Section 1

Advancing Alzheimer's Disease Therapies in a Collaborative Science Ecosystem

Chapter 1

Alzheimer's Disease Drug Development: A Research and Development Ecosystem

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1.1 Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease with a long preclinical asymptomatic period followed by progressive decline in cognition manifested as mild cognitive impairment (MCI) and then by mild, moderate, and severe dementia [1, 2]. The key pathologies include amyloid (A), tau (T), and neurodegeneration (N) (A/T/N). A myriad of contributing factors have been identified including inflammation, oxidation, genetic and epigenetic factors, hormonal factors, metabolic and bioenergetic changes, autophagy dysfunction, proteostasis, apolipoprotein E (ApoE) effects and lipid abnormalities, and vascular factors.

AD can occur in individuals as young as their 30s but is more commonly of late onset, with AD dementia doubling in frequency every 5 years after age 60 from affecting approximately 1% of individuals at age 60 and increasing to affect approximately 40% of those 85 and older [3]. The current global population of 46.8 million AD dementia patients worldwide is projected to rise to 74.7 million by 2030 with a corresponding increase in cost of care from the current $1 trillion to $2 trillion [4].

Despite the urgent need for treatment for this burgeoning population, until 2021 there were only five drugs approved and on the market (donepezil; rivastigmine; galantamine, memantine, Namzaric™) with no new drugs approved in the United States or Europe since 2003 [5]. One additional agent was approved in China in 2019 (GV-971 [oligomannate]) [6]. In 2021, the ecosystem delivered a new treatment – aducanumab – approved for treatment by the US Food and Drug Administration (FDA) for treatment of MCI due to AD and mild AD dementia. Approval of aducanumab is a breakthrough in AD treatment and a milestone in development of disease-modifying therapies (DMTs) for neurodegenerative disorders (NDDs). This is an important step forward, while still leaving many phases and aspects of AD untreated and introducing an agent that makes exceptional demands on healthcare systems [7]. Aducanumab is expected to have modest impact on the needs of the broader AD population and continuous involvement in new drug discovery for AD is required.

AD drug development takes a long period of time to progress from laboratory studies to possible human availability, is very expensive, and requires a complex ecosystem spanning the translational journey from non-clinical studies, to clinical trials, through regulatory review, to market. The process begins with an unmet medical need and ends with an agent that begins to address the problem; the solution is then subject to reiterative refinement and more unmet needs are identified and addressed (Figure 1.1). The ecosystem has scientific, patient and caregiver, healthcare delivery,

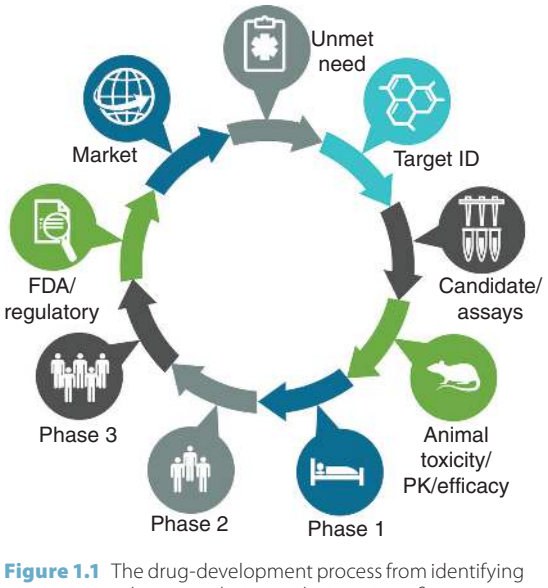

Figure 1.1 The drug-development process from identifying an unmet need to its resolution and reiterative refinement.

business/financial, advocacy, governmental, and policy dimensions that interact dynamically as the candidate agent progresses from molecule to market. Aducanumab is an example of the successful traversal of this complex process to success. Here we provide an overview of the steps in AD drug development and consider the complex multidimensional infrastructure that supports the process. We begin with a description of the phases of drug discovery and development, followed by the resources needed to advance the process including the funding. We end with a discussion of how the process might be improved.

