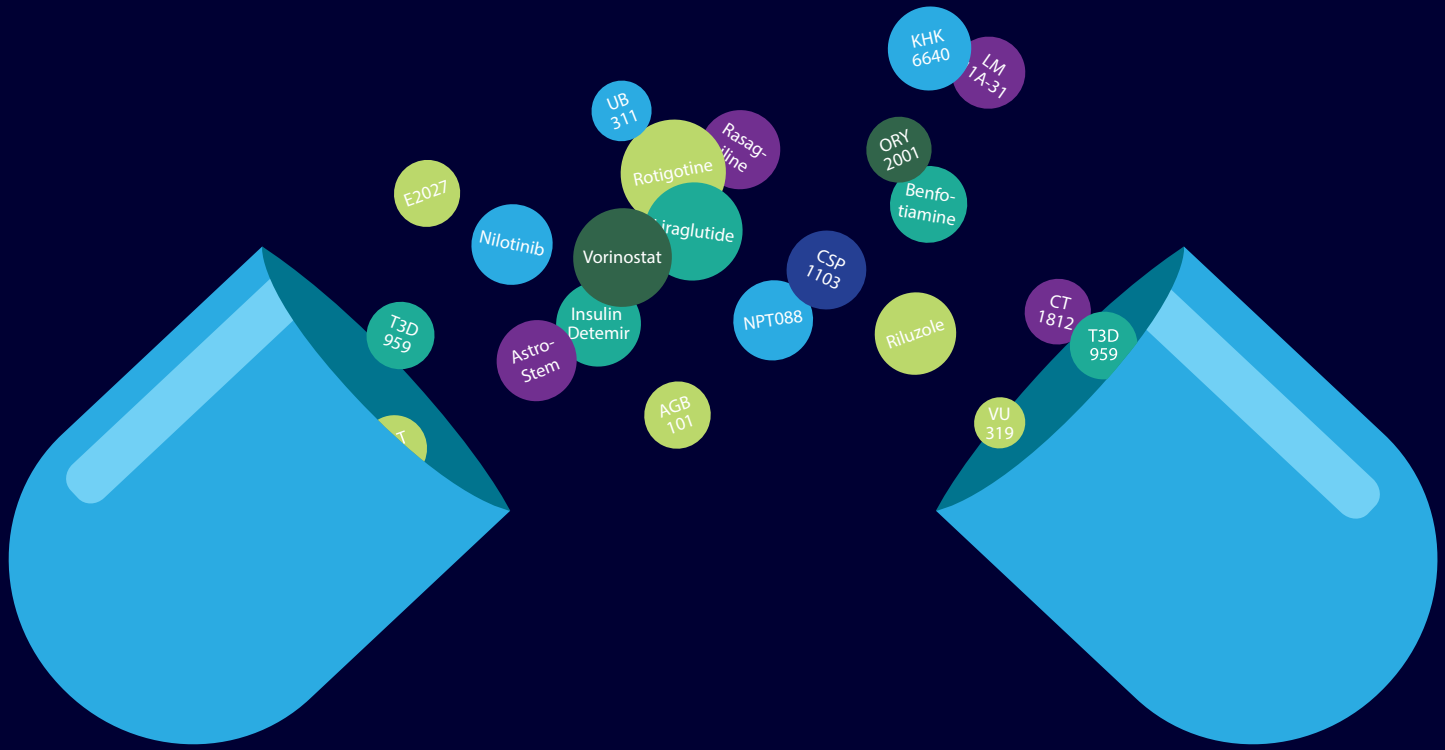
Alzheimer's
Drug Discovery
Foundation

CLOSING IN ON A CURE

2017 Alzheimer's Clinical Trials Report



PUBLISHED BY
Alzheimer's Drug Discovery Foundation
57 West 57th Street, Suite 904
New York, NY 10019
AlzDiscovery.org

November 2017

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"We see ideas that were called crazy a decade ago and are now the most exciting drugs being tested."

Dear Friends,

The Alzheimer's Drug Discovery Foundation (ADDF) was founded in 1998 with a singular mission—find and fund the best ideas to prevent and treat Alzheimer's. Back then, there wasn't much in the drug pipeline for this disease. We had to change that, and we have.

There are now 126 drug programs in clinical trials for Alzheimer's, and **the ADDF has provided support to nearly 20%.** Every single one represents hope for the tens of millions of people across the globe affected by this disease, and the millions more who will get it if we don't succeed.

For too long, Alzheimer's drugs have been a story of failure. That's not the whole story.

In this report, we strove to present **all drugs in clinical development** and provide a more comprehensive picture. Clinical trials are the final stages of a drug's development, and there are more drugs for Alzheimer's in the clinic than ever before. Others have published overviews of active trials in Alzheimer's. Because there can be breaks between trial phases, we knew that there were drugs in clinical stages that weren't on these lists, and we strove to find and include those.

We hope this report serves as a call to action. Looking at the drugs in clinical trials today, we see perseverance. We see ideas that were called crazy a decade ago and are now the most exciting drugs being tested. We see hope. We have to keep going.

Together, we will get effective drugs for Alzheimer's into the hands of patients and conquer this disease.

Sincerely,

Howard

HOWARD FILLIT, MD

Founding Executive Director and Chief Science Officer

Alzheimer's Drug Discovery Foundation

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EXECUTIVE SUMMARY

Alzheimer's disease is a leading cause of death worldwide. In the United States, it is the only cause of death among the top 10 without definitive prevention or treatment options. The five FDA-approved drugs for Alzheimer's relieve symptoms such as memory loss and cognitive impairments, but these effects wear off over time and none alter the course of the disease.

In this report, the Alzheimer's Drug Discovery Foundation (ADDF) surveys the potential disease-modifying drugs for Alzheimer's in clinical development. These drugs are designed to slow, stop, or possibly even reverse the course of Alzheimer's. Human clinical trials are the final stages of a drug's development, and the drugs in trials today could be available to patients in just a few years, if they report positive results and receive FDA approval. Highlights of our report follow:

126 Disease-Modifying Drugs

There are 126 potential treatments for Alzheimer's disease in clinical development.

Half of the Drugs are in Phase 2

We found 33 drugs in phase 1 trials, 68 in phase 2, and 25 in phase 3.

Beta-Amyloid is Most Common Target

Despite a history of failures, 30 drugs in clinical trials are targeting beta-amyloid, a misfolded protein that comprises the plaques found in Alzheimer's. An additional 11 drugs target other misfolded proteins such as tau or mechanisms to clear such proteins.

