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

Disclosures

- JC has provided consultation to Acadia, Alkahest, AlphaCognition, AriBio, Avanir, Axsome, Behren Therapeutics, Biogen, Biohaven, Cassava, Cerecin, Cortexyme, Diadem, EIP Pharma, Eisai, GemVax, Genentech, Green Valley, Grifols, Janssen, LSP, Merck, NervGen, Novo Nordisk, Oligomerix, Ono, Otsuka, PRODEO, Prothena, ReMYND, Renew, Resverlogix, Roche, Signant Health, Suven, United Neuroscience, and Unlearn AI pharmaceutical, assessment, and investment companies.
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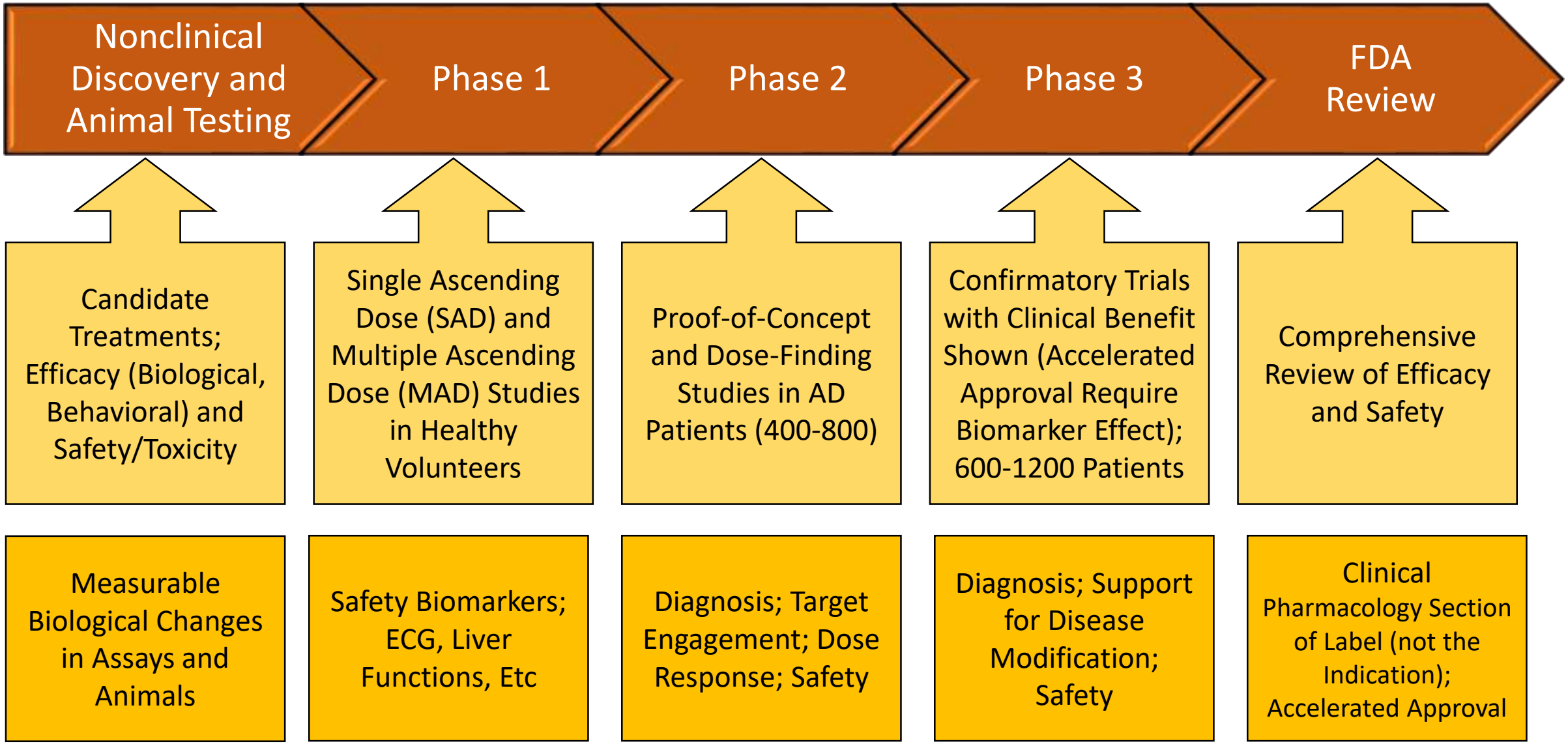
Alzheimer's Disease Drug Development Pipeline: Innovations and New Directions

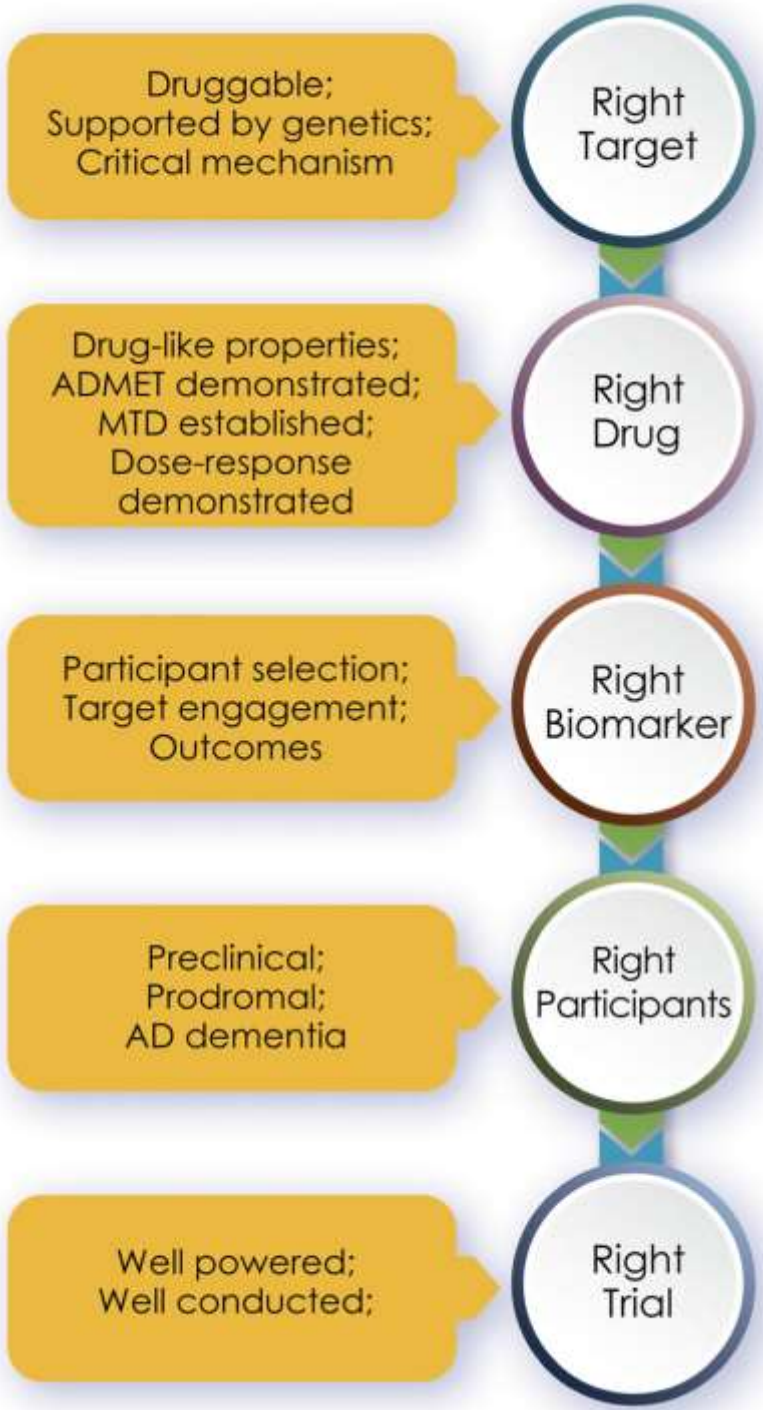
- Drug development
- Pipeline overview
- Target categories
- Monoclonal antibodies
- Aducanumab Appropriate Use Recommendations

Drug Development Overview (with Biomarkers)



Rights of Drug Development[1]

- 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[2]



[1]Cummings J, Scheltens P, Feldman H. The rights of precision drug development for Alzheimer’s disease. Alz Res & Therapy, 2019; 11: 76-90; [2]Paul S, et al. Nat Rev Drug Disc 2010; 9: 203-214