1.2 Alzheimer's Disease Drug Discovery and Development

1.2.1 Overview of Drug Discovery and Development

Development of a new drug begins with identification of a target for treatment and progresses through development of assays for drugs that may modulate target-related processes, and assessment of the candidate(s) in relevant animal models for efficacy, toxicity, and pharmacokinetics (PK). Agents with desirable drug-like properties are then advanced to Phase 1 first-in-human (FIH) trials to assess PK, safety, and tolerability. Drugs with acceptable features in FIH trials are advanced to Phase 2 proof-of-concept (POC) and dose-ranging studies and then to Phase 3 if the Phase 2 studies suggest that the agent is efficacious and safe. If Phase 3 trials confirm efficacy, the drug is submitted for review to the FDA or other regulatory agencies [8]. A successful review results in marketing approval and the ability to make the agent available to patients and prescribing clinicians [8]. Figure 1.2 shows the elements of this process.

1.2.2 Target Identification and Drug Discovery

Common targets for DMTs in AD are processes that eventually lead to cell dysfunction and death [9, 10]. Targets for cognitive-enhancing agents and treatment for behavioral syndromes of AD commonly include receptors, enzymes, and ion channels. Targets must be "druggable" with properties that can be modulated by small molecules (e.g., drugs) or antibodies, or other biologicals such as antisense oligonucleotides, and other forms of gene therapy [11].

After a target has been identified, an assay with a reporter for interactions suggesting that candidate agents are modulating the target is developed and used to screen candidate therapies. Libraries of compounds are screened for "hits" that have the desired effects in the assay. These libraries are constructed from agents with similar structures and multiple molecular forms, traditional medications (e.g., Chinese traditional medications), natural sources (e.g., bark, seaweed, etc.), repurposed agents that may have AD-related effects, and compounds designed computationally *in silico* [12]. Several hundred thousand compounds may be screened to identify a sufficient number of hits for further development. The hits are reviewed by medicinal chemists for "drug-likeness" including features that predict good absorption and membrane penetration [13, 14]. Compounds with promising characteristics are optimized for molecular features that enhance the likelihood of success as a human therapy – potency, half-life, blood–brain barrier (BBB) penetration, etc. Once a lead compound and several backups are identified testing in animals can begin [15].

An alternative to high-throughput screening with mechanistic assays is high content analysis, conducted in intact cells using automated microscopy and image analysis. High content analysis can be used to screen for effects on protein aggregation, synaptic integrity, and neuron and synapse number or survival as well as other cellular processes relevant to AD treatment [16].

1.2.3 Non-clinical Assessment

Assessment of the lead candidate in animals establishes the PK characteristics, toxicity, and preliminary efficacy of the molecule. These studies may

Figure 1.2 Phases in the discovery and development of therapeutic agents.

be done in parallel with or following evidence of proof of mechanism in an animal model (discussed below). Testing involves both short-term and long-term treatment in a wide range of doses to establish the absorption, distribution, metabolism, excretion (ADME), and toxicity of the potential treatment [17]. Testing is required in at least two species – usually mice and rats. Dogs are sensitive to cardiac effects of drugs and are used to assess possible cardiac toxicity [18]. Laboratory and necropsy studies are performed to thoroughly assess any off-target adverse effects in the animals; special attention is paid to liver, cardiac, bone-marrow, and reproductive organ toxicity. Panels of enzymes, ion channels, and other biological mechanisms are used to search for unanticipated off-target effects of the candidate therapy [19]. If no unusual toxicity is identified, the highest drug dose level at which no adverse events are seen is determined and becomes the basis for dose calculations for the recommended safe starting dose for FIH studies [20].

Development of monoclonal antibodies (mAbs) differs from developing small molecules. Monoclonal antibodies are manufactured to interact with a specific epitope of a target such as a portion of amyloid beta protein (Aβ) or tau protein [21, 22]. Monoclonal antibodies have fewer risks for off-target effects since they are exquisitely targeted to specific molecular sites.

Animal species are used to explore the proof of mechanism of candidate therapies. Although success in animal models has not yet predicted success of a DMT in humans, failure to see the desired effect on AD pathology in an animal model system would make one hesitant to advance the agent to human testing [23]. The most commonly used animal model systems are transgenic (Tg) mice that carry one or more human genes known to cause familial AD. Anti-Aβ approaches can be tested in this model. Tau transgenic model animals as well as many types of gene knock-in (KI) and knock-out (KO) models are available. The National Institute on Aging (NIA) and the National Institutes of Health (NIH) Library have created a publicly available data repository of non-clinical/preclinical studies (AlzPED) that includes the available animal models of AD. The model animals exhibit specific aspects of the AD pathology but not the complex multifactorial AD process observed in humans [24].