The ADDF Has Supported 20% of Clinical-Stage Drugs

We have provided funding to support the development of 25 of the 126 treatments now in clinical development.

Additional 19 Drugs to Address Associated Symptoms

There are also 19 drugs in clinical trials designed only to address associated symptoms experienced by Alzheimer's patients, such as agitation, depression, and insomnia.

OUR METHODS

On July 1, 2017, we accessed trial data from **ClinicalTrials.gov** using the following criteria:

Condition / Disease
Alzheimer's

Intervention / Treatment
Drug or Biological

Study Type
Interventional Studies

Status
Not yet recruiting, Recruiting, Enrolling by Invitation, or Active, not recruiting

Trial Phase
Early Phase 1, Phase 1, Phase 2, Phase 3

We eliminated trials testing new delivery systems (e.g., transdermal patch) for Alzheimer's drugs that are already FDA-approved. We did include FDA-approved drugs for other diseases that were being repurposed for Alzheimer's or included in combination therapy trials. To cast a wider net and include drugs in clinical development but between trial phases, we cross-checked this list against the trials we are currently funding and the following three sources:

1. Alzforum.org's Therapeutics Database
2. PhRMA's "Medicines in Development for Alzheimer's 2016 Report"
3. Cummings, Jeffrey, Garam Lee, Travis Mortsdorf, Aaron Ritter, and Kate Zhong. "Alzheimer's disease drug development pipeline: 2017." *Alzheimer's & Dementia: Translational Research & Clinical Interventions* 3, no. 3 (September 2017): 367-84.

If the status of a drug was unclear, we sought information from the relevant sponsor's (e.g., pharmaceutical company or university) current pipeline on its website. When drugs appeared on a supporting list but not on ClinicalTrials.gov, we checked sponsor websites as well as the European Union's Clinical Trials Register.

TRIAL DATA

The ADDF's scientific staff carefully reviewed information about each of the 126 drug programs and assigned them to the categories that follow:

Type of Therapy

Small Molecule: These are organic compounds that can regulate biological processes. Most drugs are small molecules.

Biologic: This includes antibodies, hormones (e.g., insulin, allopregnanolone), oligonucleotides (e.g., DNA or RNA), and peptides. Immunotherapies are biologics.

Cell Therapy: These are exclusively stem cell therapies.

Natural Product: This refers to supplements such as vitamins and amino acids as well as plant extracts.

Trial Phase

We include drugs in phase 1, 2, and 3 clinical trials. Drug programs are listed by 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. A drug that has completed a phase 1 trial and announced but not yet started a phase 2 is listed in phase 1.

Target

This is the primary biological target the drug is attempting to affect.

Genetics & Epigenetics: These therapies may target certain genes, such as APOE, which can affect our risk for Alzheimer's. Epigenetic processes regulate how much our genes are expressed.

Inflammation: Chronic inflammation in the brain can accelerate Alzheimer's and may be a trigger of the disease. But inflammation is also part of our normal immune responses and can protect the brain from damage.

Misfolded Proteins: In Alzheimer's, proteins including beta-amyloid and tau can misfold and become toxic. These misfolded proteins accumulate into plaques, tangles, and other aggregates if not cleared by the brain's self-repair mechanisms.

Mitochondria & Metabolic Function: All cells need energy to maintain healthy function, and neurons (i.e., brain cells) are among the highest energy users. As we age, mitochondria, the energy center of our cells, can become impaired as can other aspects of cellular metabolism.

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

Synaptic Activity & Neurotransmitters: Synapses are connections between our neurons. Neurotransmitters carry chemical signals across synapses, which is critical for memory and cognition.

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

Path to the Clinic

Novel

These drug programs were wholly developed by researchers and generate "novel composition of matter" intellectual property.

Repurposed

This refers to existing drugs that are FDA-approved for other diseases or conditions and are now being tested for Alzheimer's.

Repositioned

These drugs entered clinical trials for other indications, have not yet been FDA-approved, and are now being tested for Alzheimer's.

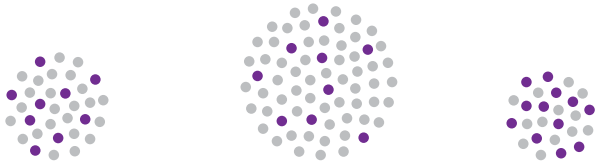
Overview:

2017 CLINICAL TRIALS BY THE NUMBERS

- Neuroprotection **19**
- Misfolded Proteins **41**
- Inflammation **12**
- Genetics & Epigenetics **3**
- Synaptic Activity & Neurotransmitters **23**
- Mitochondria & Metabolic Function **14**
- Vascular **11**
- Unknown **3**

The ADDF has funded **20%** of these clinical trials

Trial Phase



PHASE 1
33

PHASE 2
68

PHASE 3
25

Beta-Amyloid Trials

Beta-amyloid remains a major target in all phases of clinical trials, despite high-profile failures in the past few years.

Type of Therapy*

**Some combination therapies fall into multiple categories and are represented here twice.*

SMALL MOLECULE
80

BIOLOGIC
32

CELL THERAPY
5

NATURAL PRODUCT
11

UNKNOWN
1

Path to Clinic

NOVEL
67

REPURPOSED
41

REPOSITIONED
2

OTHER /UNKNOWN
16

PHASE 1

Clinical Trials

NEUROPROTECTION

Drug	Type of Therapy	Path to Clinic
● Allopregnanolone	Biologic	*Other*

MISFOLDED PROTEINS

Drug	Type of Therapy	Path to Clinic
ACI-35 (Tau)	Biologic	💡
ALZ-801 (Amyloid)	Small Molecule	*Other*
BIIB076 (Tau)	Biologic	💡
KHK6640 (Amyloid)	Biologic	💡
Lu AF20513 (Amyloid)	Biologic	💡
LY3002813 (Amyloid)	Biologic	💡
LY3303560 (Tau)	Biologic	💡
MEDI1814 (Amyloid)	Biologic	💡
NGP 555 (Amyloid)	Small Molecule	💡
NPT088 (Amyloid & Tau)	Biologic	💡
PF-06648671 (Amyloid)	Small Molecule	💡
RO 7105705 (Tau)	Biologic	💡
SAR228810 (Amyloid)	Biologic	💡
TPI-287 (Tau)	Small Molecule	💡

