ALZHEIMER’S DISEASE
THERAPEUTIC RESEARCH IN 2019

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PS 1, PS 2, AND APP MUTATIONS
DOWN SYNDROME (TRISOMY 21)

β-SECRETASE
γ-SECRETASE

OXIDATIVE STRESS; INFLAMMATION
DIRECT TOXICITY; EXCITOTOXICITY

SYNAPTIC FAILURE;
NEURON DEATH

PLAQUE BUILDUP
OLIGOMERS

APP MUTATIONS

PS 1, PS 2 MUTATIONS

BETA-AMYLOID

BETA-SECRETASE
GAMMA-SECRETASE COMPLEX

NEURONAL SIGNAL
MICROTUBULE
AD Continuum

Cognitive performance, FDG-PET, tau PET, atrophy

Magnitude of change

Clinical stage of disease

NORMAL

COGNITIVELY NORMAL

MCI

DEMENTIA

Clinical function

$\alpha \beta$
Remove amyloid for a cure?

Ongoing studies in pre-symptomatic Alzheimer’s: A4, A3, A45

Negative trials in symptomatic AD
2019: the year in AD therapeutic research

- Aducanumab failure
  - Need earlier intervention
- BACE inhibitor cognitive toxicity
  - Dose-related, reversible
  - Path forward requires careful dose selection, cognitive monitoring and early intervention
- Other targets
  - Microglia, tau, many others
- Blood tests for AD
  - Plasma abeta ratio
  - NFL