Human-derived induced pluripotent stem cells are increasingly used to move the early drug screening process toward a more humanized biological context with the hope of having greater predictability for human responses [25, 26]. The induced pluripotent stem cell models show both Aβ and tau protein accumulation, recapitulating the human disease and creating a more ecologically valid system for drug efficacy studies [25].

1.2.4 Phase 1 Clinical Trials

Phase 1 clinical trials involve the FIH exposure of the drug. In small molecule development programs, the persons participating in the Phase 1 trial are healthy volunteers [27]. If a vaccine is being developed, the FIH testing is usually done with patients with AD dementia. Vaccines can permanently alter the immune system and the unknown consequences of this cannot be risked in young healthy individuals.

At the end of Phase 1, the maximum tolerated dose (MTD), human PK, preliminary drug safety and tolerability, and BBB penetration should be known [28]. Single ascending dose (SAD) studies where cohorts of individuals are exposed to progressively higher doses of the agent are followed by multiple ascending dose (MAD) studies where cohorts are treated for 14–28 days with increasing doses of the agent [29]. A cohort is typically 8–12 individuals randomized in a 4:1 ratio of active agent to placebo. In some MAD approaches, at least one cohort of elderly individuals is included to assess PK, ADME, and toxicity differences in older adults. Phase 1b or 1/2 programs may include cohorts of individuals with AD to gather preliminary information on the effects in patients with the disease state.

Ideally, an MTD is determined at this stage of drug development. Maximum doses can be determined by tolerability and safety limits, volume of administration limits, receptor occupancy studies which show that increasing the dose no longer increases occupancy of a positron emission tomography (PET) ligand, or PK studies that demonstrate that increasing the dose no longer increases the maximum serum concentration or area under the curve. Failure to establish an MTD/maximal dose in Phase 1 can lead to future challenges in the development process; if later trials are negative, it may be difficult to know whether the agent is ineffective or was not given in a sufficient dose [30].

Assessing cerebrospinal fluid (CSF) drug levels in Phase 1 is critical to establishing the candidate

compound's ability to penetrate the human BBB and exert central nervous system (CNS) effects. Treatments should not exit Phase 1 without evidence of BBB penetration and an understanding of plasma/CSF ratios.

1.2.5 Phase 2 Clinical Trials

Phase 2 generally encompasses Phase 2a POC trials and Phase 2b dose-determination studies. At the end of Phase 2, doses to be advanced to Phase 3, target engagement, preliminary information on biomarker or clinical responses, and insight into safety and tolerability in the population of interest should be available [28]. Phase 2 involves patients with AD dementia or prodromal AD/MCI due to AD [31]. The decision to advance an agent to Phase 3 may be based on a clinical outcome or on changes in a biomarker or repertoire of biomarkers considered likely to predict a clinical outcome (no biomarker is currently proven to predict clinical benefit). Alternatively, one can require clinical POC with benefit on a traditional clinical measure such as the AD Assessment Scale – cognitive subscale (ADAS-cog) [32] or Clinical Dementia Rating – sum of boxes (CDR-sb) [33]. Demonstration of clinical benefit typically requires a large long trial virtually equivalent to a Phase 3 trial [34]. Thus, some development programs move from Phase 1 directly to Phase 3, advancing an agent with limited information regarding safety, tolerability, biomarker effects, or dosing.

Biomarkers may be used as Phase 2 outcomes to support decision making for development programs [35]. Target engagement biomarkers are critical to demonstrating that the drug is having the desired pharmacological effect on a near-term target. Without evidence of target engagement, the potential disease-related biological impact of a putative DMT cannot be assessed [36, 37]. Examples of POC studies in AD drug development include demonstration of reduced Aβ production following administration of beta-site amyloid precursor protein cleaving enzyme (BACE) inhibitors or gamma-secretase inhibitors using stable isotope labeled kinetics (SILK) [38], reduced CSF Aβ with BACE inhibitors [39], and increased Aβ fragments in plasma and CSF with gamma-secretase inhibitors and modulators [40]. Candidate target engagement/proof-of-pharmacology (POP) biomarkers include peripheral indicators of inflammation and oxidation for use in trials of anti-inflammatory and antioxidant compounds. Demonstration of target engagement does not guarantee efficacy in later stages of development but provides important de-risking of a candidate agent by showing biological effects that may translate into clinical efficacy.