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

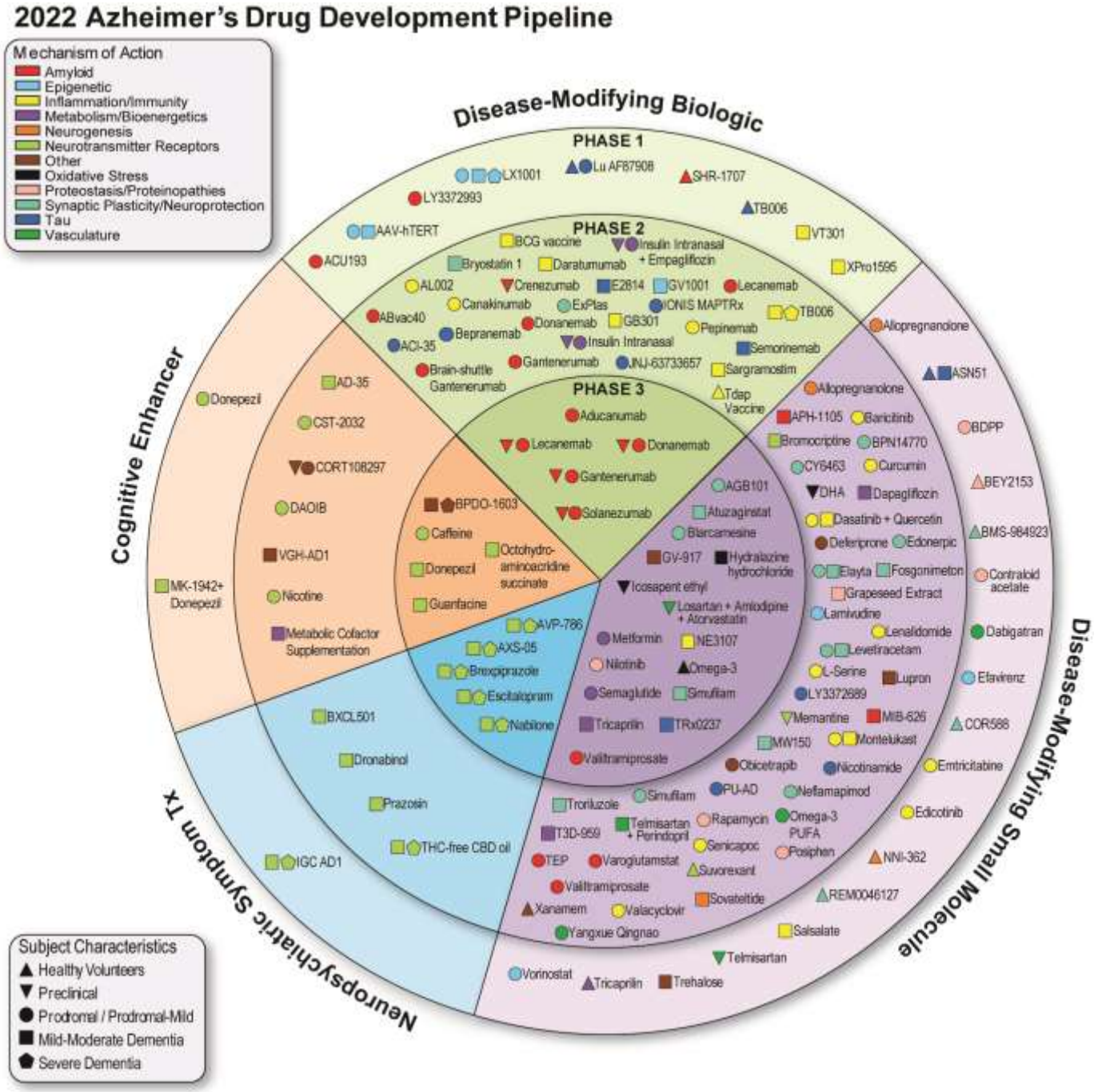
Cummings J, et al. Alz&Dem: TRCI, 2016, 2017, 2018, 2019, 2020, 2021

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

150

500

1000



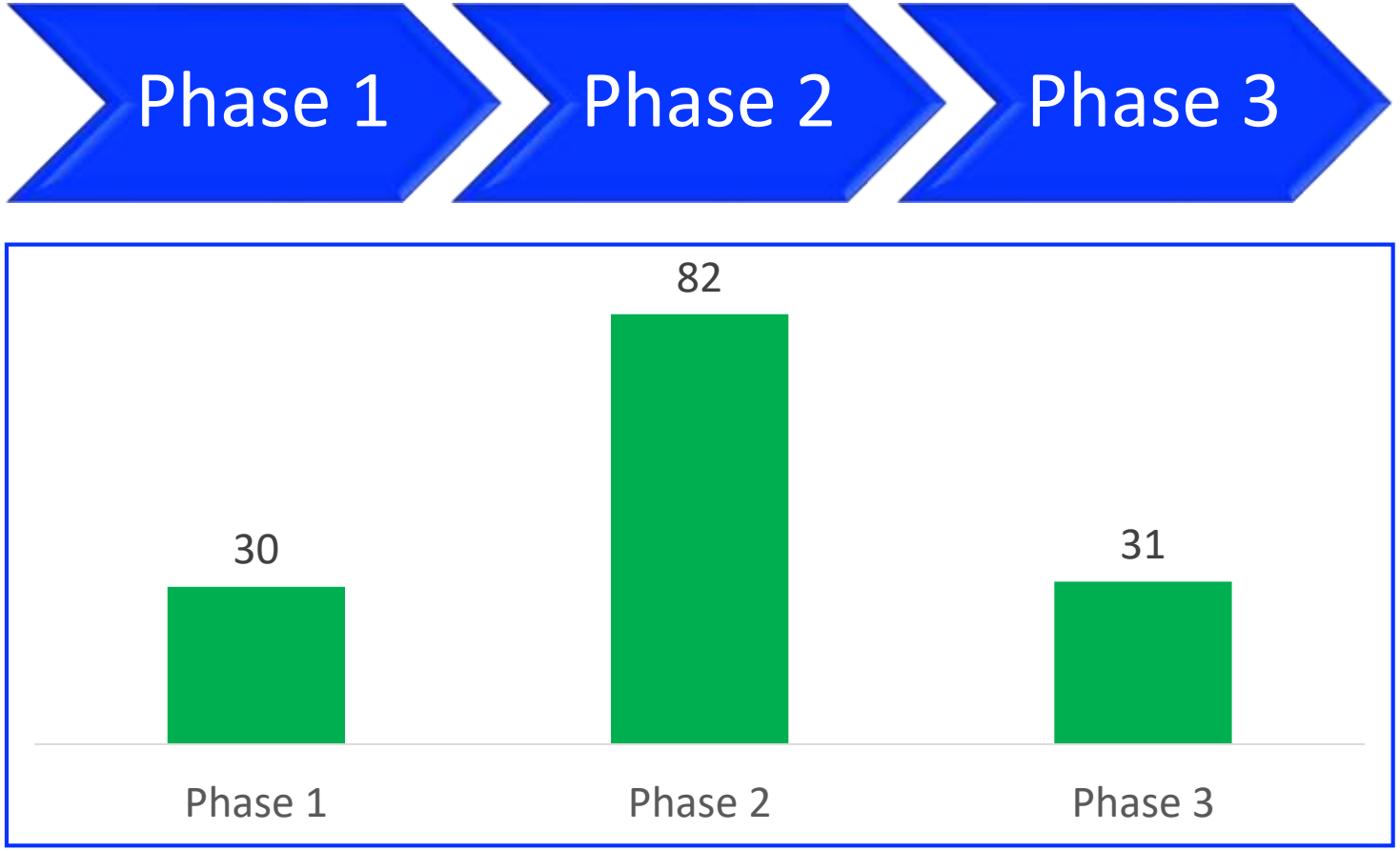
Universe of Alzheimer's Drug in Current Clinical Trials

- 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%

Cummings J, et al. Alz&Dem:TRCI (submitted)