INFLAMMATION

Drug	Type of Therapy	Path to Clinic
● GC021109	Small Molecule	💡
NP001	Small Molecule	💡
Plasma	Biologic	*Other*

GENETICS & EPIGENETICS

Drug	Type of Therapy	Path to Clinic
● ORY-2001	Small Molecule	💡
Vorinostat	Small Molecule	🔄

SYNAPTIC ACTIVITY & NEUROTRANSMITTERS

Drug	Type of Therapy	Path to Clinic
Bisnorcymserine (BNC)	Small Molecule	💡
● BPN14770	Small Molecule	💡
E2027	Small Molecule	💡
HTL0009936	Small Molecule	💡
TAK-071 | Donepezil	Small Molecule	➕🔄
● VU319	Small Molecule	💡

MITOCHONDRIA & METABOLIC FUNCTION

Drug	Type of Therapy	Path to Clinic
Grape Seed Polyphenolic Extract, Resveratrol	Natural Product	➕🔄
Insulin aspart	Biologic	🔄
Oxaloacetate (OAA)	Natural Product	*Other*

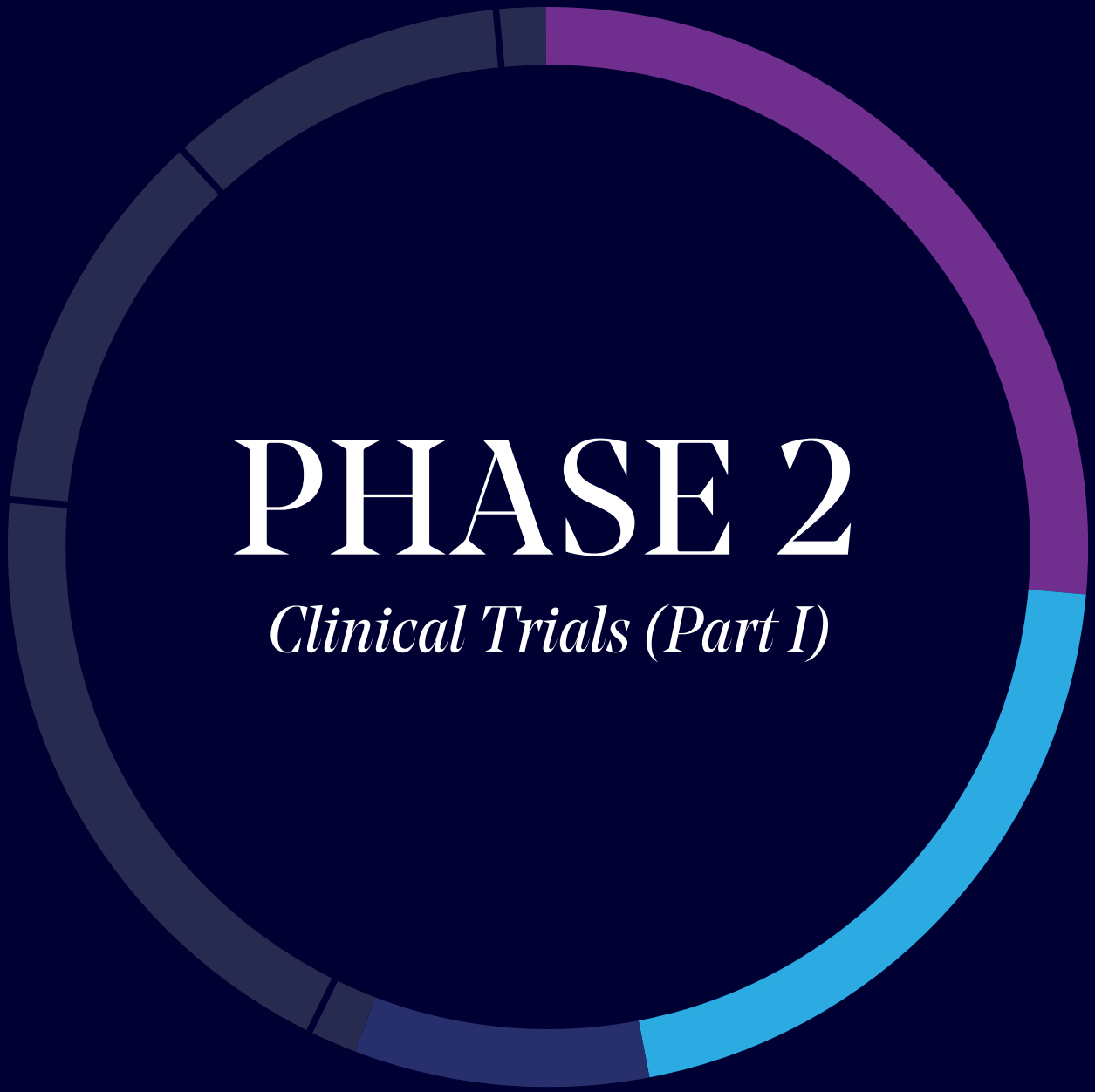
VASCULAR

Drug	Type of Therapy	Path to Clinic
Gemfibrozil	Small Molecule	🔄
Telmisartan	Small Molecule	🔄

UNKNOWN

Drug	Type of Therapy	Path to Clinic
PF-05251749	Small Molecule	💡
PF-06751979	Small Molecule	💡

Legend: ● **Funded by ADDF** 💡 **Novel** 🔄 **Repurposed** **Repositioned** ➕🔄 **Combination Therapy**



PHASE 2

Clinical Trials (Part I)

NEUROPROTECTION

Drug	Type of Therapy	Path to Clinic
Adipose Derived Stromal Cells	Cell Therapy	Novel
ANAVEX2-73	Small Molecule	Novel
AstroStem	Cell Therapy	Novel
AZD0530	Small Molecule	Repositioned
● Bryostatin 1	Small Molecule	*Other*
CB-AC-02	Cell Therapy	Novel
● CT1812	Small Molecule	Novel
GV1001	Biologic	Repurposed
L-Serine	Natural Product	*Other*
● LM11A-31	Small Molecule	Novel
Mesenchymal Stem Cells (Allogeneic)	Cell Therapy	Novel
Mesenchymal Stem Cells (Umbilical Cord)	Cell Therapy	Novel
MLC901	Natural Product	*Other*
● Rasagiline	Small Molecule	Repurposed
S -Equol	Natural Product	*Other*
STA-1 | Donezepil	Small Molecule	Combination Therapy
T-817 MA	Small Molecule	Novel
Xanamem	Small Molecule	Novel

