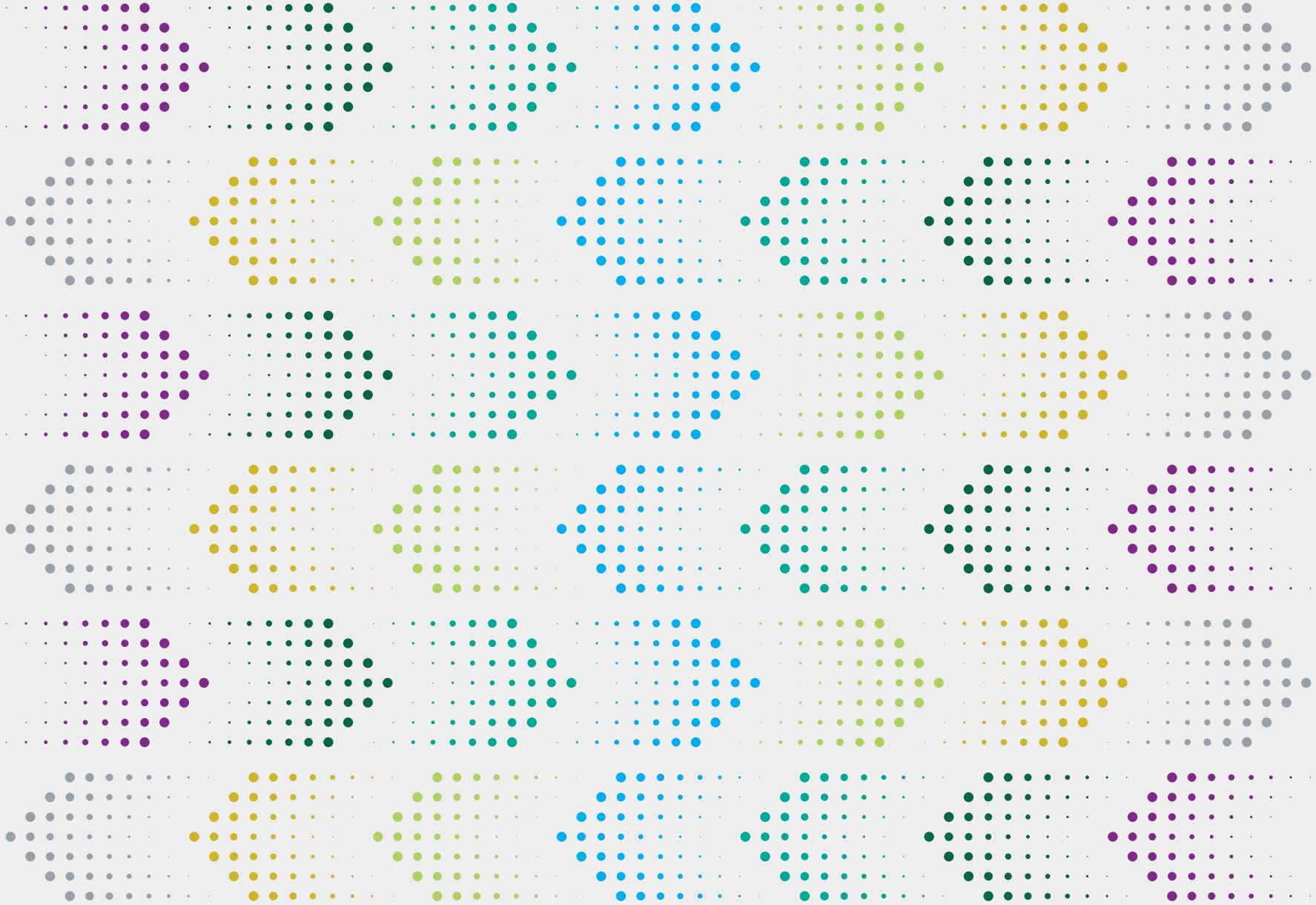
Alzheimer's
Drug Discovery
Foundation

2021 ALZHEIMER'S CLINICAL TRIALS REPORT



"Building on years of innovative, systematic and tireless research, today's Alzheimer's research pipeline holds more promise than ever."

DEAR FRIENDS,

More than 20 years ago, the Alzheimer's Drug Discovery Foundation began advocating the biology of aging theory, which maintains that many biological processes weaken with age and contribute to Alzheimer's disease. This approach is now a mainstream research focus that is reflected in the wide array of novel drug targets being evaluated today to not just treat Alzheimer's symptoms, but to modify its course—slowing and perhaps even halting its progression.

The majority of trials summarized in this new clinical trials report go well beyond the once traditional focus on toxic build-up of amyloid and tau proteins in the brain. They are testing drugs to reduce inflammation, improve blood flow, protect neurons, improve how the brain metabolizes energy, and more.

Today's trials also benefit from more rigorous trial design than ever before thanks in large part to the availability of new Alzheimer's biomarkers. Biomarkers are very important to medicine in general and are integral to drug development. We need, and are rapidly validating, new biomarkers that can measure the impact of each biology of aging target, and the drugs designed to treat them.

Over six million people in the United States and 55 million globally are living with Alzheimer's and related dementias, and that number is expected to grow substantially with an aging population. They are the reason the ADDF is so committed to its mission to find more effective ways to prevent and treat Alzheimer's disease.

As a neuroscientist and geriatrician involved in clinical research and patient care for over 40 years, it is also personally rewarding for me to see such a robust pipeline and know the ADDF has contributed greatly to it. We're on the cusp not only of individual treatments, but the exciting possibility of drug combinations that can provide personalized medicine.

I hope you share in my sense of excitement as we move into this modern era of Alzheimer's clinical trials with a pipeline primed to deliver results.

