The Role of Senescence in Alzheimer's Disease

A NEW FRONTIER IN THE SEARCH FOR A CURE

In the season finale cliffhanger of the television show *Grey's Anatomy*, the fictional character Dr. Meredith Grey proclaimed, "We have to question everything we know about Alzheimer's if we're going to cure it." Fiction often borrows issues from real life to spark interest in characters and storylines, so it's no wonder the screenwriters zeroed in on curing Alzheimer's disease (AD) as a timely topic.

"Dr." Grey may have been referring to the amyloid cascade hypothesis, which has been the central focus of AD therapeutic research for more than two decades.

THE AMYLOID HYPOTHESIS POSITS THAT ACCUMULATING AMYLOID BETA PROTEIN IN THE BRAIN TRIGGERS A CASCADE OF EVENTS THAT KILLS NEURONS, LEADING TO MEMORY LOSS AND DEMENTIA.

Those events include the development of abnormal tau proteins that build into threads and eventually form tangles inside neurons.

After many years of research into amyloid as a target, the first two treatments that remove amyloid beta from the brain, called anti-amyloid antibodies, were approved by the U.S. Food and Drug Administration (FDA). (See sidebar on page 44 for more details.)

In general, these drugs known as aducanumab (Aduhelm®) and lecanemab (Leqembi®) demonstrated a 30% reduction in the rate of cognitive decline in people with early-stage AD in clinical trials. While confirming amyloid plays a role in AD, these modest results indicate a large portion of the AD puzzle remains unsolved.

Since aging is the most significant risk factor for developing AD, researchers are investigating biological processes associated with aging as potential new treatment targets for altering AD progression.

The process in which cells stop dividing and do not die, called senescence, has emerged as a hot frontier of inquiry. →

Mind Over Matter® spoke with two researchers at the cutting edge of research into senescence in AD. Both agree that rather than representing an alternative to the amyloid hypothesis, senescence may be a central character in the cascade of events that occurs as AD develops and progresses.

Their translational work in the lab, insights from the first human clinical trials of a drug therapy for clearing senescent cells in patients with early signs of AD, and a new concept for a smart drug delivery system for combination therapies may lead to more effective ways to halt AD progression or prevent AD from developing in the future.

SENESCENCE: A PIVOTAL CHARACTER

Originally discovered by scientists in 1961, cellular senescence is not all bad: it's beneficial during normal early development, for maintaining tissues and repairing wounds, and limiting tumour progression. However, as we age, senescent cells can build up in various body tissues, including the brain.

Some people call senescent cells "zombie cells" because they remain partially active and can release harmful substances that damage nearby cells or even turn them into senescent cells, too.

Scientists have found senescent neurons, astrocytes, microglia, and endothelial cells in postmortem brain tissue of patients with AD and in animal models of the disease.

Dr. Julie Andersen, a scientist and professor at the Buck Institute for Research on Aging in Novato, California, studies the age-related processes driving neurodegenerative diseases, including AD and Parkinson's. She and the members of her lab use 3D human central nervous system cell cultures they developed to investigate the role of senescent cells and the toxic substances they secrete.

Dr. Chaska Walton, a research scientist working in Dr. Andersen's lab, spearheaded a review paper the group published in *Frontiers in Cellular Neuroscience* in 2020. They hypothesized that while some scientists have proposed senescence as an alternative treatment target for addressing AD, it may instead constitute an essential component of the cascade of brain damage that occurs as amyloid proteins accumulate.

"The accumulation of amyloid beta can also induce senescence. Once senescence is present, the damage may reach a point where senescence becomes the main problem, more so than the accumulation of amyloid," said Dr. Andersen. "At that point, removing amyloid plaques with anti-amyloid immunotherapies may have little impact."

Your brain has its own immune system, kept separate from the rest of your body by the blood–brain barrier.

"We know that senescent microglia, a type of immune cell resident in the brain, contribute to the development of Alzheimer's and that senescence initially spreads in the brain without being removed effectively due to the blood-brain barrier," explained Dr. Andersen.

"As the blood-brain barrier becomes increasingly leaky with aging and a fair number of senescent cells have accumulated in the brain, immune cells from the body can enter the brain, causing even more neuroinflammation and damage."