MISFOLDED PROTEINS

Drug	Type of Therapy	Path to Clinic
AADvac1 (Tau)	Biologic	Novel
ABBV-8E12 (Tau)	Biologic	Novel
Abvac40 (Amyloid)	Biologic	Novel
ACI-24 (Amyloid)	Biologic	Novel
BAN2401 (Amyloid)	Biologic	Novel
IONIS MAPTRx (Tau)	Biologic	Novel
LY3202626 (Amyloid)	Small Molecule	Novel
Meganatural-Az Grapeseed Extract (Amyloid)	Natural Product	*Other*
Methylene Blue (Proteostasis)	Small Molecule	Repurposed
NewGam 10% IVIG (Amyloid)	Biologic	*Other*
● Nilotinib (Protein Clearance)	Small Molecule	Repurposed
Posiphen (Amyloid, Tau, Synuclein)	Small Molecule	Novel
PQ912 (Amyloid)	Small Molecule	Novel
UB-311 (Amyloid)	Biologic	Novel

INFLAMMATION

CSP-1103	Small Molecule	Novel
● Etanercept	Small Molecule	Repurposed
Minocycline	Small Molecule	Repurposed
● Sargramostim	Biologic	Repurposed
Valaciclovir	Small Molecule	Repurposed
VX-745	Small Molecule	Repurposed

Legend: ● **Funded by ADDF** **Novel** **Repurposed** **Repositioned** **Combination Therapy**

PHASE 2

Clinical Trials (Part II)

GENETICS & EPIGENETICS

Drug	Type of Therapy	Path to Clinic
Probucol	Small Molecule	Repurposed

SYNAPTIC ACTIVITY & NEUROTRANSMITTERS

Drug	Type of Therapy	Path to Clinic
● AGB101	Small Molecule	Repurposed
● Atomoxetine	Small Molecule	Repurposed
BI 409306	Small Molecule	Novel
CPC-201	Small Molecule & Biologic	Combination Therapy
DHP1401 / Donepezil	Small Molecule	Combination Therapy
Formoterol	Small Molecule	Repurposed
Levetiracetam	Small Molecule	Repurposed
● Nicotine Transdermal Patch	Natural Product	*Other*
Piromelatine	Small Molecule	Repositioned
PXT00864	Small Molecule	Combination Therapy
● Riluzole	Small Molecule	Repurposed
● Rotigotine	Small Molecule	Repurposed
SUVN-502	Small Molecule	Novel

MITOCHONDRIA & METABOLIC FUNCTION

Drug	Type of Therapy	Path to Clinic
● Benfotiamine	Small Molecule	Repurposed
Exendin-4	Small Molecule	Repurposed
Insulin detemir	Biologic	Repurposed
Insulin glulisine	Biologic	Repurposed
● Liraglutide	Small Molecule	Repurposed
● MSDC-0160	Small Molecule	Novel
Nicotinamide	Natural Product	*Other*
T3D-959	Small Molecule	Novel

VASCULAR

Drug	Type of Therapy	Path to Clinic
● Candesartan	Small Molecule	Repurposed
Cilostazol	Small Molecule	Repurposed
Omega-3 PUFA	Natural Product	*Other*
Simvastatin	Small Molecule	Repurposed
Simvastatin, L-Arginine & Tetrahydrobiopterin	Small Molecule & Natural Product	Combination Therapy
● Tadalafil	Small Molecule	Repurposed
● Telmisartan | Perindopril	Small Molecule	Repurposed

UNKNOWN

BAC	*Unknown*	*Unknown*

Legend: ● **Funded by ADDF** **Novel** **Repurposed** **Repositioned** **Combination Therapy**

PHASE 3

Clinical Trials

MISFOLDED PROTEINS

Drug	Type of Therapy	Path to Clinic
Aducanumab (Amyloid)	Biologic	Novel
Albumin / Immune globulin (Amyloid)	Biologic	Repurposed
CNP520 (Amyloid)	Small Molecule	Novel
CNP520 / CAD106 (Amyloid)	Small Molecule + Biologic	Combination Therapy
Crenezumab (Amyloid)	Biologic	Novel
E2609 (Amyloid)	Small Molecule	Novel
Gantenerumab (Amyloid)	Biologic	Novel
Gantenerumab / Solanezumab (Amyloid)	Biologic	Combination Therapy
JNJ-54861911 (Amyloid)	Small Molecule	Novel
Lanabecestat (Amyloid)	Small Molecule	Novel
Sodium oligo-mannurarate (Amyloid)	Small Molecule	Novel
TRx0237 (Tau)	Small Molecule	Repurposed
Verubecestat (Amyloid)	Small Molecule	Novel

INFLAMMATION

ALZT-OP1	Small Molecule	Combination Therapy
Azeliragon	Small Molecule	Novel
Masitinib	Small Molecule	Repurposed

SYNAPTIC ACTIVITY & NEUROTRANSMITTERS

Drug	Type of Therapy	Path to Clinic
Guanfacine	Small Molecule	Repurposed
Lu AE58054	Small Molecule	Novel
Lu AE58054 | Memantine	Small Molecule	Combination Therapy
RVT-101	Small Molecule	Novel

MITOCHONDRIA & METABOLIC FUNCTION

AC-1204	Natural Product	*Other*
● Insulin (Humulin R U-100)	Biologic	Repurposed
Pioglitazone	Small Molecule	Repurposed

VASCULAR

icosapent ethyl (IPE)	Small Molecule	*Other*
● Nilvadipine	Small Molecule	Repurposed

Legend: ● **Funded by ADDF** **Novel** **Repurposed** **Repositioned** **Combination Therapy**

SYMPTOMATIC AGENTS IN TRIAL

Drugs in this category target associated symptoms experienced with Alzheimer's. Though these drugs aren't disease-modifying, they have the potential to improve quality of life for Alzheimer's patients and their caregivers. The list to the right is color-coded according to the key below.