Sincerely,

HOWARD FILLIT, M.D.
Founding Executive Director and Chief Science Officer
Alzheimer's Drug Discovery Foundation

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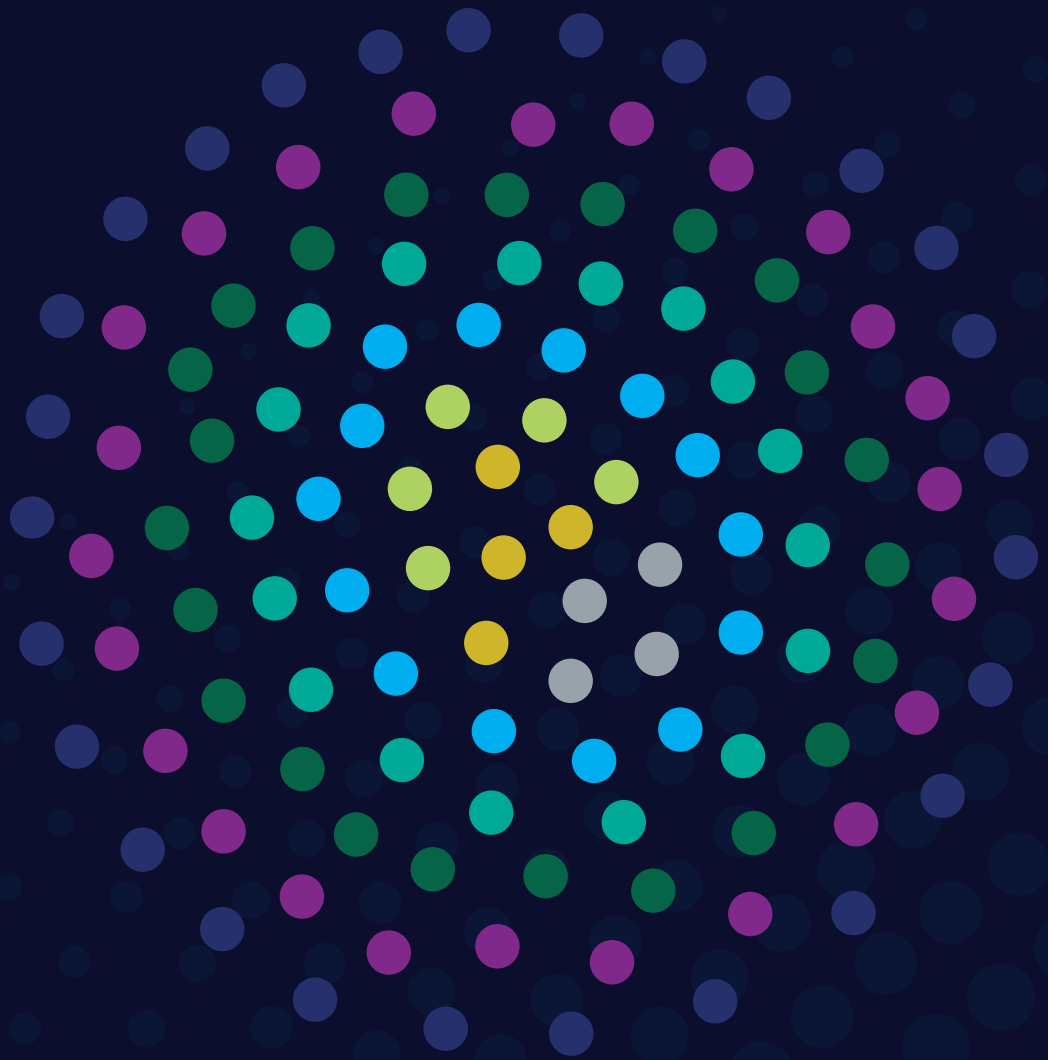


EXECUTIVE SUMMARY

It has long been understood that the number one risk factor for Alzheimer's disease is aging. But it has only been over the last few decades that researchers are digging deeper into the biology of aging to understand what happens in the aging brain that makes Alzheimer's the fifth leading cause of death for people 65 and older.

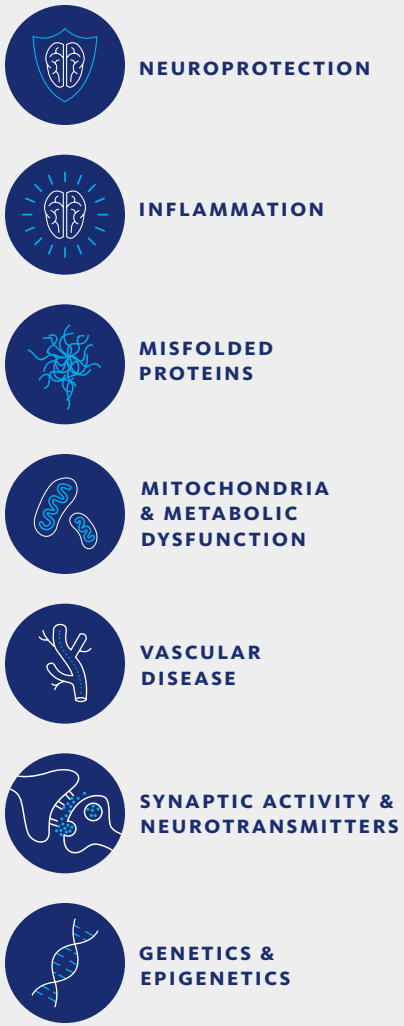
A deeper understanding of the underlying mechanisms that cause Alzheimer's, an approach the ADDF has long advocated, has led to a more robust and diverse pipeline of drugs and other treatments to target each of them.

