development
- Stopping development of flawed agents early saves resources that can be redirected to other agents

Alzheimer’s Disease Drug Development Pipeline:

Methods

- Annual review beginning in 2016
- Based on clinicaltrials.gov
- Index date 1/25/2022
- Artificial intelligence and machine learning strategies
- Publicly accessible portal anticipated Q2/3 2022
- NIA-funded Alzheimer Clinical Trial Innovation (ACTION) Initiative

Audience Question: About how many drugs do you think are currently in Alzheimer trials?

<table>
<thead>
<tr>
<th>150</th>
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<tbody>
<tr>
<td>500</td>
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<td>1000</td>
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Universe of Alzheimer’s Drug in Current Clinical Trials

- 143 agents in 172 trials
  - Phase 3 – 31 agents
    - DMTs – 21 (5 biologics)
  - Phase 2 – 82 agents
    - DMTs – 71 (26 biologics)
  - Phase 1 – 30 agents
  - DMTs – 83.2% of the agents
  - Cog Enhancers – 9.8%
  - NPS tx – 6.9%
  - Repurposed – 37%

### Alzheimer’s Disease Drug Development Pipeline

- **Phase 1**: some trials done ex-US and not registered in the US
- Repurposed agents enter pipeline at Phase 2 or Phase 3 without Phase 1
- **Phase 2**:  
  - Proof of concept; many drugs stopped for lack of efficacy  
  - Some trials terminated for lack of recruitment other administrative reasons
- **Phase 3**: fewer, larger trials to meet regulatory requirements

<table>
<thead>
<tr>
<th>Phase</th>
<th>Count</th>
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<tbody>
<tr>
<td>Phase 1</td>
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<tr>
<td>Phase 2</td>
<td>82</td>
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<tr>
<td>Phase 3</td>
<td>31</td>
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Audience Question: Which of the following is the target most represented in the Alzheimer drug development pipeline?

1) Amyloid
2) Inflammation
3) Tau
4) Gene therapy
Common AD Research Ontology (CADRO)

- Amyloid
- Tau
- Inflammation/Immunity
- Synaptic plasticity/Neuroprotection
- Metabolism and Bioenergetics
- Proteostasis/Proteinopathies
- Epigenetics
- Oxidative Stress
- Vasculature
- Neurogenesis
- Neurotransmitter Receptors
- Other

<table>
<thead>
<tr>
<th>Category</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tbody>
<tr>
<td>Amyloid</td>
<td>3</td>
<td>11</td>
<td>6</td>
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<td>Tau</td>
<td>3</td>
<td>9</td>
<td>1</td>
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<tr>
<td>Inflammation/Immunity</td>
<td>5</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Synaptic plasticity/Neuroprotection</td>
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<td>4</td>
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<tr>
<td>Metabolism and Bioenergetics</td>
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<tr>
<td>Proteostasis/Proteinopathies</td>
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<tr>
<td>Epigenetics</td>
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<tr>
<td>Oxidative Stress</td>
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<td>3</td>
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<tr>
<td>Vasculature</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Neurogenesis</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurotransmitter Receptors</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>4</td>
<td>1</td>
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Much of the AD Drug Development Pipeline is Devoted to the Non-Canonical Targets (Amyloid, Tau)

- Amyloid: 14% of the pipeline (20 agents)
- Tau: 9% of the pipeline (13 agents)
- Non-canonical targets: 72% of pipeline (110 agents)
  - Inflammation: 16% (23 agents)
  - Synaptic plasticity: 13% (19 agents)
  - Metabolism/bioenergetics: 6% (8 agents)

Marci H, et al. FCDR Alzheimer’s Disorder 2016; 5: 3-33
Inflammation is a Primary or Secondary Target of Many Agents in the AD Drug Development Pipeline

- Allopregnenolone
- Baricitinib (Janus kinase inhibitor)
- BCG vaccine (immunomodulator)
- Blarcamesine (Sigma-1 agonist; M2 antagonist)
- Canakinumab (IL-1 mAb)
- Curcumin (NSAID)
- Daratumumab (CD38 mAb)
- Edicotinib (CSF-1R antagonist)
- Emtricitabine (NRTI)
- GB301 (regulatory T cells)
- GV-971 (dysbiosis reduction)
- L-serine (decreased inflammation)
- Lenalidomide (cytokine antagonist)
- Montelukast (leukotriene antagonist)
- NE3107 (MAPK inhibitor)
- Pepinemab (semaphoring 4D mAb)
- Salsalate (NSAID)
- Sargramostim (granulocyte stimulator)
- Semaglutide (GLP-1 agonist)
- TB006 (galatin 3 mAb)
- Tdap vaccine (immunomodulator)
- TREM2 antibody
- XPro1595 (TNF inhibitor)

