Alzheimer's drug development pipeline: Promising therapies, pharma investment drive momentum in clinical trials

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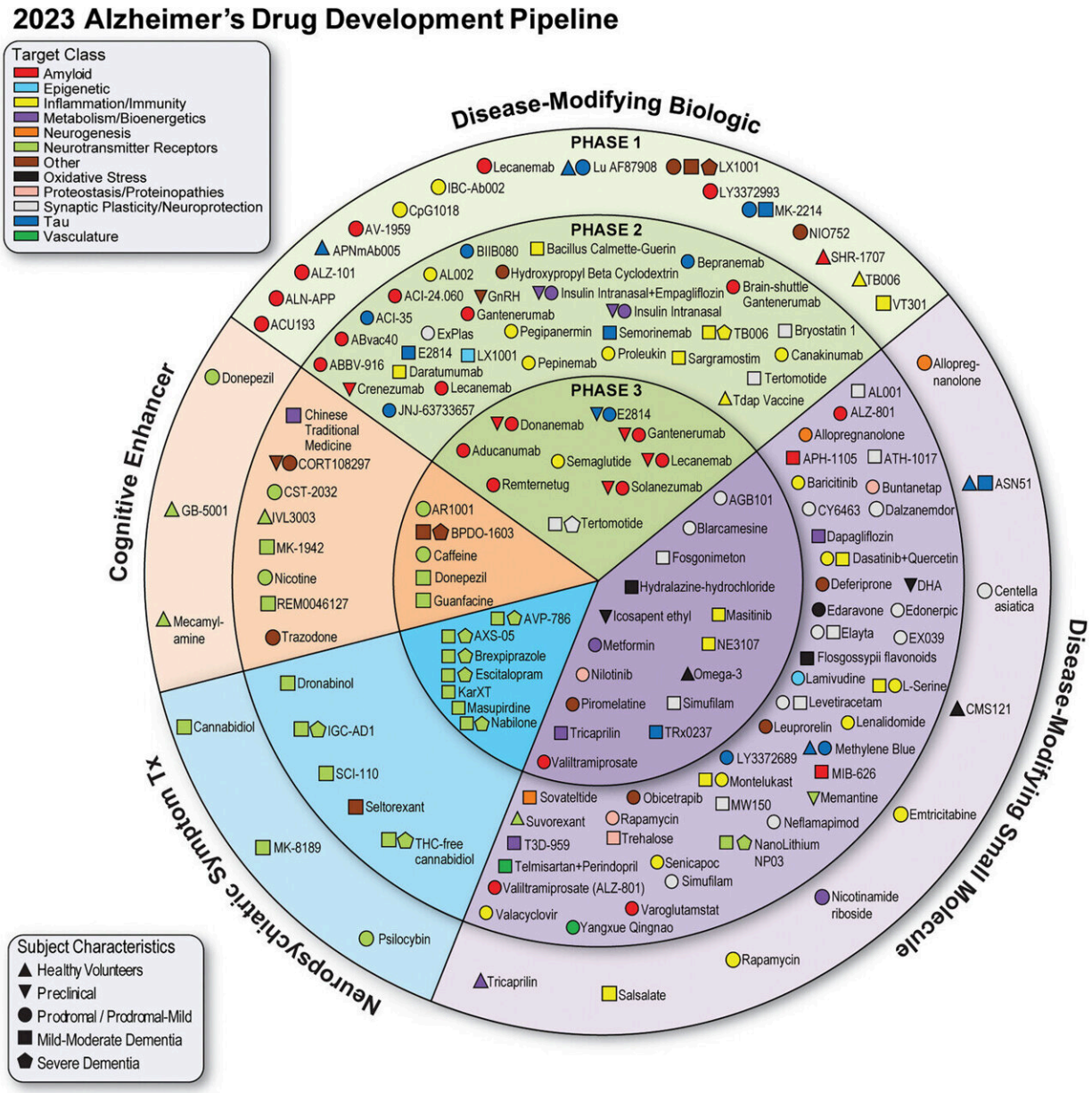

Agents in clinical trials for treatment of Alzheimer's disease in 2023 (from ClinicalTrials.gov as of the index date of January 1, 2023). The inner ring shows Phase 3 agents; the middle ring comprises Phase 2 agents; the outer ring presents Phase 1 therapies; agents in green areas are biologics; agents in purple are disease-modifying small molecules; agents in orange areas are symptomatic agents addressing cognitive enhancement or behavioral and neuropsychiatric symptoms; the shape of the icon shows the population of the trial; the icon color shows the CADRO-based class of the agent ("Other" category includes CADRO classes that have three or fewer agents in trials). CADRO, Common Alzheimer's Disease Research Ontology; Tx, treatment. Credit: J Cummings; M de la Flor, PhD, Illustrator

More than 6 million Americans are living with Alzheimer's disease, a staggering number that's expected to double within the next 30 years.

But there are signs of optimism in the fight against Alzheimer's, with two new therapies approved by the FDA since 2021. Both drugs—Aduhelm (aducanumab) in 2021 and Leqembi (lecanemab) earlier this year—were approved to treat early-stage symptoms of the disease. They're the first-ever disease-modifying therapies (DMTs) to earn the green light for use against Alzheimer's, and they signal a new era of hope for millions who've been affected by the disease.