In this report, the Alzheimer's Drug Discovery Foundation (ADDF) reviews the Alzheimer's research pipeline and reports on not just the wide range of targets in research, but also a growing list of therapy types. We also take a look at how the ADDF has contributed to this progress.

As of the date of the analysis for this report, the Alzheimer's research pipeline included 208 active Alzheimer's clinical trials, including 118 evaluating disease-modifying therapies. These trials, which are the focus of the first section of this report, are evaluating therapies that both treat Alzheimer's symptoms and address its underlying causes—aiming to stop, slow or even reverse the course of the disease.

Earlier Alzheimer's research was heavily focused on the role of two misfolded proteins, amyloid and tau, that make up the hallmark Alzheimer's plaques and tangles in the brain. While these and other misfolded proteins continue to have an important place in the research pipeline, the focus on the many other biology of aging targets is increasing quickly.

Diverse Targets in the Alzheimer's Research Portfolio



1 *in* 5

disease-modifying trials are testing drugs designed to protect the brain's neurons.

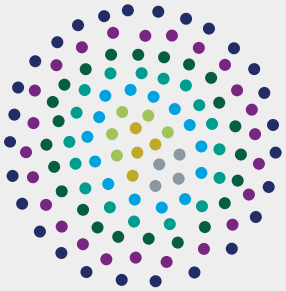
1 *in* 5

trials are studying drugs designed to improve the brain's synapses and the electrical systems that carry impulses across the brain.

The disease-modifying trials that are the focus of the first section of this report are complemented by the trials reviewed in section 2 assessing treatments that do not alter the course of the disease, but that address Alzheimer's symptoms like agitation, anxiety, depression and difficulty swallowing. Dozens of additional trials are looking at ways to prevent Alzheimer's with both drug and lifestyle interventions, like stress reduction and changes in diet and exercise.

The goal—which we are closer to than ever—is to find many effective treatments that doctors can combine to provide individualized treatment and care. This type of personalized medicine has driven recent advances in cancer care and the current research pipeline is poised to deliver the same for patients with Alzheimer's.

All of this adds up to an exciting landscape detailing an incredibly promising Alzheimer's research pipeline.



118 potential treatments for Alzheimer's disease are in clinical development

Each phase includes trials studying the full range of targets defined by the biology of aging

77% of disease-modifying trials across all phases have novel targets other than amyloid and tau approaches

1 in 7 trials are studying drugs to reduce chronic brain inflammation

1 in 8 trials are looking at ways to improve how brain cells use energy—a key factor in maintaining their health.

[1] This report includes active clinical trials identified through ClinicalTrials.gov as of April 8, 2021. See Our Methods (page 25) for details.

TERMS & DEFINITIONS

Path to Clinic

Novel drugs are newly developed by researchers. These drugs generate new intellectual property.

Repurposed drugs are already approved by the FDA for other diseases and are now being tested for Alzheimer's disease. Development costs and time are reduced because the drug's safety in humans is already established.

Repositioned drugs have entered clinical trials for other diseases, but are not yet approved by the FDA, and are now being tested for Alzheimer's.

Combination refers to a combination of more than one of the above.

Type of Therapy

Small Molecule drugs are manufactured chemical compounds. They are almost always taken orally as pills and can enter cells to engage with their biological target. Most drugs are small molecules.

Biologics are derived from living organisms and include treatments such as antibodies, hormones like insulin, vaccines and immunotherapies. Biologics are usually given by injection or infusion.

Cell Therapy introduces certain types of human cells (stem cells) into the body to replace or repair defects of damaged tissue.

Devices are non-pharmacologic (drug-free) medical instruments or machines to treat a disease.

Genetic Therapy is a technique that modifies a person's genes to treat or prevent disease, for example; replacing a mutated gene with a healthy one.

Natural Products refer to chemicals and supplements derived from natural sources, such as plant extracts, including vitamins, amino acids and other substances.

Type of Target

This is the primary biological process the drug is designed to target. The seven biological targets described below are all part of the "biology of aging"—biological changes that are more common with aging and that contribute to Alzheimer's.

Genetics & Epigenetics: Specific genetic traits, such as inheriting the APOE4 gene, can increase risk of Alzheimer's disease. Epigenetics are processes that regulate how active each gene is (i.e., the level of "gene expression"). Epigenetics can act like a volume control that can make genes quieter or louder, or as an "on/off switch."

Inflammation: Chronic (long-term) inflammation in the brain can accelerate Alzheimer's disease and may be a trigger for the disease. Most inflammation in the brain is regulated by special cells called microglia.

Misfolded Proteins: The three-dimensional folding of a protein is critical to its function. In Alzheimer's, proteins like amyloid, tau and others can misfold and become toxic. These misfolded proteins accumulate into plaques, tangles, and other forms in the brain if they are not cleared by the brain's self-repair mechanisms.

Mitochondria & Metabolic Function: All cells need energy to maintain healthy function, and neurons are among the highest energy users. As we age, mitochondria—the internal energy centers of our cells—can become impaired, as can the way our cells use external energy, such as glucose and oxygen (metabolism).

Neuroprotection: As Alzheimer's progresses, neurons in the brain lose their connections and begin to die, causing the loss of memory and other cognitive functions. Neuroprotective strategies protect brain cells from multiple causes of damage and death.

Synaptic Activity & Neurotransmitters: Synapses are the connections between neurons and are important for communication between these cells, creating circuits. Neurotransmitters carry signals across these connections. In Alzheimer's, synapses can become damaged and their ability to send or receive neurotransmitters and transmit messages is often impaired.

Vascular: Healthy blood flow is required for optimal brain function. Blood vessel damage can affect how misfolded proteins and toxins are removed from the brain and can limit the ability of neurons to get sufficient oxygen, glucose and vital nutrients.