Alzheimer's Disease Drug Development Pipeline

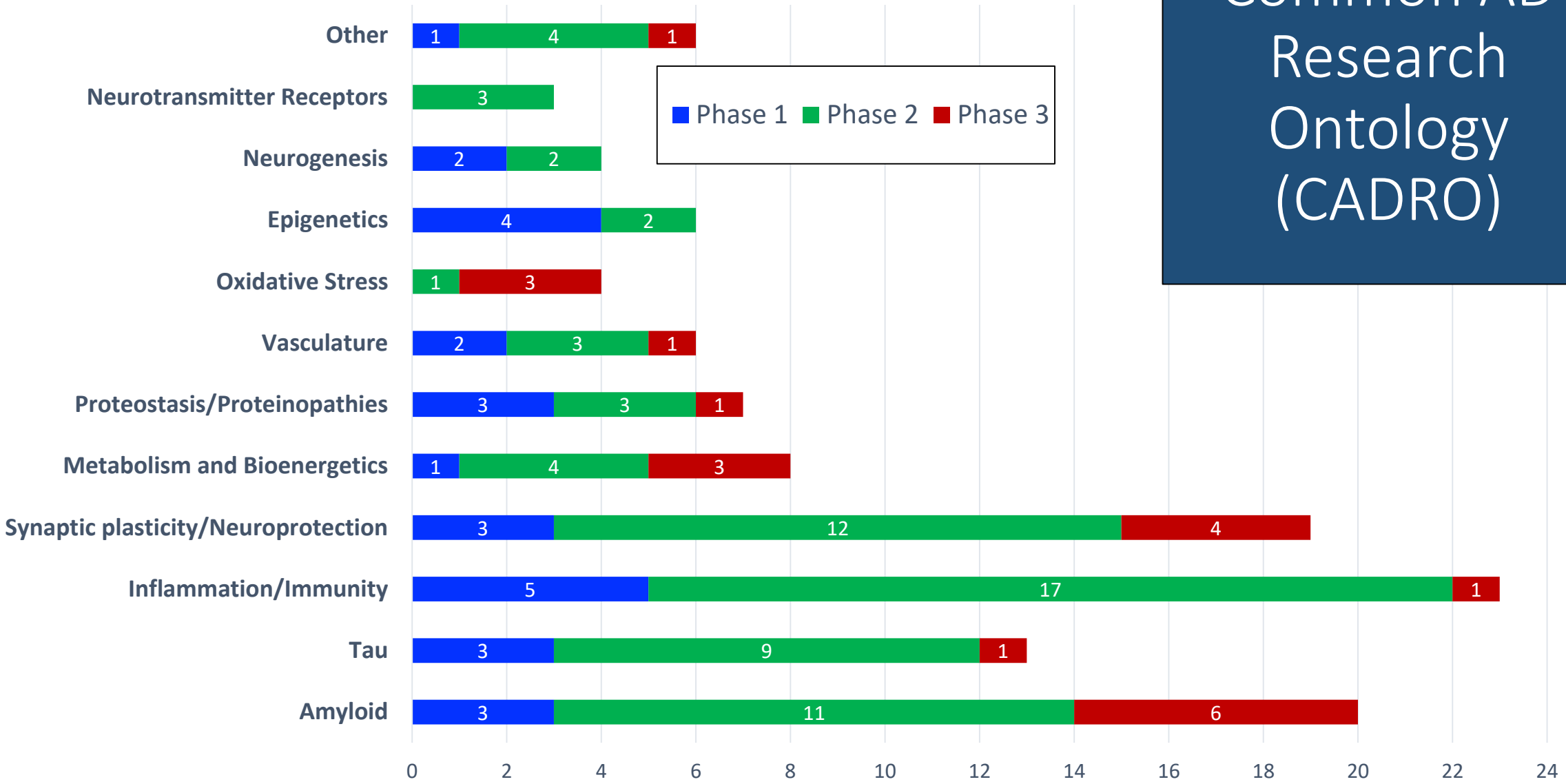
- Phase 1: some trials done ex-US and not registered in the US
- Repurposed agents enter pipeline at Phase 2 or Phase 3 without Phase 1
- Phase 2:
  - Proof of concept; many drugs stopped for lack of efficacy
  - Some trials terminated for lack of recruitment other administrative reasons
- Phase 3: fewer,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



Audience Question: Which of the following is the target most represented in the Alzheimer drug development pipeline?

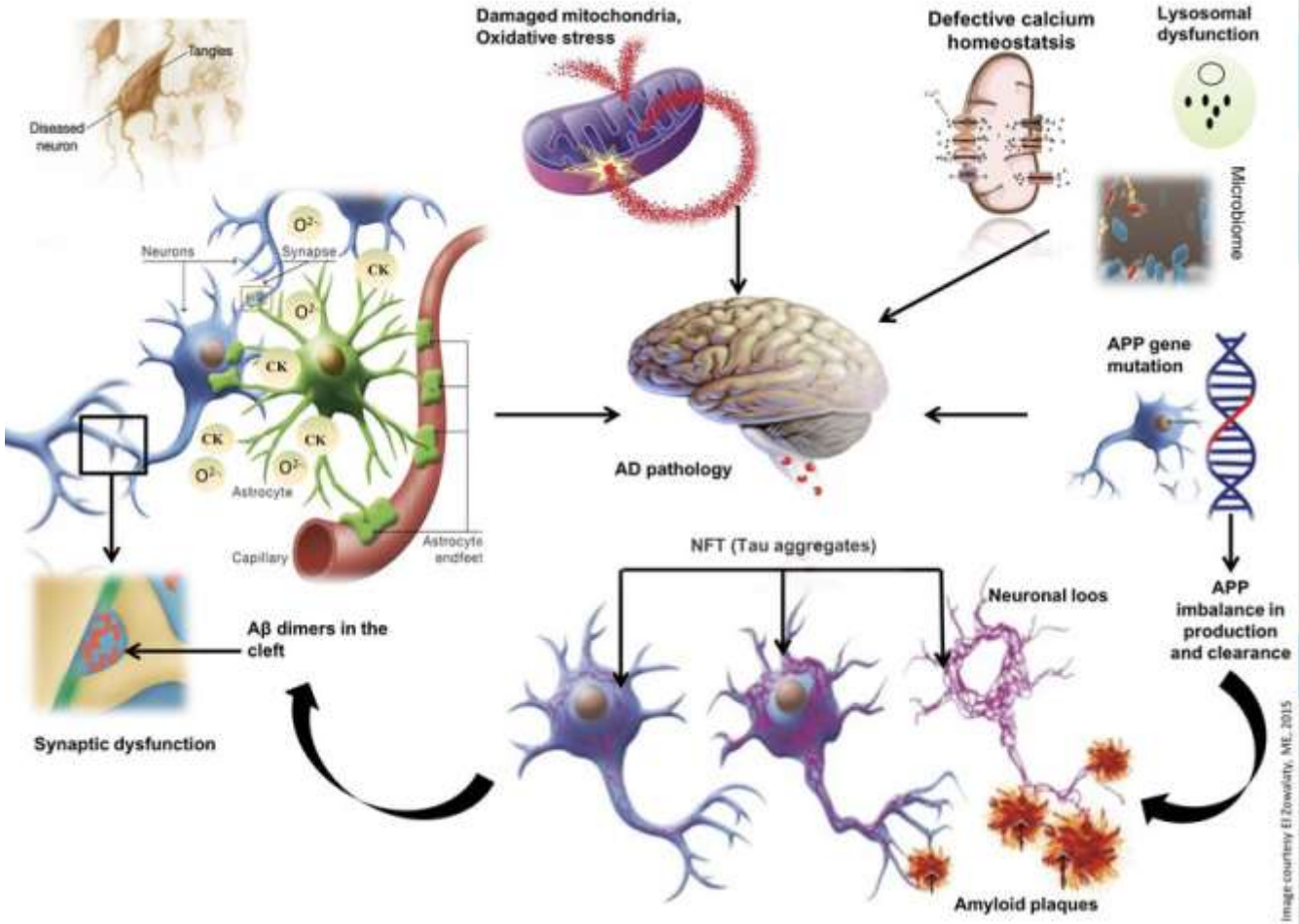
1) Amyloid
2) Inflammation
3) Tau
4) Gene therapy

Common AD Research Ontology (CADRO)