There could be more on the way.

According to the "Alzheimer's Disease Drug Development Pipeline: 2023," there are currently 187 clinical trials in the Alzheimer's drug development pipeline—the most ever on record. This momentum is driven in part by greater investment from the pharma industry and a bump in biologic therapies—particularly monoclonal antibodies—that

were central to the success of both recent FDA-approved drugs.

The annual pipeline report, published May 25 in *Alzheimer's & Dementia: Translational Research and Clinical Interventions*, is led by Dr. Jeffrey Cummings, a leading Alzheimer's clinician-scientist and research professor in UNLV's School of Integrated Health Sciences. The goal of the annual report, Dr. Cummings says, is to spot trends in clinical trial design and outcome measures, and also investigate the types of agents and biological targets that are being pursued.

"Our database has gotten stronger and our ability to draw analysis from the pipeline is ever better," said Cummings, who first began the annual pipeline project in 2016. "We can derive lessons from both positive and negative trials that will inform and accelerate the development or new treatments."

Pipeline highlights

Researchers pulled data from all current phase 1, 2, and 3 clinical drug trials for Alzheimer's Disease and Mild Cognitive Impairment, as of Jan. 1, 2023. The team tracked all therapies in the pipeline, the types of agents used, and how far along each is in the drug development process. They also analyzed the agencies and industries funding clinical trials, and assessed the number of participants in current trials. Among the highlights:

- 187 current trials, which consist of 141 unique treatments—just off last year's record of 143 unique treatments
- 58 new drugs have entered the pipeline in the past year
- DMTs are the most common agents used in trials: 111 agents, or 79%, of the total number of drugs in the pipeline
- 28% of candidate therapies are repurposed from other diseases
- 57,465 participants are needed for all currently active trials

"We are at an inflection point in the Alzheimer's field. The recent landmark FDA approvals we've seen for both disease-modifying and symptomatic treatments, as well as the diversification of the pipeline of potential new Alzheimer's therapies, provide hope to those impacted by this devastating disease," said Maria C. Carrillo, Ph.D., Alzheimer's Association chief science officer. "Yet, Medicare stubbornly continues to block access for people who could benefit."

Biologics gaining momentum

Cummings notes that the use of biologic therapies—particularly monoclonal antibodies—has become increasingly popular. Among DMTs, related trials have risen more than 10% over the past year (44% of drugs in the pipeline). These therapies are mainly given by IV infusion, as opposed to small molecule therapies (56% of DMTs in the pipeline) that can be taken orally.

"The recent approval of two anti-amyloid monoclonal antibodies specifically for Alzheimer's is certainly influencing the pipeline, but these are complex therapies," Cummings said. "We're in a steep learning period for how we incorporate these advances into care. They require intense resources and regular MRI scans during the initial phase, which can lead to unprecedented demands on health care systems."

In addition to the growth of biological therapies aimed at amyloid and tau—two hallmark signs of Alzheimer's disease in the brain—Cummings anticipates more investment in small molecules aimed at amyloid. The use of biomarkers has also become more prevalent in clinical trials, particularly in DMT trials, and their foundational role in drug development has been shown to increase probability of success throughout the pipeline.

Pharma investment growing

After a recent decline, the pharma industry has also started to become more of a player in clinical trials. Of all the trials in development, 108 (58%) are industry sponsored, up nearly 8% over the past year. Public-private partnerships accounted for 9% of trials, and 32% were funded by academic medical centers—a group that includes the NIH, universities, advocacy groups, and related organizations.

"We see many more phase 1 biologics than agents in any other therapeutic class, which again reflects an increased enthusiasm of pharma for biological agents such as monoclonal antibodies," said Cummings. "Overall, the recession has impacted biotech investment, but I expect to see the Alzheimer's investment arena rebound with the economy, which will drive investment compared to previous years when the capital becomes available."

Recruitment struggles slowing progress

Recruitment continues to be a challenge for phase 2 and 3 clinical trials, with the average recruitment time for various trials stretching more than 100 weeks, or as many as 200-plus weeks for certain trials. The timing for phase 1 trials is only slightly better.

Though Cummings expects a bump in interest following recent FDA-approved therapies and the related marketing that will follow, recruitment—both in the number and diversity of participants—remains an area that's delaying the pipeline and stalling therapies that could otherwise progress more quickly toward approval.

"We need to find a way to expand trial populations, as this remains a major challenge when surveying the pipeline," Cummings said. "These

drugs are expensive, and access will be limited if there is not Medicare funding for them. The availability of approved and funded treatments may decrease interest in participating in clinical trials."

Study authors include Cummings, Kate Zhong, and Garam Lee from the UNLV Chambers-Grundy Center for Transformative Neuroscience and the UNLV Department of Brain Health; Yadi Zhou from the Cleveland Clinic; and Jorge Fonseca and Feixiong Cheng from Case Western Reserve University.

More information: Jeffrey Cummings et al, Alzheimer's disease drug development pipeline: 2023, *Alzheimer's & Dementia: Translational Research & Clinical Interventions* (2023). DOI: 10.1002/trc2.12385

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