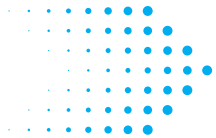
THE CLINICAL TRIALS PIPELINE

Clinical trials—the stage of development when drugs are evaluated in humans—are the final steps before a drug can be approved by the FDA and made available to the public. Each phase builds on the one before.

PHASE 1

Testing for Safety

This is generally the first time drugs are tested in a small number of normal and disease-affected people. Phase 1 follows rigorous laboratory and often animal studies. At this stage, the drug is evaluated for safety and possible side effects. Sometimes, biomarkers can be included at this phase to determine participants' reaction to the treatment's effects.



PHASE 2

Testing for Drug Effect

Drugs that succeed in phase 1 move to this "proof-of-concept" stage. Researchers continue to evaluate safety and evaluate a drug's efficacy in larger numbers of people. Phase 2 trials may also use biomarker tests to begin to evaluate target engagement, that is, to determine whether a drug interacts with its biological target (e.g., reducing inflammation or clearing misfolded proteins in the brain).

PHASE 3

Proof of Efficacy in Larger Trials

Drugs that succeed in phase 2 are then tested in large groups of patients over a longer time. These trials can include thousands of patients at multiple sites and last for many years. Alzheimer's phase 3 trials are more rigorous than ever and most measure both clinical outcomes such as changes in people's memory and cognitive functions, as well as biomarker outcomes such as neuroimaging, spinal fluid and blood tests. Once this phase is complete, a drug can be submitted for FDA approval.

CLINICAL TRIALS BY THE NUMBERS—DISEASE-MODIFYING DRUGS

Disease-modifying drugs not only aim to improve memory and other cognitive symptoms related to Alzheimer's disease, but to change its course. At one end of the spectrum is the "holy grail": curing Alzheimer's disease. But even slowing the disease's progression would have a substantial impact on improving the quality of life and extending the lifespan of people with Alzheimer's disease.

Treatment will likely rely on combination drug therapy that works against a range of targets to provide personalized medicine tailored to each person with Alzheimer's disease.

TYPE OF TARGET

- Misfolded Proteins / **27**
- Neuroprotection / **24**
- Synaptic Activity & Neurotransmitters / **23**
- Inflammation / **17**
- Mitochondria & Metabolic Function / **14**
- Genetics & Epigenetics / **5**
- Vascular / **4**
- Other / **4**

** Including Alzheimer's dementia and mild cognitive impairment*

PHASE 1

By Type of Target

Genetics & Epigenetics
- AAV-hTERT
- Emtricitabine
- LX1001*
- Vorinostat

Inflammation
- AL003
- Bacillus Calmette-Guerin (BCS)
- JNJ-40346527
- Salsalate
- Sirolimus
- XPro1595*

Misfolded Proteins
- BEY2153
- E2814
- Lu AF87908
- LY3372993
- Trehalose

Mitochondria & Metabolic Function
- Grape seed polyphenolic extract
- Nicotinamide riboside

Neuroprotection
- Allopregnanolone*
- Dasatinib + Quercetin*
- Efavirenz*
- Mesenchymal Stem Cells
- NNI-362
- REM0046127
- SNK01

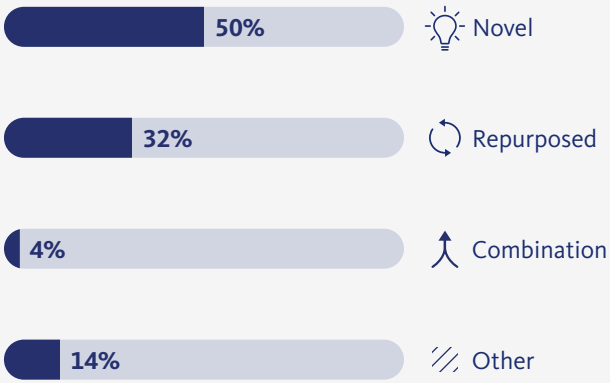
Vascular
- Dabigatran

Other
- MK-1942 + Donepezil
- MK-4334

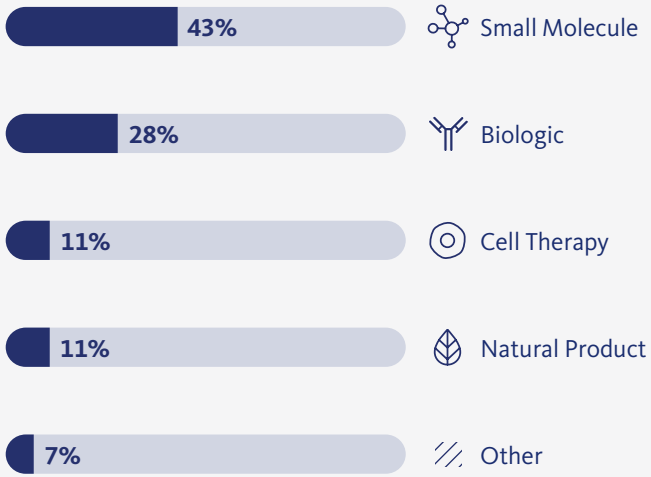
** Funded by the ADDF*

More than 4 in 5 drugs in phase 1 trials are focused on novel, diverse targets other than the traditional misfolded proteins such as amyloid and tau.