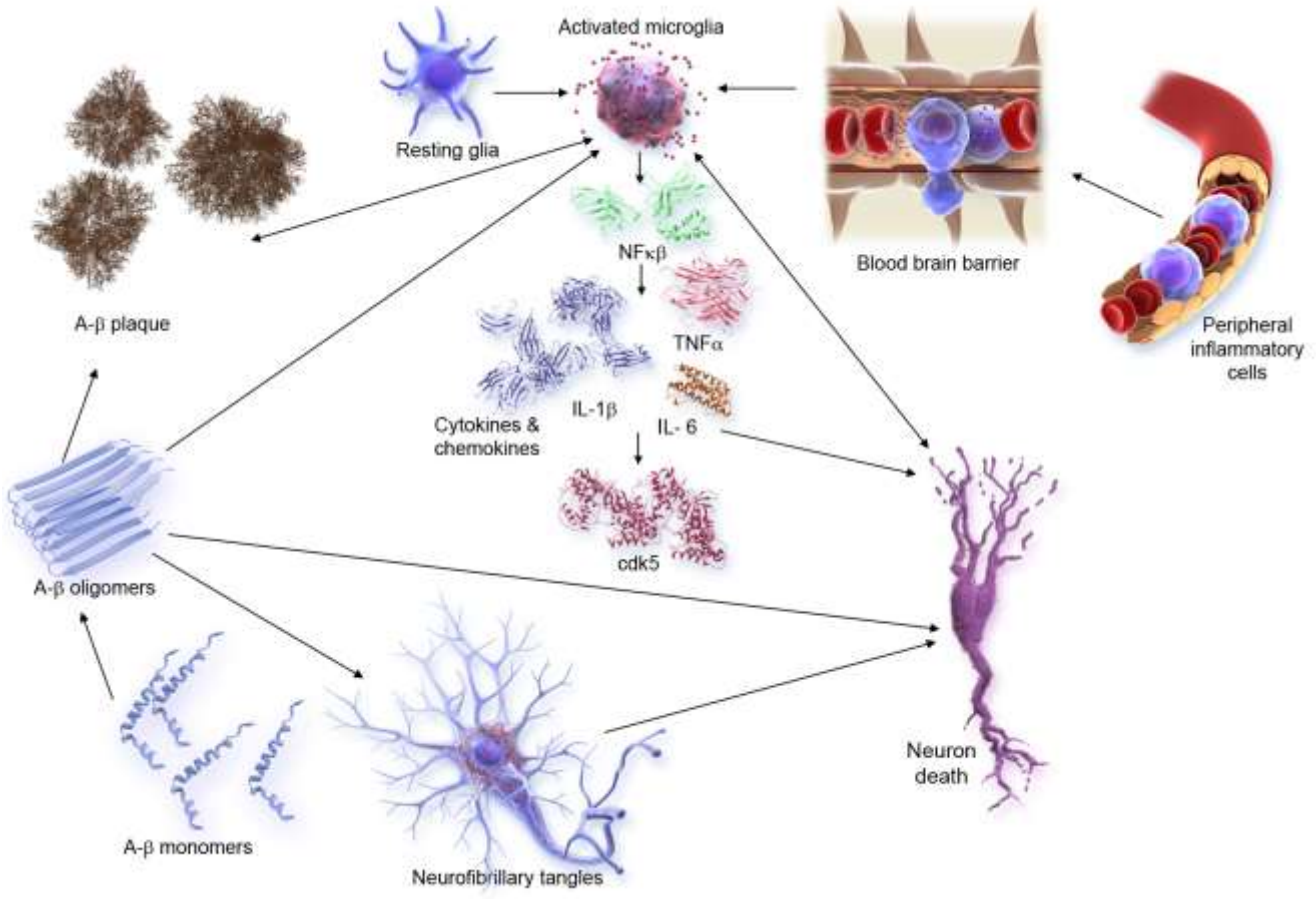
Much of the AD Drug Development Pipeline is Devoted to the Non-Canonical Targets (Amyloid, Tau)

- 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

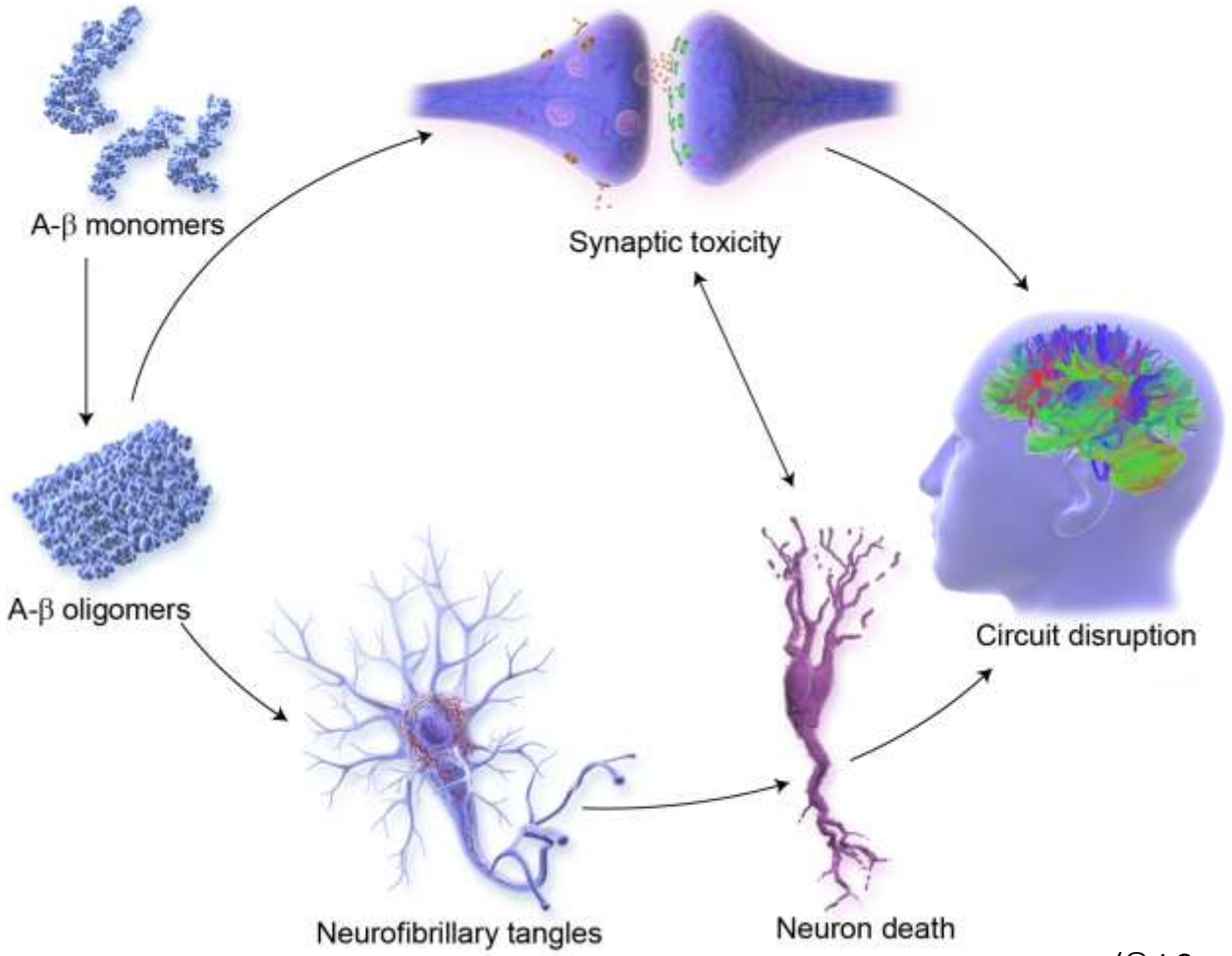
Inflammation is a Primary or Secondary Target of Many Agents in the AD Drug Development Pipeline



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

- 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)

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

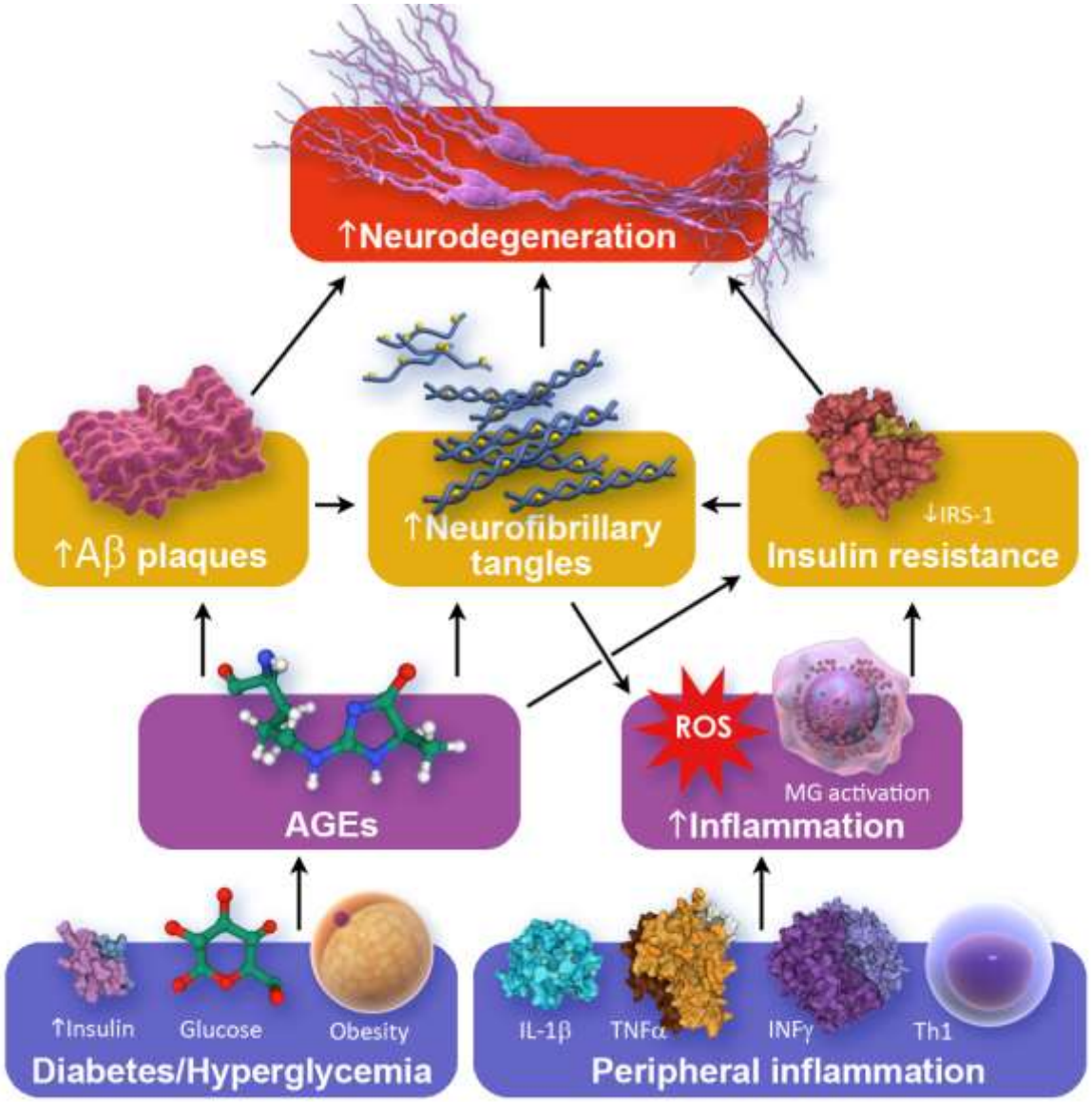


(© J Cummings; M de la Flor, PhD, Illustrator

- 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 (p 38 MAPK inhibitor; RAB-5 modulator)
- REM0046127 (calcium channel regulator)
- Simuflam (filamen A inhibitor)
- Troriluzole (glutamate modulator)