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Synaptic Integrity/Plasticity is a Primary or Secondary Target of Many Agents in the AD Drug Development Pipeline

- Allopregnanolone (GABA-B modulator)
- ATH-017 (HGF activator)
- Blarcamesine (Sigma-1 agonist; M2 antagonist)
- BMS-984923 (mGluR5 modulator)
- BPN14770 (PDE4 inhibitor)
- Bryostatin 1 (PKC inhibitor)
- COR388 (gingipain inhibitor)
- COR588 (gingipain inhibitor)
- CY6463 (Guanylate cyclase modulator)
- Endoerpic (neurotrophic)
- Elayta (sigma-2 antagonist)
- ExPlas (plasma transfusion)
- Levetirectam (SV2A modulator)
- MW150 (p38 MAPK inhibitor)
- Neflamapimod (p38 MAPK inhibitor; RAB-5 modulator)
- REM0046127 (calcium channel regulator)
- Simuflam (filamen A inhibitor)
- Troriluzole (glutamate modulator)
Anti-Diabetic Agents are Being Assessed in the AD Clinical Trials

- **Phase 3**
  - Metformin (insulin sensitizer)
  - Semaglutide (GLP-1 agonist)
- **Phase 2**
  - Dapagliflozin (SGLT2 inhibitor)
  - T3D-959 (PPAR agonist)
  - Insulin

AGES – advanced glycation end products; IRS-1; insulin receptor substrate 1; MG – microglia; ROS – reactive oxygen species

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Tau-Directed Therapeutics are Advancing

**Tau-Related Target** | **Agents**
--- | ---
Aggregation inhibition | TRx0237; PU-AD
Vaccine | ACI-35
Monoclonal antibody | Bepranemab; E2814; JNJ-63733657; semorinemab
Antisense oligonucleotide | MAPTRx
O-GlycNAcase inhibitor | LY3373689
Microtubule depolymerization | Nicotinamide

Amyloid Processing Provides Targets for Small Molecules

<table>
<thead>
<tr>
<th>Amyloid (Aβ) Target</th>
<th>Small Molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhance non-Aβ alpha-secretase pathway</td>
<td>APH-1105</td>
</tr>
<tr>
<td></td>
<td>MIB-626</td>
</tr>
<tr>
<td>Reduce APP by decreasing RNA transcription</td>
<td>Posiphen</td>
</tr>
<tr>
<td>Decrease pyroglutamate Aβ production</td>
<td>PQ912</td>
</tr>
<tr>
<td>Activates ABCC1 Aβ transporter</td>
<td>Thiethylperazine</td>
</tr>
<tr>
<td>Inhibits Aβ aggregation</td>
<td>Valitramiprosate (ALZ-801)</td>
</tr>
</tbody>
</table>

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Amyloid Species are Important Targets for Anti-Amyloid Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Amyloid (Aβ) Species</th>
<th>Monoclonal Antibody</th>
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</thead>
<tbody>
<tr>
<td>Aβ plaques</td>
<td>Aducanumab</td>
</tr>
<tr>
<td></td>
<td>Lecanemab</td>
</tr>
<tr>
<td></td>
<td>Donanemab</td>
</tr>
<tr>
<td></td>
<td>Gantenerumab</td>
</tr>
<tr>
<td>Pyroglutamate Aβ</td>
<td>Donanemab</td>
</tr>
<tr>
<td>Protofibrillar Aβ</td>
<td>Lecanemab</td>
</tr>
<tr>
<td>Oligomeric Aβ</td>
<td>Aducanumab</td>
</tr>
<tr>
<td></td>
<td>Gantenerumab</td>
</tr>
<tr>
<td></td>
<td>Crenezumab</td>
</tr>
<tr>
<td>Monomeric Aβ</td>
<td>Solanezumab</td>
</tr>
<tr>
<td></td>
<td>Crenezumab</td>
</tr>
<tr>
<td>Peripheral Aβ monomer</td>
<td>Solanezumab</td>
</tr>
</tbody>
</table>
Novel Directions in the AD Drug Development Pipeline

- **Phase 3**
  - Gut-brain axis (GV-971)

- **Phase 2**
  - Amyloid vaccine (ADvx40)
  - Tau vaccine (ACI-35)
  - Antisense oligonucleotide targeting tau expression (BIIB080)
  - Epigenetic intervention (nicotinamide; lamivudine)
  - Stem cells (allogenic human MSCs; autologous natural killer cells)

- **Phase 1**
  - Epigenetic interventions (AAV-hTERT; vorinostat)
  - Stem cells (allogenic adipose MSC-exosomes; placental-derived MSCs; human umbilical cord-blood-derived MSCs; allogenic human MSCs)

Epigenetic modifications (© J Cummings; M de la Flor, PhD, Illustrator)

MSC– mesenchymal stem cells
Question: Which of the following biomarkers is the basis for accelerated approval of monoclonal antibodies?