Path to Clinic



Type of Therapy



PHASE 2

By Type of Target

Genetics & Epigenetics
- 3TC

Inflammation
- AL002
- ALZT-OP1 (cromolyn and ibuprofen)
- Bacillus Calmette-Guerin (BCG)
- Daratumumab
- GV1001
- Lenalidomide*
- Montelukast
- Tacrolimus
- VX-745

Misfolded Proteins
- ABBV-8E12
- ABvac40
- ACI-35.030 + JACI-35.054
- ALZ-801
- APH-1105
- BIIB092
- IONIS MAPTRx
- JNJ-63733657
- LY3303560
- Meganatural-Az Grapeseed Extract
- NewGam 10% IVIG
- Nilotinib*
- Posiphen
- PQ912
- RO7126209
- Semorinemab
- TEP

Mitochondria & Metabolic Function
- Benfotiamine*
- Dapagliflozin
- L-Serine Gummy

** Funded by the ADDF*

More than 6 in 10 of the ADDF's current investments are in phase 2 research.

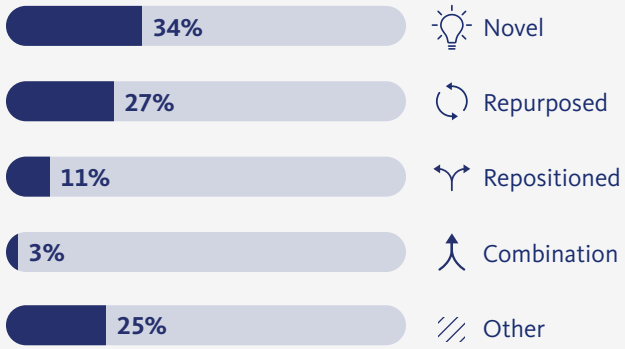
Liraglutide*
Metabolic Cofactor Supplementation
Nicotinamide
Pepinemab*
T3D-959

Neuroprotection
AMX0035*
AstroStem and Donepezil
CB-AC-02
CORT108297
HB-adMSCs
Human Mesenchymal Stem Cells
Leuprorelin
Mesenchymal Stem Cells
PTI-125
Rapamycin
Regulatory T cells
S-equol
Sovateltide
T-817MA
Valacyclovir

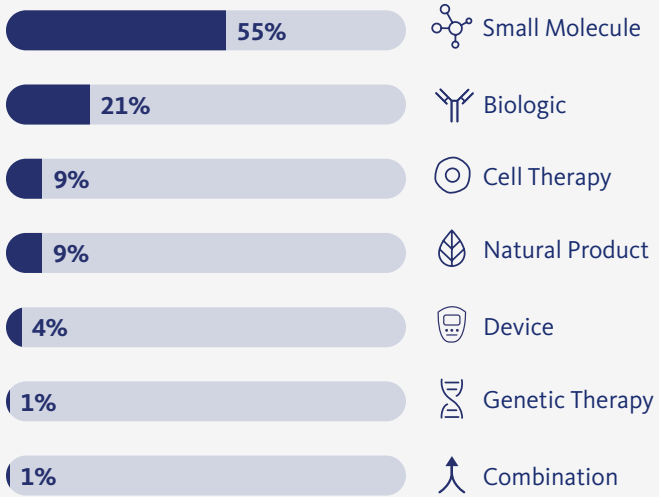
Synaptic Activity & Neurotransmitters
AD-35
AD-35 60mg
ATH-1017*
BPN14770*
Bromocriptine
Bryostatin 1*
CT1812*
DAOI-A
intermittent Theta Burst Stimulation (iTBS)
Levetiracetam
MemorEM
Nicotine Transdermal Patch*
SAGE-718
Transcranial Alternating Current Stimulation (tACS)

Vascular
AR1001
Perindopril|Telmisartan*

Path to Clinic



Type of Therapy



PHASE 3

By Type of Target

Inflammation
NE3107

Misfolded Proteins
Aducanumab
Donanemab
Gantenerumab
Lecanemab
Trx0237

Mitochondria & Metabolic Function
Extended-release metformin
Ginkgo biloba
GV-971
Tricaprilin

Synaptic Activity
AGB101*
ANAVEX2-73
Donepezil
Guanfacine
Octohydroaminoacridine succinate
Troriluzole

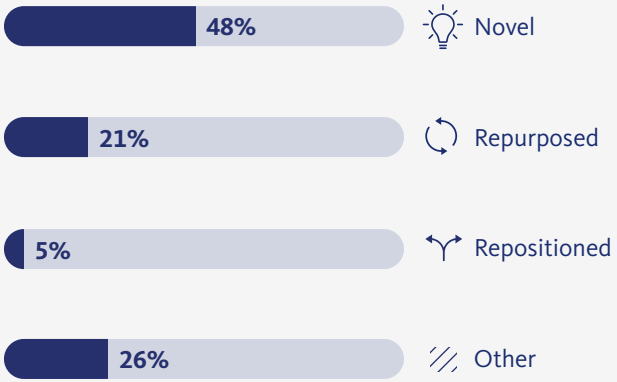
Vascular
Renew NCP-5

Other
BPDO-1603
COR388

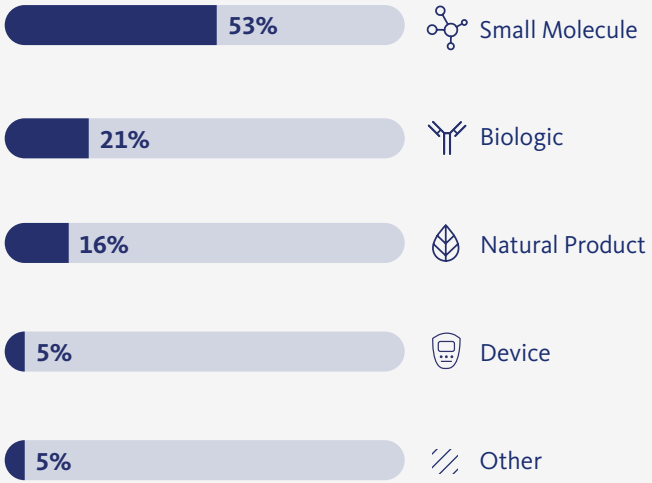
** Funded by the ADDF*

Even in phase 3, where drugs are closest to market, the majority of trials are exploring novel targets.