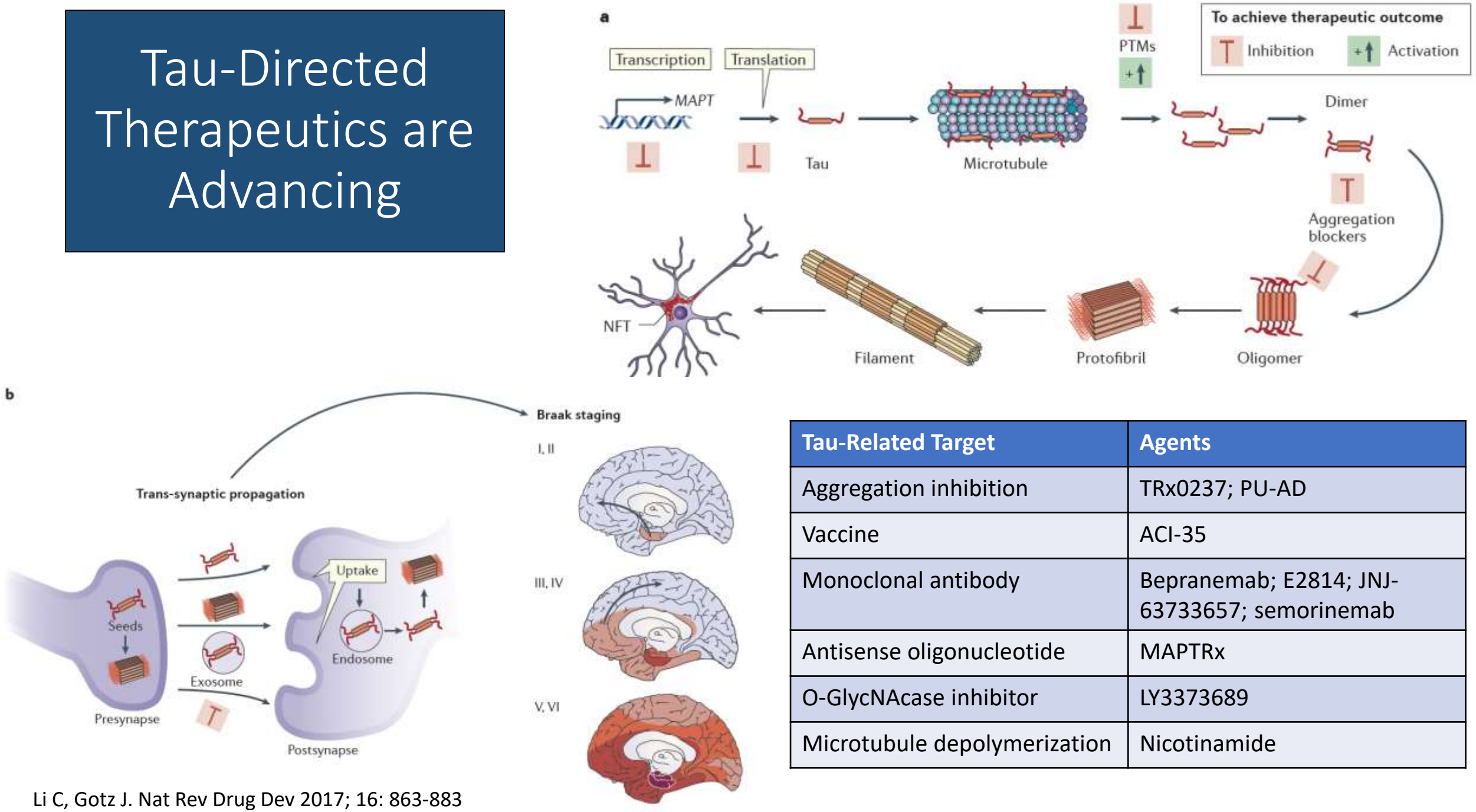
Anti-Diabetic Agents are Being Assessed in the AD Clinical Trials