Agitation

Aggression

Apathy

Psychosis

Depression

Sleep Disorders

PHASE 2

Drug	Type of Therapy	Path to Clinic	Symptom
DAOIB	Small Molecule	*Unknown*	*Various*
Dronabinol (Marinol®)	Small Molecule		
Lemborexant	Small Molecule		
Lithium	Small Molecule		
MP-101	Small Molecule		
ORM-12741	Small Molecule		
Pimavanserin	Small Molecule		
S47445	Small Molecule		

PHASE 3

Drug	Type of Therapy	Path to Clinic	Symptom
Aripiprazole	Small Molecule		
AVP-786	Small Molecule		
AXS-05 | Bupropion	Small Molecule		
Brexpiprazole	Small Molecule		
Carbamazepine | Mirtazapine	Small Molecule		
Escitalopram	Small Molecule		
ITI-007	Small Molecule		
Methylphenidate	Small Molecule		
● Nabilone	Small Molecule		
Suvorexant	Small Molecule		
Zolpidem | Zopiclone	Small Molecule		

Legend: ● **Funded by ADDF** **Novel** **Repurposed** **Repositioned** **Combination Therapy**

WHERE WE ARE

Innovative Targets Emerging

Alzheimer's is a complex disease that slowly develops over decades. It has many contributing factors, including our genetics, environment, and lifestyle, but the main driver is aging. As we age, several things can go awry and harm our brains, such as inflammation, misfolded proteins, mitochondrial dysfunction, oxidation, vascular issues, and epigenetic processes. And the self-repair mechanisms that should correct them can also become impaired.[1] For some people, this leads to a cascade that damages and ultimately kills brain cells (i.e., neurons). And when neurons are damaged in specific regions of the brain, we experience memory and cognitive problems associated with Alzheimer's disease.

Research continues to deepen our understanding of this cascade and reveals new ways to combat it. Yet, a third of current clinical trials in Alzheimer's disease are focused on one area: misfolded proteins, and the majority of these on just beta-amyloid. This protein comprises the plaques that are hallmarks of Alzheimer's. Plaques were the first major discovery in Alzheimer's—Alois Alzheimer saw them in the brain of his deceased patient Auguste D. in 1906. A century later, no drugs targeting beta-amyloid have yet been successful. Some, like Biogen's aducanumab, have some preliminary positive data and may ultimately prove to be beneficial to patients. But even if they do, they may only affect one of the disease's underlying causes. More treatments will be needed.

To stop—or even reverse—Alzheimer's, we need to treat more of its underlying causes. Despite the prevalence of beta-amyloid as a target for new therapies, other strategies are gaining ground. One example is chronic inflammation, which a growing body of evidence suggests is linked to the development of Alzheimer's. Previous studies found that people taking anti-inflammatories were less likely to get Alzheimer's disease. Unfortunately, early clinical trials of Alzheimer's patients treated with anti-inflammatories failed. But, recent research has laid the groundwork for new inflammation drug targets. Inflammation in the brain is remarkably complex. While overactive inflammation can damage and destroy neurons, enhancing the function of immune cells to remove toxic proteins can be beneficial. Drugs that promote the removal of toxic proteins by immune cells (e.g., GC021109 from GliaCure) and those that dampen the immune system response (e.g., etanercept) are both being tested in clinical trials, with support from the Alzheimer's Drug Discovery Foundation (ADDF).

Neuroprotection is another promising target area in Alzheimer's. These drugs broadly aim to protect neurons from multiple sources of damage or enhance neuron survival and regeneration. Neuroprotective targets now represent 15% of the drugs in clinical trials, and are the most prevalent type of target represented in phase 2 trials. The ADDF invested in one of these drugs, LM11A-31 from PharmatrophiX, over a decade ago because we believed in the potential of neuroprotection for Alzheimer's. Other promising neuroprotective drugs in clinical trials supported by the ADDF include allopregnanolone, a neuro-steroid being tested by the University of Southern California, and rasagiline at the Cleveland Clinic.

The first epigenetic therapy for Alzheimer's, ORY 2001 by Oryzon Genomics, entered clinical trials two years ago with ADDF funding. (Epigenetic processes regulate how much our genes are expressed and can turn them "up" or "down" like a dimmer switch.) It is continuing to advance and has been joined by vorinostat, which was originally developed as a chemotherapy drug, with more epigenetic pro-

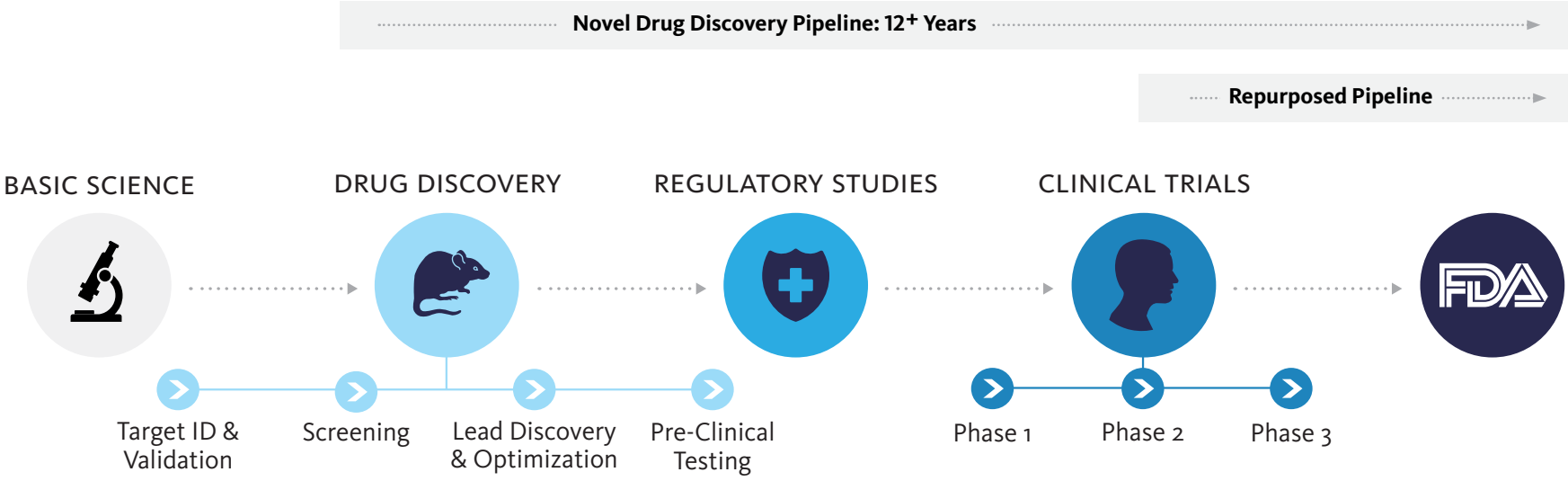
1. Mattson, Mark P., and Tim Magnus. "Ageing and neuronal vulnerability." *Nature Reviews Neuroscience* 7, no. 4 (April 2006): 278-94.

grams nearing clinical stages. Epigenetic treatments represent fewer than 2% of drugs in Alzheimer's trials, but this emerging area holds great promise.