THE RATIONALE FOR SENOLYTIC THERAPY

Dr. Miranda Orr and her lab at the Sam and Ann Barshop Institute for Longevity and Aging Studies at the University of Texas Health Science Center at San Antonio, Texas, were the first to demonstrate that drugs called senolytics selectively destroyed and cleared senescent cells without harming healthy cells in AD mouse models.

They used dasatinib, an approved drug for treating chronic myeloid leukemia and acute lymphoblastic leukemia, together with quercetin, a plant-based flavonoid with anti-inflammatory and antioxidant properties.

Their groundbreaking findings, published in the journal *Aging Cell* in 2018, showed that these senolytics effectively removed senescent cells and improved brain structure and function in rodent models at risk of developing AD and with advanced tau tangles, a hallmark of AD.

"Another lab validated our findings in the same year, and then a third group found similar findings in a different AD mouse model," said Dr. Orr. "We've been very excited about our progress, moving quickly from preclinical findings in mice to human clinical trials."

THE FIRST CLINICAL TRIAL OF SENOLYTICS FOR AD

Now an associate professor of gerontology and geriatric medicine and scientist at the Wake Forest University School of Medicine in Winston-Salem, N.C., Dr. Orr is a primary investigator

of the first clinical trial of dasatinib plus quercetin for people with early-stage symptoms of AD.

The study is called the Senolytic Therapy to Modulate the Progression of Alzheimer's Disease (SToMP-AD) trial and it is supported by funding from the Alzheimer's Drug Discovery Foundation.

In the phase 1 part of the study, five patients with early AD symptoms received oral dasatinib plus quercetin over two consecutive days, followed by two weeks of no drugs, and then repeated this pattern for six more cycles.

Investigators collected cerebrospinal fluid (CSF) and blood samples to see whether the medicines penetrated the central nervous system. They also looked for biomarkers of senescence in CSF and evaluated patients' cognition and brain images before treatment and after 12 weeks.

THE RESULTS SHOWED THAT THE SENOLYTIC THERAPY WAS SAFE, FEASIBLE, AND WELL TOLERATED BY PATIENTS.

Dr. Orr and colleagues found evidence of dasatinib in CSF but did not detect quercetin. "We expected to find quercetin in CSF. We're not sure if that was because we looked at the wrong time or because it has a lower bioavailability than we thought," said Dr. Orr. "We may conduct a phase 1b trial of dasatinib with different doses of quercetin to answer the question in the future."

The CSF analyses showed some promising signs of activity. The investigators noted a trend toward higher levels of amyloid beta-42, a main component of amyloid plaques and a positive indication that the senolytic therapy was clearing some amyloid.

They also observed lowered levels of several toxic substances associated with senescence, called cytokines and chemokines. However, levels of biomarkers called interleukin-6 (IL-6) and glial fibrillary acidic protein (GFAP) rose after treatment, indicating a trend toward increased inflammation.

"More research is needed to determine whether increases in these biomarkers indicated a brief inflammatory response to the treatment or merely the presence of debris from cleared senescent cells that produce those markers," Dr. Orr said.

Keep in mind that these CSF results provided directional learning only. It's not possible to say the medications caused these effects given the small number of patients, and as an open-label study, there was no placebo group for comparison. Cognitive performance and brain imaging results did not change much over the short 12-week time frame. The paper was published in *Nature Medicine* in September 2023.

Now, phase 2 of the SToMP-AD trial is recruiting patients, with results anticipated in late 2025.

The study is offered at Wake Forest Health University Sciences, the University of Texas Health Science Center at San Antonio, and will soon expand to additional sites in Europe. Patients with early-stage AD will receive either oral dasatinib plus quercetin or a placebo and undergo blood and cognitive testing over one year.

Dr. Orr and colleagues will evaluate the safety and efficacy of the treatment, as well as changes in cognitive impairment, including memory, orientation, judgement, problem-solving, and daily life activities. They will also assess tau levels in the brain using positron emission tomography (PET).

"At the end of trial, patients can opt in to have a lumbar puncture, and several have volunteered," said Dr. Orr. "CSF analysis will hopefully shed light on whether the rise in inflammation we saw previously is transient, falls over time, or is something we need to be concerned about."