1) CSF p-tau
2) Plasma p-tau
3) Amyloid PET
4) CSF amyloid
Aducanumab (Aduhelm)

- First approved disease-modifying therapy
- Anti-amyloid monoclonal antibody
- 30% slowing of decline in those on 10 mg/kg x 14 months
- Dramatic reduction of plaque burden\(^1\)
- Accelerated approval based on amyloid plaque reduction
- Amyloid-related imaging abnormalities (ARIA) as main side effect
- ARIA is associate with APOE4 genotype
- Appropriate Use Recommendations (AURs)\(^2\) bridge Prescribing Instructions and clinical practice

ADUHELM: Appropriate Use Recommendations

**Emerging/Engage**
- Protocol
- Inclusion/exclusion
- Amyloid confirmed
- Standardized treatment approach
- Monitored

**Accelerated Approval**
- Amyloid plaque reduction
- Supportive clinical benefit
- Confirmatory trial required

**Prescribing Instructions**
- Indication (MCI/mild AD dementia)
- Administration and titration
- ARIA monitoring
- Pharmacology (from clinical trials)

**Appropriate Use Recommendations**
- Expert Panel*
- Best practices
- Safety emphasis
- Patient-centered care

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Aducanumab Appropriate Use Recommendations\(^1\) and AUR Update: Appropriate Patient

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**AUR**

- MCI or mild AD dementia due to AD
- MRI with specific cerebrovascular factors exclude the patient from treatment
- Amyloid positive (amyloid PET or abnormal CSF amyloid or amyloid/p-tau)
- Anticoagulants (except aspirin) excluded the patient from treatment

**AUR Update**

- Exclude history of immune disorders or seizures
- Exclude patients with extensive white matter changes
- APOE genotyping recommended\(^2\)
  - Noncarriers – 20.3% had ARIA
  - Heterozygotes – 43% had ARIA
  - Homozygotes – 66% had ARIA

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Aducanumab Appropriate Use Recommendations and AUR Update: Appropriate Patient

- Patient and care partner/family education is very important
- Understand
  - Anticipated benefits – slowing of loss of cognition and function, not improvement
  - Possible harms – ARIA-related
  - Adherence expectations – monthly infusion, MRI at baseline, amyloid PET or lumbar puncture, MRI monitoring, communication with clinicians (ARIA-related symptoms)
  - Duration of therapy – at least until beyond mild AD dementia
- Inclusivity, equity of treatment opportunity, and culturally-appropriate communication important
ADUHELM: Identifying Appropriate Patients

- MCI/ Mild AD Dementia
- Med/ Neuro Hx & Exam
- MRI
- Amyloid Confirmation
- ADUHELM

Cognitive, functional assessment (MMSE, MoCA); Patient-centered discussion
Autoimmune disorders, seizures, stroke, clotting disorders, medications
Macro-hemorrhage, infarcts, lacunes, microhemorrhages, siderosis
Amyloid PET or CSF amyloid measures
Titration and monitoring
Aducanumab Appropriate Use Recommendations and AUR Update: Appropriate ARIA Monitoring

- AUR update: add MRI prior to the 5th, 7th, 9th, 12th dose
- Most ARIA occurs within the titration period
Aducanumab Appropriate Use Recommendations and AUR Update:
Appropriate ARIA Management

- Most ARIA has no symptoms (74%)
- Treatment is suspended if any symptoms are present
- Treatment is suspended for moderate or severe ARIA-E or ARIA-H
- Treatment can be reinitiated if ARIA-E resolves or ARIA-H stabilizes
- ARIA update specifies ARIA-related stopping rules
- Severe ARIA is rare (0.3%); preparedness for these rare cases is important
### AD Drug Development Pipeline: Summary

<table>
<thead>
<tr>
<th>Mechanism overlap; artificially separated (e.g., inflammation, oxidation, reactive oxygen species)</th>
<th>Combination approaches are uncommon (limited to vascular targets)</th>
<th>Amyloid and tau are common targets but these they comprise a minority of the pipeline agent mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarkers are enormously helpful; more are needed</td>
<td>Most drugs in the pipeline are DMTs; few cognitive enhancers or treatments for neuropsychiatric symptoms</td>
<td>Aducanumab is the first approved DMT for AD; other anti-amyloid monoclonal antibodies are promising</td>
</tr>
</tbody>
</table>
Chambers-Grundy Center for Transformative Neuroscience

• Department of Brain Health
  • Jefferson Kinney
  • Samantha John
  • Kate Zhong

• Clinical Trial Observatory
  • Garam Lee
  • Jorge Fonseca
  • Sidkazem Taghva
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