The ADDF has long been committed to diversifying drugs in development for Alzheimer's, and we are heartened to see more and better drug targets represented in Alzheimer's clinical trials. Though, we note that misfolded proteins—and beta-amyloid in particular—are the most common target for phase 1 trials by a large margin. We expected to see more innovation in these earlier stage trials. For our part, we will continue to invest in new and diverse targets to treat Alzheimer's and help drug programs advance to clinical trials.

Novel and Repurposed Drugs in the Pipeline

Drugs take different paths to clinical trials. Each new discovery about how Alzheimer's develops is also a potential target for treating it. Researchers validate these new targets to build evidence on their link to Alzheimer's and attempt to create novel drugs to affect them. It is an arduous process, in which hundreds of thousands of compounds are tested. Researchers take the precious few that show potential and attempt to optimize them into drugs that are capable of passing through the blood-brain barrier (a semipermeable membrane that acts as a filter). These drugs then undergo rigorous safety and toxicity testing to ensure they are safe enough for human clinical trials. Next, the drugs can be tested in human subjects for the first time in phase 1 safety trials. If those go well, researchers can proceed to test efficacy in patients in phase 2 trials. The majority of drugs in clinical development (67 of 126) are novel and they offer new patents and potentially more return on investment if they are successful and gain Food and Drug Administration (FDA) approval. The advances of novel drugs are critical, and



we support researchers pursuing innovation. We also recognize that the development of novel drugs from scratch is a long and expensive road. Patients need disease-modifying treatments now, and repurposed drugs—with their shorter testing requirements—are a viable option. Repurposed drugs have already been approved by the FDA for at least one indication, and have some evidence that they may also be effective in Alzheimer's disease.[2] These drugs may still be on patent, though most in clinical trials today are available as generics. And they have a lot of upside.

Repurposed drugs have already made it successfully through clinical trials, so there is evidence that they are safe in humans. In many cases, this means repurposed drugs can begin testing at the phase 2 clinical trial stage for Alzheimer's, saving time and money. Repurposed drugs also have manufacturing and distribution networks in place (and may be prescribed off-label), so they could be given to patients very quickly if positive results are found. Trials of repurposed drugs can also be used as "proof of concept" for novel formulations or chemical entities that can lead to new IP.

Several classes of repurposed drugs are in clinical trials now. These include liraglutide and other medications approved for diabetes that may improve metabolic dysfunction in brain cells, anti-hypertensives such as candesartan to treat vascular problems in the brain, and anti-convulsants including levetiracetam that address brain hyperactivity. (The latter two drug trials have received ADDF support.) But there are more opportunities for repurposing that we can and should explore.

While repurposed drugs offer a faster route to patients, there is generally limited interest from pharmaceutical companies in sponsoring these trials since the drugs are already on the market and may not have patent protection. Without funding from the pharmaceutical industry, most repurposed drugs are unlikely to progress to large-scale phase 3 trials. Positive results from phase 3 trials are essential to proving a drug is effective in patients and are required for FDA approval for any new indication. Repurposed drugs can be prescribed off-label for Alzheimer's, but insurance companies don't usually reimburse such uses. So, many patients won't be able to afford them. Nonprofit and government funders can help support these trials and get effective drugs to patients quickly.

Prevention or Treatment: When Should Drugs Be Given?

As trial failures grow, researchers have begun asking whether patients need to be treated before they develop Alzheimer's disease. This has resulted in a recent emphasis on trials with "prodromal" or pre-symptomatic patients and efforts to optimize the design of these trials.[3, 4]

Pre-symptomatic patients have some biological signs of the disease, such as beta-amyloid plaques, which the beta-amyloid PET scan has revealed can be present decades before the onset of Alzheimer's. But they don't yet have dementia or other symptoms that interfere with their daily lives.

Researchers posit that by intervening earlier, they may be able to prevent the onset of Alzheimer's disease or at least delay it. A lot happens to neurons between the first abnormal beta-amyloid accumulations and the onset of Alzheimer's—synapses start becoming dysfunctional, neurons get metabolically stressed, and the first signs of neuronal loss appear. There is good rationale for drugs targeting these processes to be given to pre-symptomatic patients, and several drugs are already in trials such as the A4 trial testing solanezumab for prevention.

But trials for pre-symptomatic patients may require that invasive medical procedures, such as spinal taps, be conducted on otherwise healthy people.

2. Appleby, Brian S., Dimitrios Nacopoulos, Nicholas Milano, Kate Zhong, and Jeffrey L. Cummings. "A Review: Treatment of Alzheimer's Disease Discovered in Repurposed Agents." *Dementia and Geriatric Cognitive Disorders 35*, no. 1-2 (January 9, 2013): 1-22. 3. Schneider, Lon S. "The potential and limits for clinical trials for early Alzheimer's disease and some recommendations." *The Journal of Nutrition, Health & Aging* 14, no. 4 (April 2010): 295-98

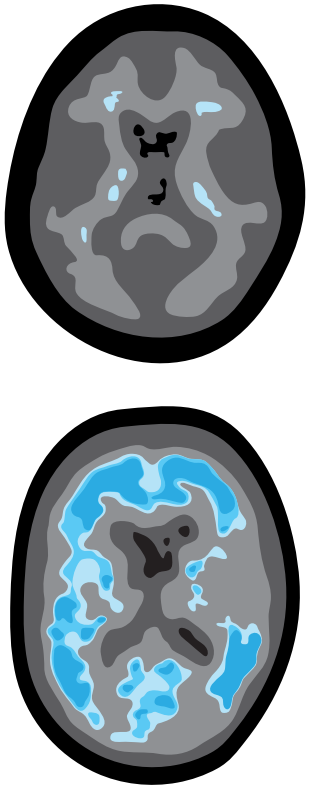
And there are ethical issues to consider when telling people they have signs of early Alzheimer's without yet having effective drugs to offer them. We do believe these concerns are outweighed by the potential to prevent the onset of Alzheimer's. Though, as more trials focus on earlier stage patients, we must also continue to develop and test treatments for patients with moderate to severe forms of the disease.

Challenges

Alzheimer's clinical trials face systemic barriers that can slow their progress and decrease their odds of success, including regulatory hurdles, slow trial recruitment, and lack of validated biomarkers.