Path to Clinic



Type of Therapy



DRUGS FOR BEHAVIORAL SYMPTOMS

In Clinical Trials

Drugs in this category target behavioral symptoms associated with Alzheimer's disease. Although these drugs do not change the course of the disease, they have the potential to improve the quality of life for Alzheimer's patients and their caregivers.

AGITATION

- AVP-786 / **Phase 3**
- Brexpiprazole / **Phase 3**
- Dronabinol / **Phase 2**
- Escitalopram / **Phase 3**
- Mirtazapine / **Phase 3**
- Placebo | AVP-786 / **Phase 3**
- Nabilone* / **Phase 3**
- Prazosin / **Phase 2**
- THC-free CBD oil / **Phase 2**

ANXIETY & AGITATION

CBD/THC / **Early Phase 1**

DEPRESSION

Psilocybin / **Early Phase 1**

DIFFICULTY SWALLOWING

ingual strengthening (device) / **Phase 2**

IMPAIRED VERBAL COMMUNICATIONS

TMS + CILT / **Phase 1**

SEIZURES

Levetiracetam / **Phase 2**

SLEEP DISORDERS

Suvorexant / **Phase 2**

*Funded by the ADDF

DRUGS FOR ALZHEIMER'S PREVENTION

In Clinical Trials

These drugs are being tested as a way to prevent cognitive decline in people who have not developed symptoms or have not been diagnosed with Alzheimer's disease. The trials are designed to include people with one or more of the following risk factors:

Age or Relevant Co-morbidities: Older individuals without symptoms or with reported memory complaints, as well as individuals deemed at higher risk due to previous traumatic brain injury, PTSD, depression or vascular-health issues.

Family History: Healthy individuals with relatives who have had dementia.

Early Biomarker Indications: Individuals without symptoms who are at-risk based on biomarker measures, such as amyloid in the brain.

Genetics: Individuals who carry genes associated with increased risk for Alzheimer's (like APOE or rare familial early onset genes).

AGE/TRAITS

Active NIR-PBM (device) / **Phase 2**
Icosapent ethyl / **Phase 2**
Memantine / **Phase 1**
Omega 3 treatment* / **Phase 3**
Losartan / **Phase 2**

FAMILY

Gantenerumab / **Phase 2**

BIOMARKERS

Crenezumab* / **Phase 2**
Deferiprone / **Phase 2**
Omega 3 PUFA / **Phase 2**
Solanezumab / **Phase 3**
Telmisartan / **Phase 1**

GENETICS

AGB101 / **Phase 2**
DHA / **Phase 2**

LIFESTYLE INTERVENTION TRIALS

Additional trials underway are examining non-drug interventions to improve symptoms and/or quality of life for people with Alzheimer's. This ranges from dietary changes and increasing exercise, to reducing stress and using technologies that help people with Alzheimer's and their caregivers adapt to the realities of the disease.

A LOOK AT THE ADDF CLINICAL TRIAL PORTFOLIO

ADDF has one of the largest and most diverse clinical trial portfolios, which spans multiple drug targets based on an understanding of the biology of aging. The ADDF venture philanthropy model allows us to take risks others cannot, supporting bold and innovative, yet sometimes overlooked research. This section includes all active clinical trials in the ADDF trial portfolio as of October 2021. ADDF-funded trials are considered "ongoing" until data analysis is complete.

Supported fully or in part by the ADDF

	Path to Clinic	Clinical Stage
GENETICS & EPIGENETICS		
Amylyx Pharmaceuticals, Kent Leslie	Prevention, Novel	Phase 2
Duke University Medical Center, Miles Berger	Prevention, Novel	Phase 2
Oryzon Genomics, Roger Bullock	Novel	Phase 2
Weill Medical College of Cornell University + LEXEO, Ronald Crystal	Prevention, Novel	Phase 1
INFLAMMATION		
Cleveland Clinic, Marwan Sabbagh	Prevention, Repurposed	Phase 2
NeuroKine Therapeutics, D. Martin Watterson & Wayne Anderson	Prevention, Novel, Repurposed	Phase 1
University of California Davis School of Medicine, John Olichney	Prevention, Repositioned	Phase 2
Treeway B.V., Ronald van der Geest	Prevention, Novel	Phase 2
Vaccinex Inc, Eric Siemers	Prevention, Novel	Phase 1
University of Kentucky, Linda Van Eldik	Prevention, Novel	Phase 1
MISFOLDED PROTEINS		
Asceneuron, Dirk Beher	Novel	Phase 1
Wake Forest School of Medicine, Miranda Orr	Repurposed, Combination	Phase 2