- 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

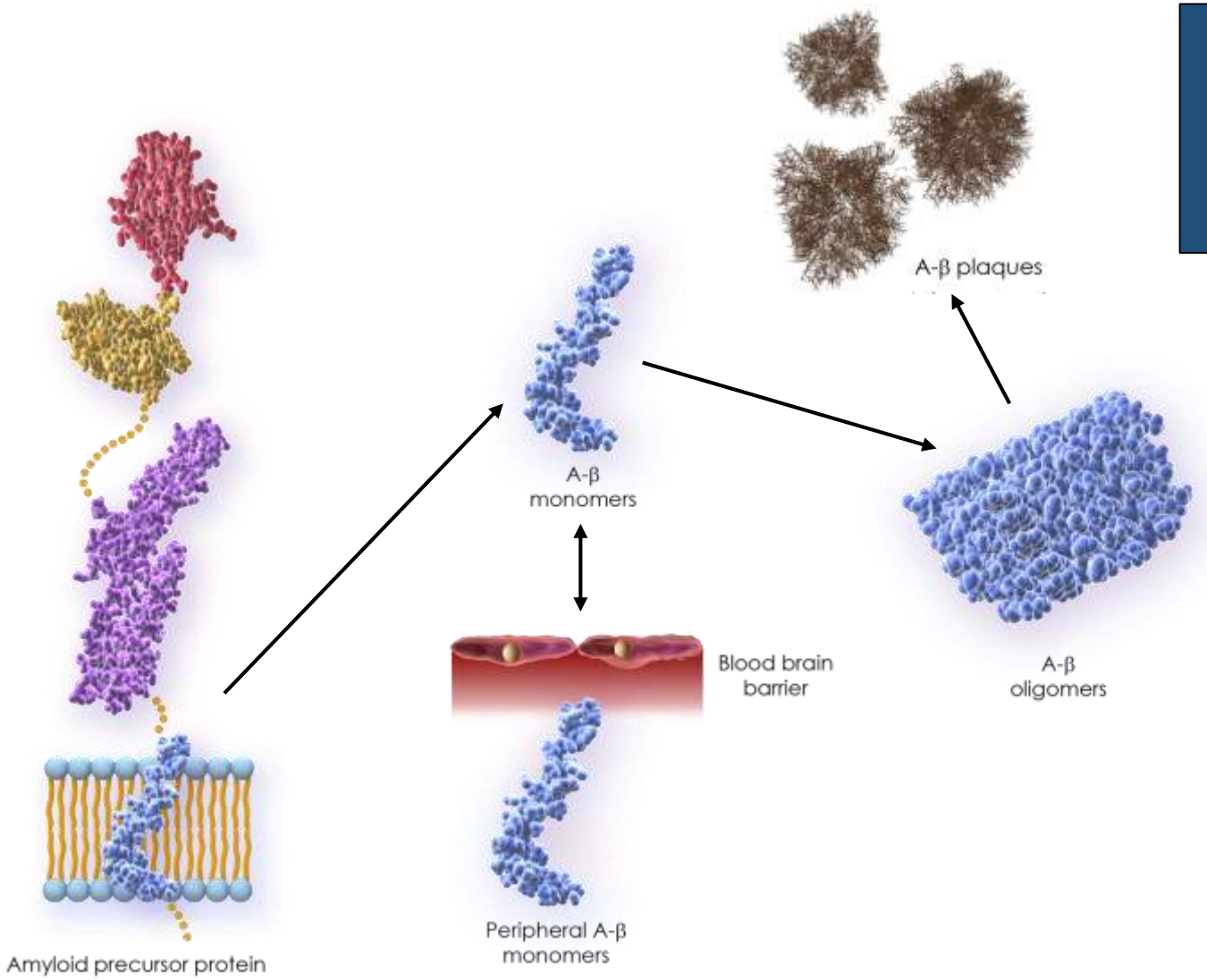
Tau-Directed Therapeutics are Advancing



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

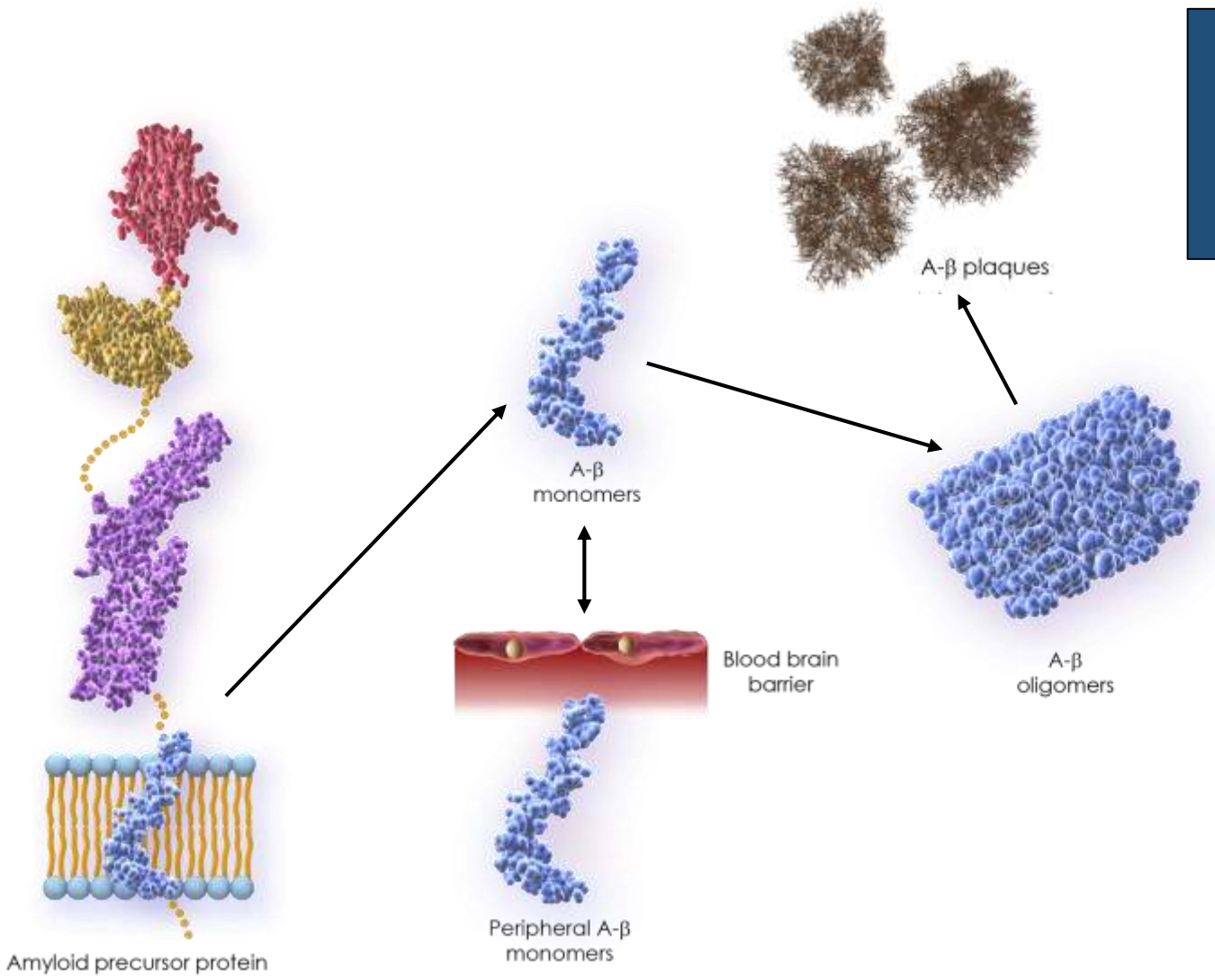
Li C, Gotz J. Nat Rev Drug Dev 2017; 16: 863-883

Amyloid Processing Provides Targets for Small Molecules



Amyloid (A$\mathcal{B}$) Target	Small Molecule
Enhance non-A$\mathcal{B}$ alpha-secretase pathway	APH-1105 MIB-626
Reduce APP by decreasing RNA transcription	Posiphen
Decrease pyroglutamate A$\mathcal{B}$ production	PQ912
Activates ABCC1 A$\mathcal{B}$ transporter	Thiethylperazine
Inhibits A$\mathcal{B}$ aggregation	Valitramiprosate (ALZ-801)

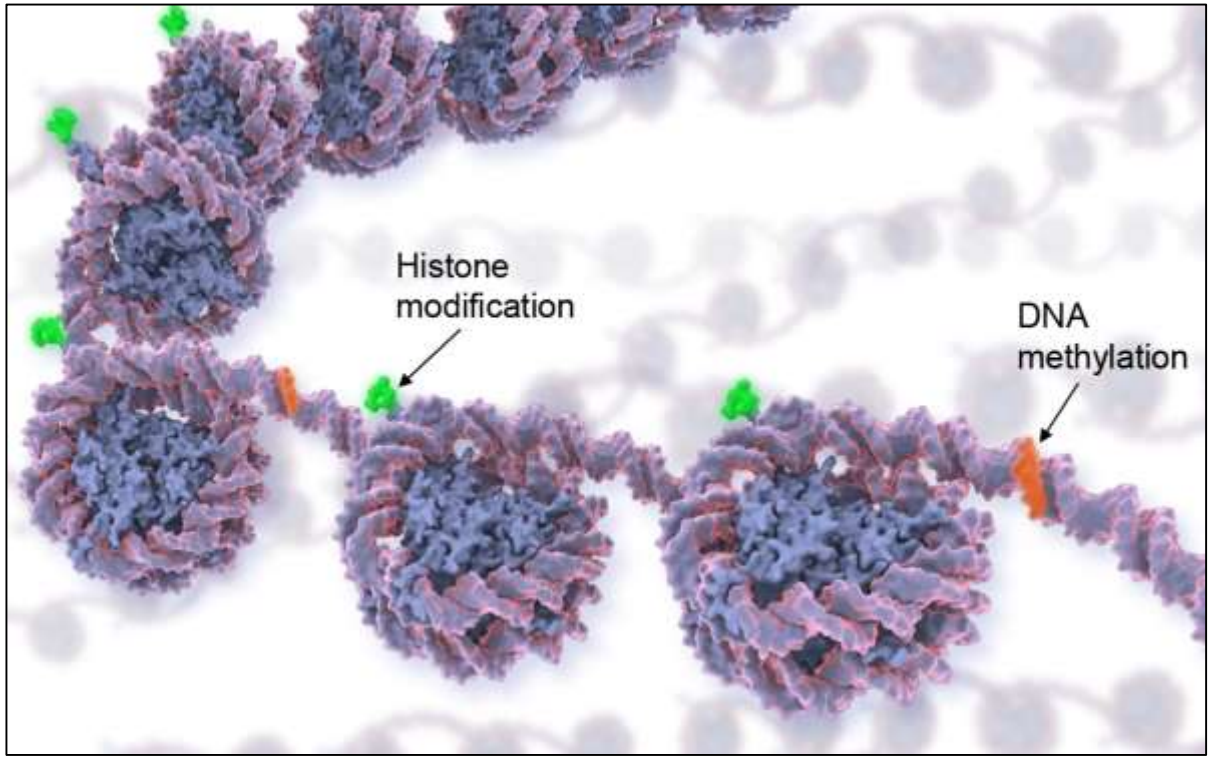
Amyloid Species are Important Targets for Anti-Amyloid Monoclonal Antibodies



Amyloid ($A\mathcal{B}$) Species	Monoclonal Antibody
$A\mathcal{B}$ plaques	Aducanumab Lecanemab Donanemab Gantenerumab
Pyroglutamate $A\mathcal{B}$	Donenamab
Protofibrillar $A\mathcal{B}$	Lecanamab
Oligomeric $A\mathcal{B}$	Aducanumab Gantenerumab Crenezumab
Monomeric $A\mathcal{B}$	Solanezumab Crenezumab
Peripheral $A\mathcal{B}$ monomer	Solanezumab