The FDA requires that Alzheimer's drug candidates prove benefit to both cognition (e.g., memory) and function (i.e., daily tasks such as cooking). This is a higher standard for approval than that of most diseases, including other neurodegenerative diseases such as Parkinson's. In fact, a single "primary endpoint" is the common standard for FDA drug approvals. We and many others have asked the FDA to remove this barrier and consider potential Alzheimer's drugs on the standard single criteria.

Recruiting volunteers for Alzheimer's trials presents challenges not found in other diseases. In most cases, you need to recruit both an Alzheimer's patient and a caregiver, who can transport the patient to and from the trial site and ensure that all instructions are followed. Eligible patients may not know they have the disease, as up to half of Alzheimer's patients in developed countries haven't been diagnosed.[5] That hurdle is even greater when recruiting pre-symptomatic patients. Because of this, patient recruitment can take years for a large trial and seriously slow the progress of potential therapies. Several groups—including the Global Alzheimer's Platform, the Brain Health Registry, and Alzheimer's Universe—have been formed in recent years to address recruitment issues, and the ADDF supports their much-needed efforts.



BIOMARKER HIGHLIGHT: AMYVID™

Amyvid™, the first diagnostic test for Alzheimer's, is a PET scan that detects beta-amyloid in the brain. It was seed-funded by the ADDF and enables researchers to ensure that patients in Alzheimer's trials actually have the disease.

Biomarkers are tools used to diagnose a disease and assess its progression and response to treatment. They are critical to the success of clinical trials. First, they can be used for trial enrollment to ensure patients have the underlying pathology you're attempting to treat. (This is especially important for patients that exhibit no outward symptoms.) Biomarkers are also needed to show that a drug actually reaches the intended target. Prognostic and predictive biomarkers can indicate disease progression and be used to measure the effectiveness of a drug in trials. A drug may reach its target, but does

4. Macklin, Eric A., Deborah Blacker, Bradley T. Hyman, and Rebecca A. Betensky. "Improved design of prodromal Alzheimer's disease trials through cohort enrichment and surrogate endpoints." *Journal of Alzheimer's Disease* 36, no. 3 (January 1, 2013): 475-86. 5. *World Alzheimer's Report 2011:* The Benefits of Early Diagnosis and Intervention. Report. London, UK : Alzheimer's Disease International, 2011.

it then go on to slow, stop, or reverse the course of Alzheimer's disease?

More trials have begun using biomarkers, particularly for enrollment, after an analysis revealed that more than a third of Alzheimer's patients in a trial for a drug targeting beta-amyloid did not have beta-amyloid plaques in their brains (and therefore did not have Alzheimer's, but other form(s) of dementia).[6] Having the wrong patients in trials skew results and make it difficult to accurately assess a drug's effect. The approval of the beta-amyloid PET scan for Alzheimer's in 2012 was a major improvement, but more biomarkers are needed for targets such as tau and neuroinflammation.

The ADDF supported the early development of the amyloid PET scan, and we continue to expand our funding for new biomarkers. We will soon launch a partnership to support research in biomarkers for neuroinflammation.

Researchers have suggested that as more accurate biomarkers complement standard cognitive testing as measures of a drug's effectiveness, trials may require fewer participants. This could make trials in Alzheimer's faster and less expensive to conduct.[7]

WHAT'S NEXT?

More Shots, More Targets

There are more drugs in clinical trials for Alzheimer's than ever before, and new drugs have entered trials since we started work on this publication. This brings us a great deal of hope.

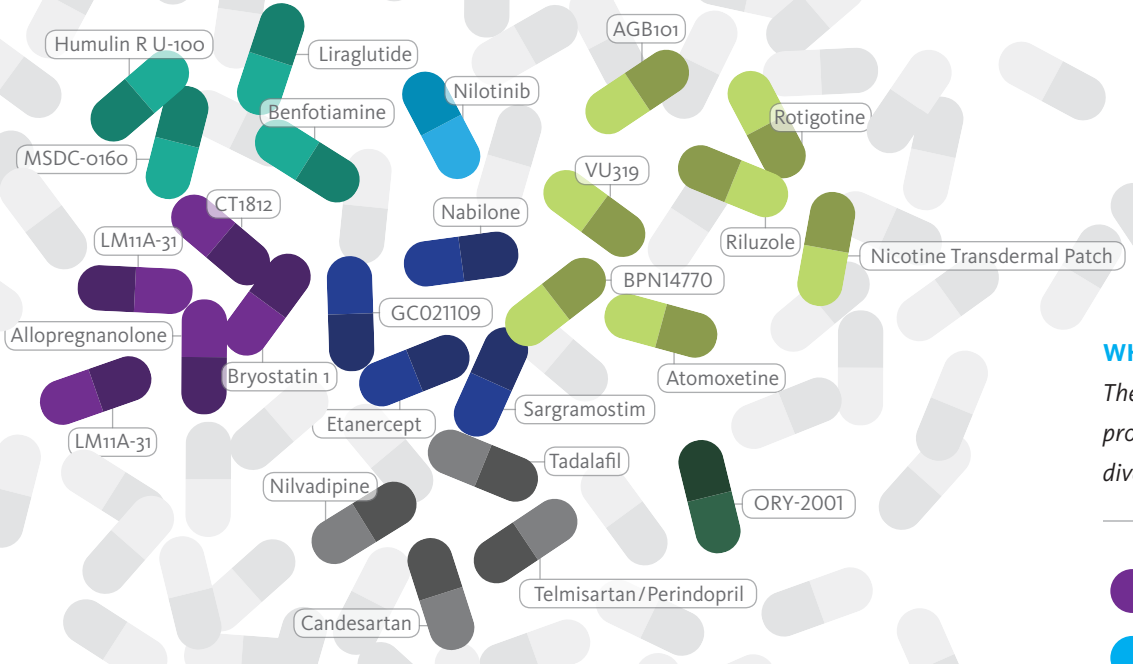
But there remain exponentially fewer drugs in trials for Alzheimer's than for treatable conditions such as breast cancer, diabetes, heart disease, and HIV/AIDS. This is due in part to limited research dollars allocated to Alzheimer's by governmental agencies and other large funders. It is also a consequence of our only recent understanding of Alzheimer's disease biology. The mechanisms underlying heart disease and cancer were uncovered several decades ago, but we're only just beginning to understand all the contributing factors involved in Alzheimer's.