Prevention · Novel · Repurposed · Repositioned · Combination

	Path to Clinic	Clinical Stage
MITOCHONDRIA & METABOLIC FUNCTION		
Imperial College London, Paul Edison		Phase 2
Metro International Biotech, David Livingston		Phase 2
NEUROPROTECTION		
PharmatrophiX, Frank Longo		Phase 2
Research Institute of the McGill University Health Centre, Hiroaki Sato		Phase 2
University of Arizona, Roberta Diaz Brinton		Phase 2
SYNAPTIC ACTIVITY & NEUROTRANSMITTERS		
AgeneBio, Sharon Rosenzweig-Lipson and Michela Gallagher		Phase 3
Cleveland Clinic, Jeffrey Cummings		Phase 2
Cognition Therapeutics, Susan Catalano		Phase 2
Santa Lucia Foundation, Giacomo Koch		Phase 2
RIO Pharmaceuticals, John Gerdes		Phase 0
Sunnybrook Research Institute, Krista Lanctôt		Phase 2
University of Exeter, Clive Ballard		Phase 2
VASCULAR		
Emory University School of Medicine, Ihab Hajjar		Phase 2
St. George's University of London, Atticus Hainsworth		Phase 2
Sunnybrook Research Institute, University of Toronto, Sandra Black		Phase 2
OTHER		
University Hospital Toulouse, Bruno Vellas		Phase 2
Columbia University, Edward Huey		Phase 2
University of Southern California, Hussein Yassine		Phase 2
Harvard Medical School/BIDMC, Emiliano Santarnecchi		Phase 2
Preventive Medicine Research Institute, Dean Ornish		Phase 2

Prevention Novel Repurposed Repositioned Combination Other

ADDF-FUNDED RESEARCH SNAPSHOTS

Susan Catalano, Ph.D.

Cognition Therapeutics, Inc.

SYNAPTIC ACTIVITY AND NEUROTRANSMITTERS

The loss of synapses, which permit communication between nerve cells, is strongly correlated to cognitive decline. Dr. Catalano and the team at Cognition Therapeutics have developed a drug candidate called CT1812 that works through a novel mechanism to stop the binding of toxic amyloid protein that builds up in the brain and damages synapses.

Ronald Crystal, M.D.

Weill Medical College of Cornell University;
LEXEO Therapeutics

GENETICS & EPIGENETICS

Dr. Crystal is a pioneer in gene therapy, which aims to modify a person's genes to treat or prevent disease. In his current phase 1 clinical trial, Dr. Crystal is testing the safety and preliminary efficacy of delivering APOE2 gene therapy into the brains of people who have two copies of the high risk APOE4 gene and are already experiencing mild cognitive decline or early dementia.

Frank Longo, M.D., Ph.D.

Stanford Medicine; PharmatrophiX

NEUROPROTECTION

Developed with funding from the ADDF beginning in 2000, the drug C-31 (LM11A-31) has been heralded as potentially revolutionary. C-31 targets the p75 receptor on the surface of neurons, which, as people age, starts to malfunction and tells the synapses that connect the neurons to degenerate. By blocking the action of the p75 receptor, the goal is to make neurons more resilient to degeneration and death. C-31 is currently completing a phase 2a trial with results expected soon.

Michela Gallagher, Ph.D.

Johns Hopkins School of Medicine;
AgeneBio

SYNAPTIC ACTIVITY AND NEUROTRANSMITTERS

AGB101 is the first drug to target hippocampal hyperactivity, which is common in the mild cognitive impairment stage of Alzheimer's disease. Neuron hyperactivity in this area of the brain is a problem because it drives the buildup of both amyloid and tau proteins in the brain. The ADDF is supporting the ongoing phase 3 clinical trial with results expected in 2023.

ALZHEIMER'S RESEARCH PIPELINE:

A Thriving Ecosystem Increases Hope and Promise of New Treatments

The Alzheimer's research pipeline has evolved in every conceivable way since the ADDF was founded over two decades ago. Not long ago, the drug pipeline was filled mostly with amyloid-targeting drugs. Now, the majority of clinical trials are focused on novel targets, a change that was catalyzed by the ADDF and its early championing of the biology of aging.

The pipeline delivered the first ever Alzheimer's disease-modifying drug in 2021, which was also the first new treatment in 17 years. But even more exciting is what's to come.

Today's clinical trials are more rigorous and have a better chance than ever of delivering innovative, new therapies to patients in the near term. What's more, the range of drugs being tested means these therapies will likely work against many of the underlying problems that contribute to the development of Alzheimer's. This will give physicians a menu of drugs from which to prescribe the unique combinations that provide personalized care to each patient.

The majority of clinical trials are focused on novel targets, a change that was catalyzed by the ADDF and its early championing of the biology of aging.

Biomarkers are key to drug development and precision medicine

As the field develops more drugs against a wide range of targets—for example, drugs to reduce brain inflammation, improve its blood flow and clear misfolded proteins—we must expand our arsenal of biomarkers to measure the impact of drugs on each of these contributors to Alzheimer's disease.

Overall, there are relatively few biomarkers for Alzheimer's disease. Some are already in use in Alzheimer's clinical trials, including Amyvid™ and Tauvid™, PET scans that measure brain levels of amyloid and tau proteins respectively. One non-invasive and easy-to-use blood test is available

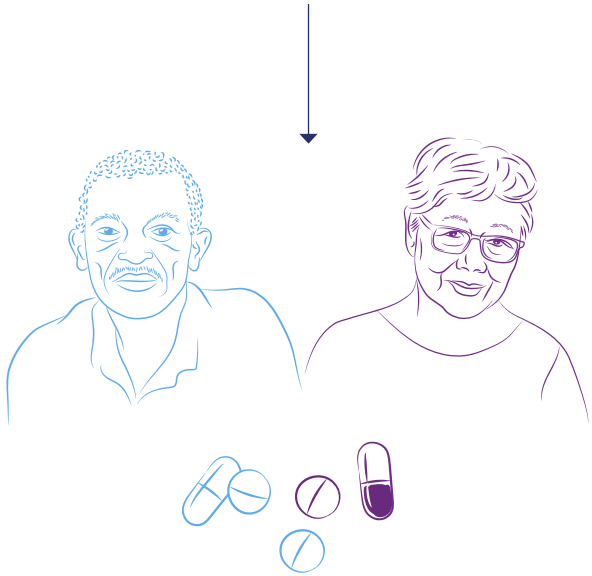
in doctor's offices for clinical use. PrecivityAD™ accurately predicts brain amyloid levels from as little as one teaspoon of blood.