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

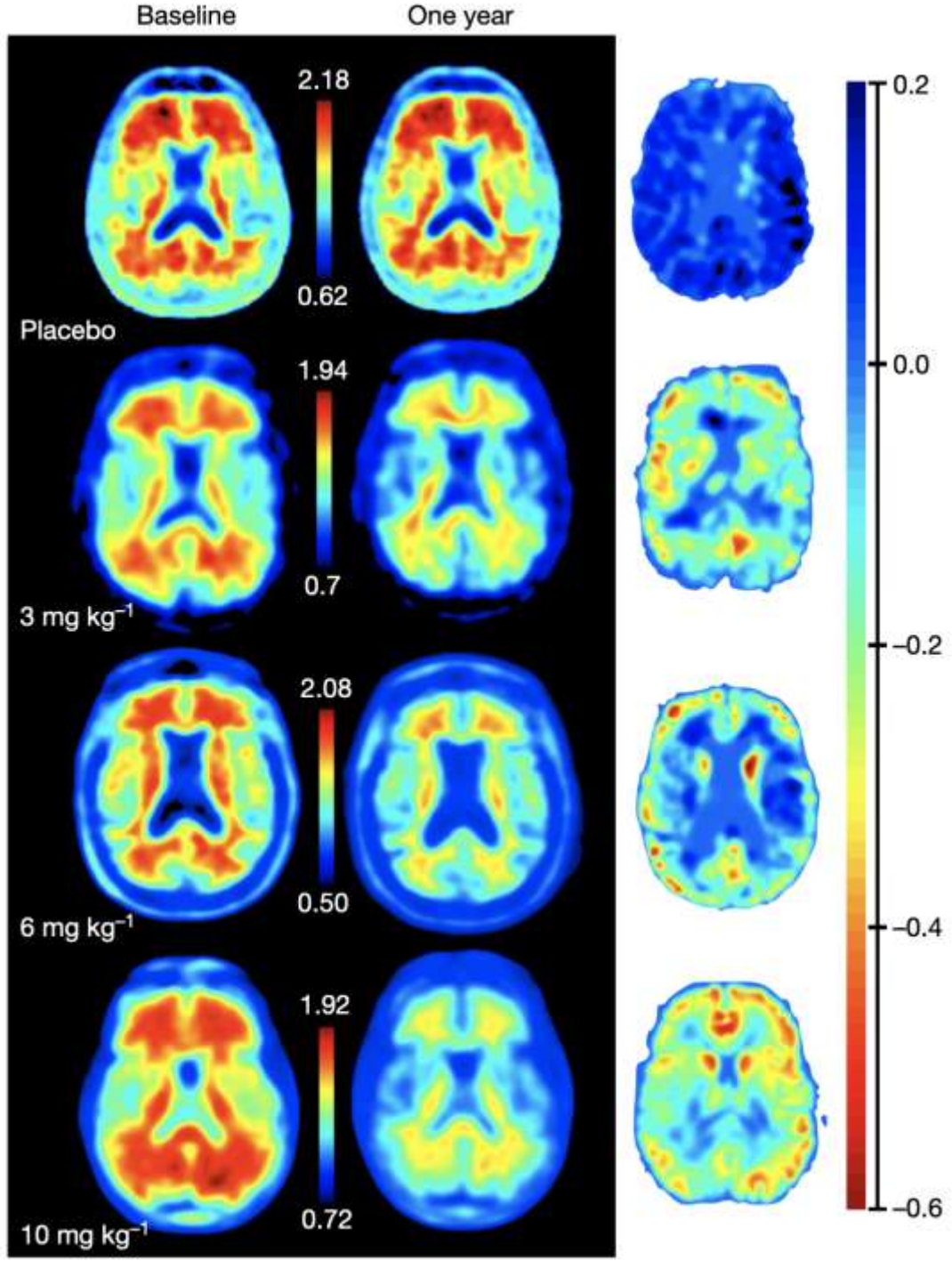
MSC– mesenchymal stem cells

Audience 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

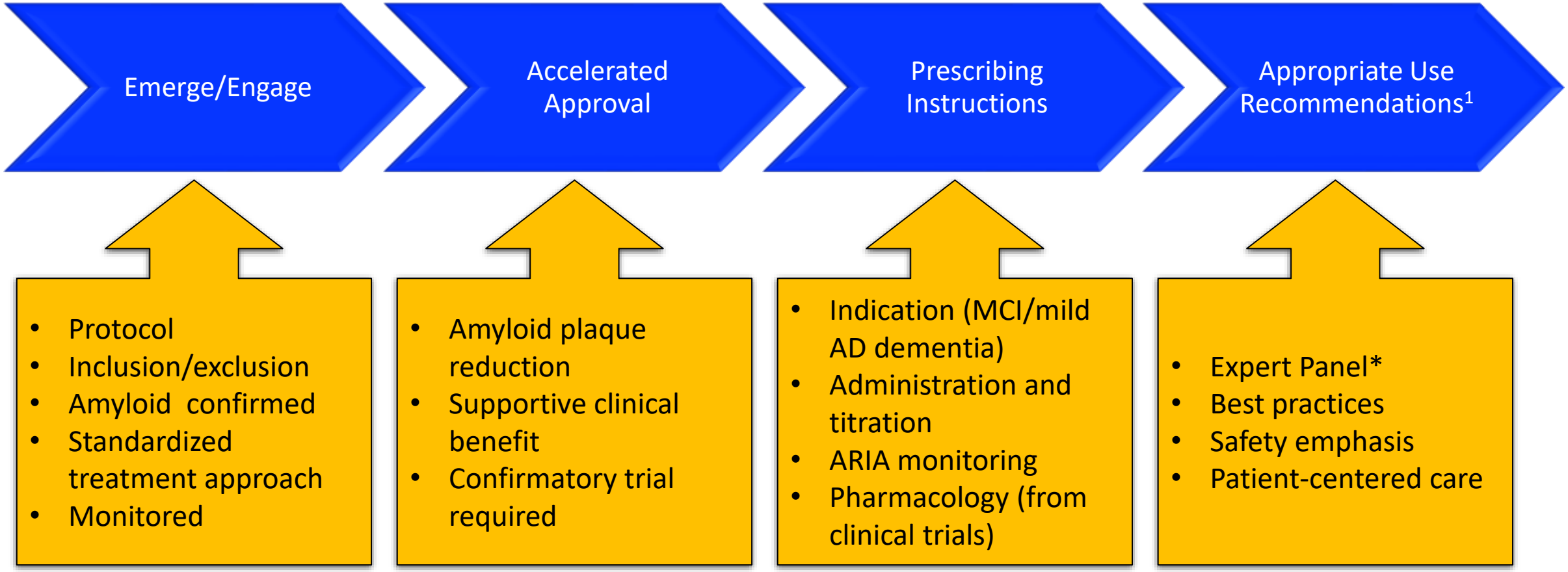
Aducanumab (Aduhelm)

- 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



[1]Sevigny J, et al. Nature 2016; 537: 50-56; [2]Cummings J, Aisen P, Apostolova L, Atri A, Salloway S, Weiner M. JPAD 2021; 4: 398-410

ADUHELM: Appropriate Use Recommendations



[1]Cummings J, Aisen P, Apostolova L, Atri A, Salloway S, Weiner M. JPAD 2021; 4: 398-410; *Alzheimer's Disease and Related Disorders Therapeutics Working Group (ADRD TWG)

Aducanumab Appropriate Use Recommendations[1] and AUR Update: Appropriate Patient

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

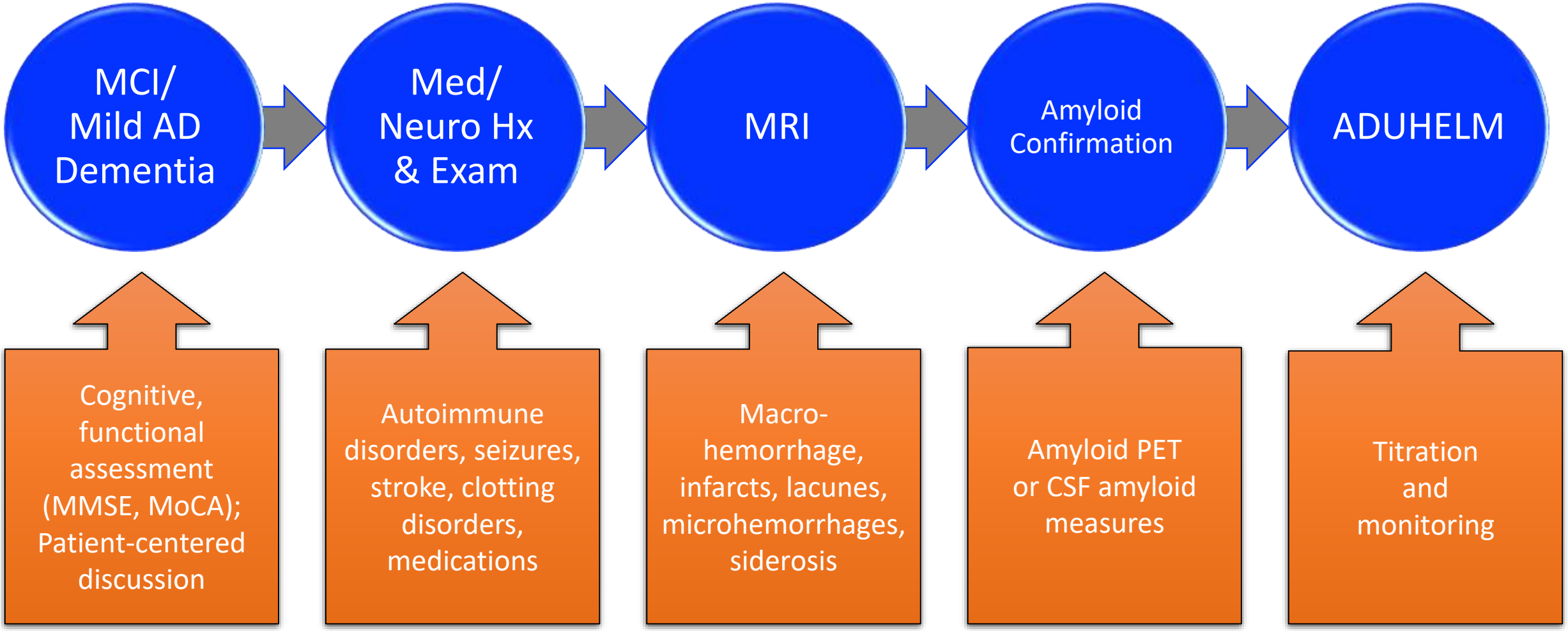
- Exclude history of immune disorders or seizures
- Exclude patients with extensive white matter changes
- APOE genotyping recommended[2]
  - Noncarriers –20.3% had ARIA
  - Heterozygotes – 43% had ARIA
  - Homozygotes – 66% had ARIA