COMING SOON: TREATING MULTIPLE TARGETS

In the meantime, Dr. Orr said there is a need to design new studies that research a combination of amyloid-lowering antibodies and senolytics since an accumulation of amyloid plaques and senescent cells are both involved in AD processes. "As amyloid-lowering drugs are now approved, we will likely have patients who are being treated with them who also want to enroll in our senolytic study," she said.

Dr. Andersen agreed a combination strategy is where the science is going next. "Ideally, anti-amyloid immunotherapies and senolytics would both be administered in early-stage AD for the best outcomes before the cascade of damage goes too far," she said. "Senescent neurons are still somewhat metabolically active, so removing too many of them at later disease stages with senolytics may prove fatal since damaged neurons can't regenerate." ⟶

ANTI-AMYLOID ANTIBODIES

The U.S. Food and Drug Administration (FDA) recently approved the first two disease-modifying therapies for AD. The anti-amyloid antibodies aducanumab (Aduhelm®) and lecanemab (Leqembi®) were approved for patients with mild cognitive impairment or mild dementia due to AD with increased levels of amyloid in the brain as confirmed by positron emission tomography (PET) scan or cerebrospinal fluid.

Administered by intravenous infusion, these medications slow cognitive decline associated with AD by reducing amyloid plaques. However, they are associated with a risk of swelling and microbleeds in the brain.

In an opinion article published in the journal *Drugs* in May 2023, Dr. Jeffrey Cummings, Director of the Chambers-Grundy Center for Transformative Neuroscience at the University of Nevada, Las Vegas, wrote that these drugs are transformative and support the amyloid hypothesis and amyloid as a treatment target. He also noted that it will be challenging for patients and care partners to decide whether a 30% reduction in disease progression is worth accepting the inconvenience and potential harm associated with these new therapies.

FAST FACTS ON ANTI-AMYLOID ANTIBODY APPROVALS*

Aducanumab (Aduhelm®):

- FDA granted accelerated approval in June 2021 with a view to meeting a significant unmet need;
- the approval was controversial: one of two phase 3 clinical trials showed a statistically significant reduction in cognitive decline compared to placebo, while the other study was inconclusive; and
- Health Canada and the European Medicines Agency (EMA) did not approve the drug.

Lecanemab (Leqembi®):

- FDA granted accelerated approval in January 2023 and traditional approval in July 2023;
- the approval was based on phase 3 clinical trial results that showed a reduction in amyloid plaques and slowed disease progression compared to placebo; and
- Health Canada and the EMA accepted the manufacturer's application for approval with decisions pending.

Donanemab:

- in the phase 3 study, many patients were able to stop treatment earlier than anticipated after reaching a predefined level of amyloid plaque clearance;
- phase 3 trial results reported in July 2023 showed the drug significantly slowed disease progression at 76 weeks in patients with early AD symptoms and amyloid and tau pathology compared with the placebo group; and
- the manufacturer expects the FDA's decision on their application for full approval by the end of 2023.

*As of Aug. 8, 2023

It's expensive for drug companies to conduct combination clinical trials. To address this issue, Drs. Andersen and Walton are co-principal investigators working on designing a novel smart-cell drug delivery platform for delivering therapies directly to brain cells. Their cutting-edge project is funded by a High-Risk, High-Reward grant from the U.S. National Institutes of Health.

> **"THE IDEA IS THAT THE SMART DELIVERY SYSTEM WOULD GO DIRECTLY TO AFFECTED BRAIN CELLS, SENSE WHAT'S REQUIRED, RELEASE AN ANTI-AMYLOID ANTIBODY, A SENOLYTIC, OR AN ANTI-INFLAMMATORY DRUG AS NEEDED, AND THEN TURN OFF," SAID DR. ANDERSEN.**

They are looking at intravenous and intranasal formats and conducting tests in lab models of AD to screen the most promising candidates for later research in human clinical trials.

Much work is ahead as scientists continue to explore senescence as a promising target in Alzheimer's disease.

Time will tell if the new season of *Grey's Anatomy* pulls from actual scientific advances and reveals senescence as the new insight in their storyline about solving AD. In the meantime, real scientists are working hard on this promising new frontier of AD research to discover new therapeutic approaches that may prevent or slow AD progression in the future.