As our knowledge of Alzheimer's grows, we need to take more shots, investing in a greater number of drugs with more targets. Drugs in clinical trials are weighted too heavily toward amyloid and tau at the expense of other targets that may have more potential, including those in neuroinflammation or neuroprotection.

As our knowledge of Alzheimer's grows, we need to invest in a greater number of drugs with more targets.

The ADDF follows the best available evidence when making funding decisions and that has led us to take measured risks. The 25 current clinical-stage drugs the ADDF has supported have diverse targets. And we expect even more ADDF-funded programs to reach clinical trials by this time next year. We urge others to fund more targets in Alzheimer's treatments, when they are supported by evidence.

6. Sevigny, Jeff, Joyce Suhy, Ping Chiao, Tianle Chen, Gregory Klein, Derk Purcell, Joonmi Oh, Ajay Verma, Mehul Sampat, and Jerome Barakos. "Amyloid PET Screening for Enrichment of Early-Stage Alzheimer Disease Clinical Trials." *Alzheimer Disease & Associated Disorders* 30, no. 1 (Winter 2016): 1-7.



WHAT THE ADDF IS FUNDING

The ADDF has supported nearly 20% of drug programs now in clinical trials, and they represent a diverse array of targets.

- Neuroprotection
- Misfolded Proteins
- Inflammation
- Genetics & Epigenetics
- Synaptic Activity & Neurotransmitters
- Mitochondria & Metabolic Function
- Vascular

7. Hampel, Harald, Richard Frank, Karl Broich, Stefan J. Teipel, Russell G. Katz, John Hardy, Karl Herholz, Arun L.W. Bodke, Frank Jessen, Yvonne C. Hoessler, Wendy R. Sanhai, Henrik Zetterberg, Janet Woodcock, and Kaj Blennow. "Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives." *Nature Reviews Drug Discovery* 9, no. 7 (July 2010): 560-74.

Experimental Clinical Trial Design

Alzheimer's clinical trials are expensive and often end in failure. The risk of too many late-stage failures are that investors will begin to leave the field and patients won't volunteer for drug trials. There is a growing sense that too much money is being spent on drugs with too little chance of success, and that volunteering isn't worth the effort since the drug won't be effective.

Smarter design of clinical trials could lessen the risks by weeding out ineffective drugs long before they reach phase 3 trials. The goals of this approach are to:

1. Build compelling clinical evidence of effectiveness in smaller, earlier stage trials before proceeding to very expensive phase 3 testing and

2. Recruit hundreds to thousands of patients into a large phase 3 trials only after evidence of effectiveness is established.

In earlier stage trials, we want to know as much as possible about how the drug works in humans. Does it reach the brain and engage its target? What clinical benefit does it have, if any? One way to do this is to incorporate more relevant biomarkers into trials. Another is to include more patients in phase 2 trials, to increase confidence in results. Today, drug programs are moving into phase 3 trials based on weak evidence of benefit in phase 2 trials or, worse, flawed post-hoc analysis of results showing no benefit at all.[8]

Smarter design of clinical trials could lessen the risks by weeding out ineffective drugs long before they reach phase 3 trials

A third option is to test certain drugs in phase 0 (aka exploratory IND) clinical trials. These trials, which are used in other diseases such as cancer, involve giving micro- or sub-therapeutic doses of a drug to humans and investigating how the drug and the body interact. Phase 0 trials can be used to: show how a drug gets distributed in the body and whether it reaches the brain; help choose the best drug candidate for clinical trials when several options performed well in animal models; and determine dosing when preclinical testing showed high variability. These very early trials expose a small number of patients to very limited doses of drugs that aren't intended to produce any therapeutic effects, so FDA requirements for beginning them are lower than traditional clinical trials.

The ADDF convened a meeting of Alzheimer's and oncology researchers from industry, academia, and the biotechnology sector earlier this year to discuss the potential of conducting more and better phase 0 studies for CNS (or neurodegenerative) diseases. (Oncology research uses experimental trial design successfully.) The feedback has been positive, and we now offer funding for phase 0 trials when the drug program is appropriate. We are also evaluating the phase 2 trial proposals we receive more closely

8. Gold, Michael. "Phase II clinical trials of anti–amyloid ß antibodies: When is enough, enough?" *Alzheimers & Dementia: Translational Research & Clinical Interventions* 3, no. 3 (September 2017): 402-09.

to ensure they can produce more robust results. We encourage others to do the same, because the high rate of failure in phase 3 Alzheimer's trials cannot continue.

Combination Therapies

Because Alzheimer's disease has multiple underlying causes, it will likely require a combination of drugs to effectively treat it. It's also possible that some drugs—if given alone—won't be able to slow the progression of Alzheimer's enough to benefit patients (or gain FDA approval).

Combination therapies could address both of these issues. This year, there are only 11 combination therapy clinical trials, and 5 of these are testing an add-on therapy to a currently approved Alzheimer's drug (i.e., donezepil or memantine). None of the 11 appears to focus on two or more target areas.

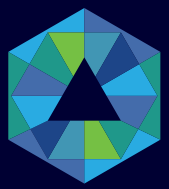
These approaches do not take full advantage of combination drug trials. Next year's report will include a clinical trial of a combination therapy from Amylyx that the ADDF co-funded with the Alzheimer's Association. This therapy combines drugs with two different targets. Early testing suggests that the drugs, when taken together, create additional positive effects.

> We intend to fund more combination therapy programs because we strongly believe in their potential

Combination trials do present specific challenges that make them more difficult and potentially expensive to conduct. The FDA reviews every drug intended for human clinical trials to ensure it is likely to be safe. For combination trials, every drug involved needs to demonstrate safety when given alone and in combination. And combination therapies can have multiple targets, requiring multiple diagnostic tools to measure effectiveness. Some of these issues can, however, be addressed by using repurposed drugs with established safety profiles in combination trials.

Combination therapies are already the standard of care for heart disease, HIV/AIDS, and many cancers. We expect they will be for Alzheimer's one day. The ADDF intends to fund more combination therapy programs because we strongly believe in their potential.

Alzheimer's is a challenging disease to treat and research continues to be underfunded. But the approval of the first disease-modifying drug for Alzheimer's is coming. This will be a breakthrough for patients and industry, and hopefully a catalyst that brings more support to the field. The ADDF will continue working to ensure that hundreds of potential new, diverse treatments for Alzheimer's reach clinical trials, advancing to patients who need them.



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