But there is much more work to be done. Dozens of ongoing trials are assessing and validating new Alzheimer's biomarkers. These trials are evaluating biomarkers that measure things like amyloid, tau and other protein levels in the brain, chronic inflammation, blood flow, how the brain metabolizes energy, and genetic alterations that increase the risk of Alzheimer's progression.

Biomarkers can take many forms, from the more invasive and expensive, such as PET scans and spinal fluid taps, to less invasive and less costly blood tests. Studies are also underway evaluating innovative new retinal scans and digital biomarkers, such as wearable devices and smartphone apps, that may provide a window into the Alzheimer's brain.

Bill Gates, longtime supporter of Alzheimer's research and an initial partner of the ADDF's Diagnostics Accelerator, recently commented on how biomarker research is fueling his optimism about what's to come from the Alzheimer's research pipeline.

Biomarkers are key to drug development and precision medicine



Repurposed drugs: reducing costs and time to market for Alzheimer's drugs

Another exciting evolution of the research pipeline is an increasing focus on repurposed drugs for Alzheimer's. Mirroring the ADDF portfolio, nearly 35% of today's Alzheimer's clinical trials are studying repurposed and repositioned drugs.

Repurposing drugs that already have FDA approval for other diseases means researchers can save time and money by proceeding directly to clinical trials in patients because drug safety is already established. This is a major benefit considering that the estimated cost of developing an Alzheimer's drug is eight times more than a cancer drug and takes nearly twice as long to develop.

High costs and longer development times mean Alzheimer's trials need to be especially efficient

Another way to trim drug development time and costs is by improving designs of phase 2a, or "exploratory," trials. The phase 2b/3 studies that follow and that are needed for FDA approval account for the largest portion of development costs, so it is vital that phase 2a trials only advance drugs with the highest likelihood of success.

The ADDF will continue to seek out and invest in the most innovative and promising research across the world to ensure no good research idea is left behind.

Well-designed biomarker-based phase 2a exploratory trials are becoming the cornerstone of these efforts. An expert panel convened by the ADDF and its partner, The Association for Frontotemporal Degeneration, published guidance in the journal *Neurology*® for better design and implementation of these trials.

By adopting best practices outlined in the guidance, researchers can be more confident that trial results are solid and can be used to make all-important decisions about whether to advance drugs to later-stage trials or to focus resources elsewhere. One of the key recommendations in the paper is to include biomarkers in the trial design that are aligned with the drug's mechanism of action.

Biomarker tests are a big part of improving exploratory trials because they allow researchers to see how well drugs are engaging with their intended target at this stage. For example, in a study reported earlier this year, ADDF-funded investigator Ana Pereira, M.D. used two types of biomarker brain scans to measure improvements in brain metabolism in patients treated with the repurposed drug riluzole. These changes correlated with improvement in cognitive changes and disease progression.

In another example, ADDF-researcher Jeffrey Cummings, M.D. and colleagues published a 2021 paper that used a biomarker PET scan to evaluate the effects of rasagiline, a drug already approved to treat Parkinson's disease, in patients with mild to moderate Alzheimer's disease. The drug met its primary endpoint, demonstrating favorable changes in FDG-PET scans, which indicate increased metabolism in the frontal regions of the brain compared to placebo.

More drug targets, efficient trials and biomarkers mean more promise for Alzheimer's patients

Now is the time to redouble our efforts to cross the finish line for Alzheimer's patients and their families. Researchers need to continue looking at innovative ways to develop novel drugs and test repurposed drugs that target the many underlying causes of Alzheimer's. The ADDF will continue to seek out and invest in the most innovative and promising research across the world to ensure no good research idea is left behind.

OUR METHODS

On April 8, 2021, the ADDF scientific team accessed clinical trial data from ClinicalTrials.gov using the search criteria listed here. These findings were cross checked and rounded out through a search of the AlzForum database, which also catalogs therapeutics being tested as treatments for Alzheimer's disease.

The ADDF scientific team performed an unbiased review of the information, with trial categorization based solely on information provided by researchers and housed on these sites (e.g., when an investigator indicated a drug was being tested to alter cognition or memory, it was categorized as disease-modifying).

Condition / Disease	Alzheimer
Study Type	Interventional studies
Status	Not yet recruiting, recruiting, enrolling, by invitation, or active not recruiting
Phase*	Early phase 1, phase 1, phase 2, phase 3

We identified 208 active Alzheimer's clinical studies, including pharmacological (e.g., drugs, natural products, stem cells) and non-pharmacological (e.g., dietary, devices) interventions. These included 118 trials of disease-modifying drugs (aimed at slowing, stopping or reversing the disease once cognitive symptoms are present), 15 trials of drugs to treat behavioral symptoms of Alzheimer's (such as agitation), and 13 trials aimed at preventing cognitive decline in at-risk subjects before a diagnosis. An additional 18 trials were found that are examining lifestyle interventions to improve symptoms and/or quality of life for people with Alzheimer's, and 44 trials were assessing Alzheimer's biomarkers. When more than one trial was listed for a single drug, we only listed that drug once, though every trial is counted in the report's statistics. Drugs that potentially affect more than one biological target are listed under the drug's primary target.

**For therapies tested in more than one trial, we listed the most advanced trial they have entered or completed. For example, a drug that is being tested in both phase 2 and 3 trials would be listed in phase 3.*

Alzheimer's
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The mission of the Alzheimer's Drug Discovery Foundation is to rapidly accelerate the discovery of drugs to prevent, treat and cure Alzheimer's disease.

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