[1]Cummings J, Aisen P, Apostolova L, Atri A, Salloway S, Weiner M. JPAD 2021; 4: 398-410; [2]Salloway S, et al. JAMA Neurol 2022; 79: 13-21

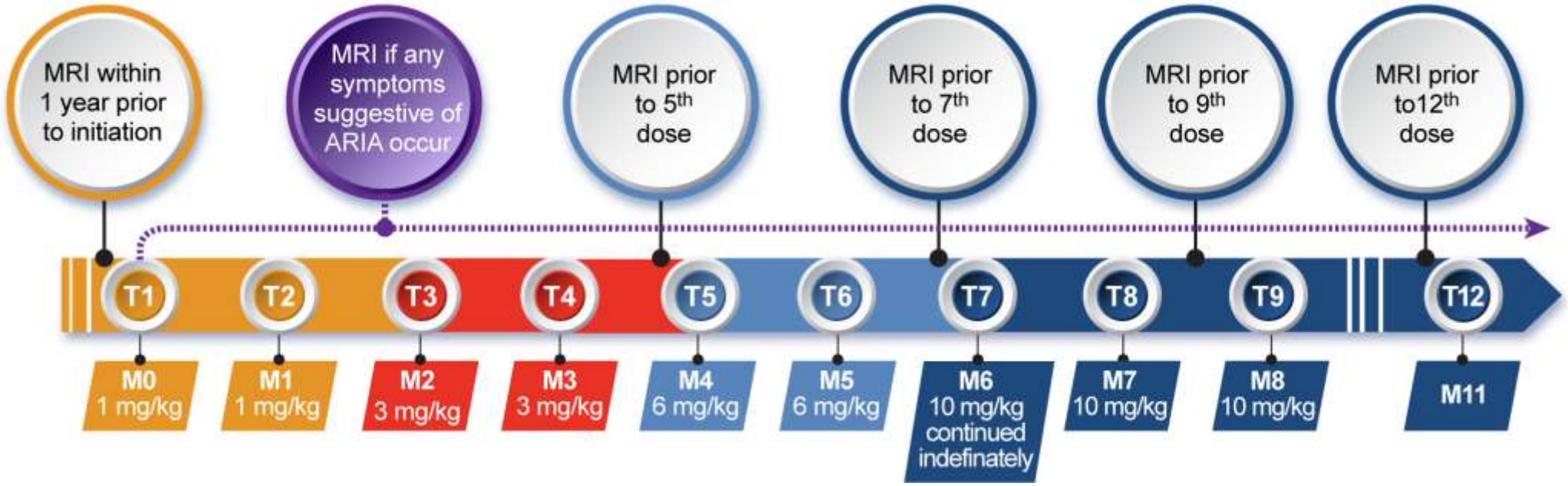
Aducanumab Appropriate Use Recommendations and AUR Update: Appropriate Patient

- 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

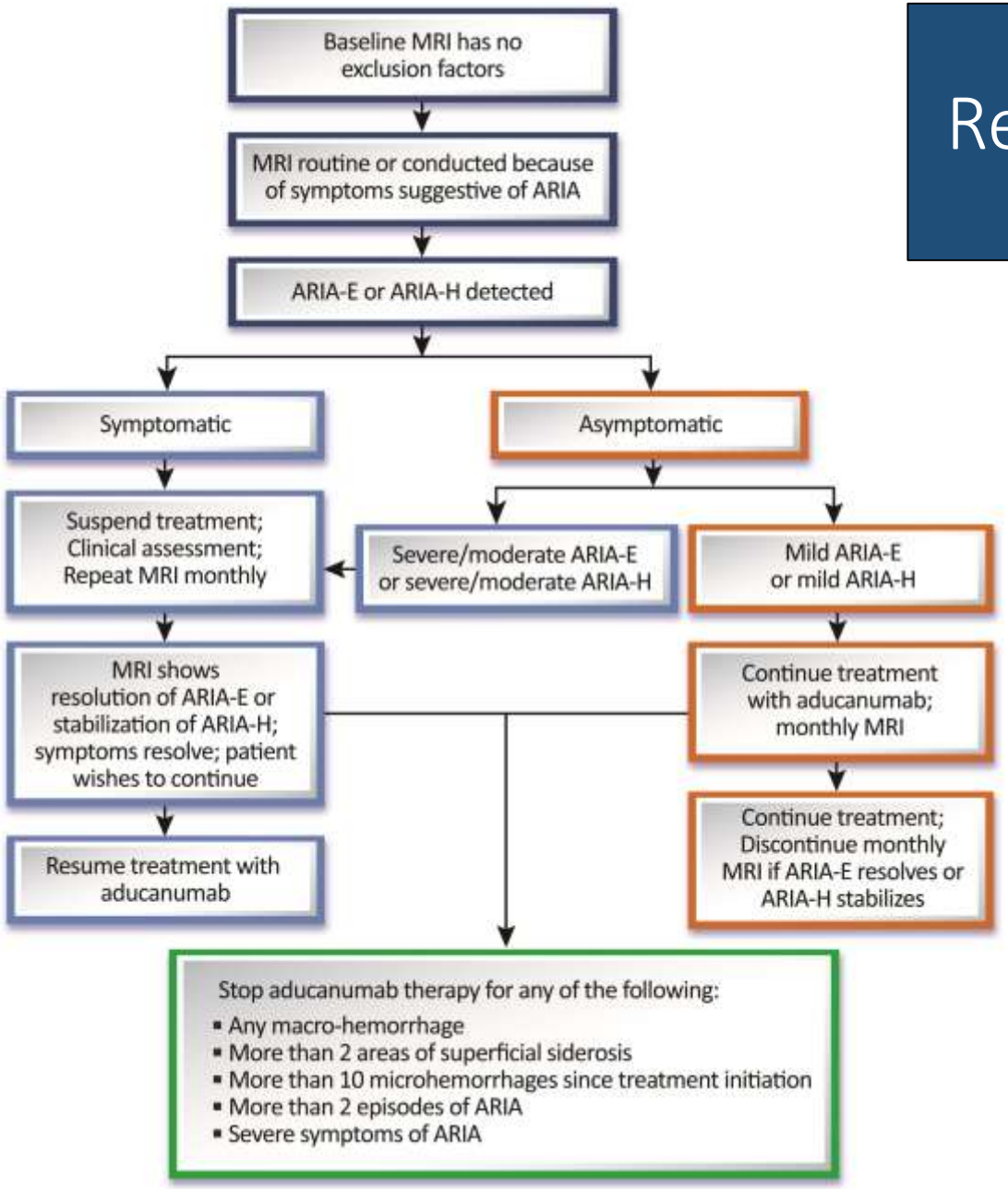


Aducanumab Appropriate Use Recommendations and AUR Update: Appropriate ARIA Monitoring



- 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

Mechanism overlap; artificially separated (e.g, inflammation, oxidation, reactive oxygen species)

Combination approaches are uncommon (limited to vascular targets)

Amyloid and tau are common targets but these they comprise a minority of the pipeline agent mechanisms

Biomarkers are enormously helpful; more are needed

Most drugs in the pipeline are DMTs; few cognitive enhancers or treatments for neuropsychiatric symptoms

Aducanumab is the first approved DMT for AD; other anti-amyloid monoclonal antibodies are promising

Chambers-Grundy Center for Transformative Neuroscience

- Department of Brain Health
  - Jefferson Kinney
  - Samantha John
  - Kate Zhong
- Clinical Trial Observatory
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  - Jorge Fonseca
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Alzheimer's Drug Discovery Foundation

NIH

Thank you