Populations in AD trials are typically characterized by ApoE genotype to identify the *APOE-4* allele carriers and non-carriers. *APOE-4* carriers have earlier onset of AD and progress more rapidly in the early phases of the illness. Allele status may affect efficacy and side effects and often influences dosing in mAb trials [41–43]. Trials are not typically stratified by genotype, but the statistical analysis plans compare carriers and non-carriers for efficacy and toxicity. Approximately, 65% of biomarker-confirmed AD patients are *APOE-4* carriers; if proportions are markedly lower in trials where biomarkers were not used to verify the diagnosis, the number of non-AD patients inadvertently included in the trial may be high.

Growing information on blood biomarkers suggests that measurement of the $A\beta_{42}/A\beta_{40}$ ratio and plasma levels of hyperphosphorylated tau ($p\text{-}tau_{181}$, $p\text{-}tau_{217}$), total tau, and neurofilament light chain (NfL) may be useful in screening populations for more advanced testing (e.g., Aβ PET imaging) and may eventually be sufficiently accurate to allow their use in diagnosis and trial enrollment. Their possible role in monitoring Aβ-targeted or tau-target therapies is being assessed.

Cognition is mediated by integrated cerebral circuits, and interventions to preserve neurons and synapses – mediated by anti-Aβ, anti-tau, or other mechanisms – will succeed to the extent that they preserve circuit function. Circuit integrity can be assessed by functional MRI (fMRI), quantitative electroencephalography (QEEG), magnetoencephalography (MEG), or fluorodeoxyglucose (FDG) PET [44, 45]. Neurogranin, synaptotagmin, and synaptophysin are synaptic proteins that may represent CSF biomarkers of circuit involvement. These circuit measures can assess the impact of treatment on circuits and may better predict or correlate with the outcome of either cognitive-enhancing agents or DMTs [46].

Biomarkers are used to confirm the diagnosis of AD. The clinical diagnosis of AD dementia based solely on the phenotype of amnestic dementia is not confirmed by Aβ PET or CSF amyloid and tau measures in approximately 25% of patients [41], indicating that they do not have the

pathobiology of AD. Approximately 50% of MCI patients have abnormal Aβ measures and constitute a prodromal AD population; 50% do not have early AD [47]. AD trials must be comprised of individuals with AD to draw accurate conclusions about efficacy of AD-directed therapies.

MRI is a measure of cerebral atrophy and neurodegeneration. It is used in DMT trials to assess effects on neuronal loss but the results have often been counter-intuitive with greater atrophy in patients for whom other evidence suggests a treatment benefit. MRI is used to monitor amyloid-related imaging abnormalities (ARIA) occurring as a side effect in patients treated with some anti-Aβ mAbs [42]. Other biomarkers commonly used to monitor adverse effects of medications include liver functions, hematological measures, and electrocardiography (ECG).

1.2.6 Phase 3 Clinical Trials

Phase 2 and Phase 3 are often conceived as "learn" (Phase 2) and "confirm" (Phase 3) trials [48]. The learnings of Phase 2 are tested in Phase 3 and, if benefits are confirmed, the agent will be submitted to the FDA for review. Phase 3 trials for DMTs are 12–24 months in duration and typically involve 600–1,000 patients per arm of the study (doses and the placebo comprise 1 arm each). Prevention trials of individuals without cognitive symptoms may be up to 5 years in duration.

1.2.6.1 Phase 3 Trial Populations

Clinical trials in Phase 3 may include preclinical populations of participants with no cognitive symptoms but genetic or biomarker evidence (Aβ PET; CSF amyloid or p-tau changes) of high risk for developing symptomatic AD; prodromal AD populations comprised of participants with MCI and biomarker evidence of AD; or AD dementia with participants exhibiting mild, moderate, or severe AD [8, 49].

The FDA has provided guidance for trials involving early AD – those in the preclinical and prodromal phases [50] (Figure 1.3). FDA Stage 1 describes individuals with positive biomarkers of AD pathophysiology and no symptoms detectable

Stage 1	Stage 2	Stage 3	Stage 4,5,6
Preclinical AD	Preclinical AD	MCI due to AD/ prodromal AD	Mild, moderate, severe AD dementia
Cognitively normal	Subtle cognitive abnormalities	Cognition abnormal	Cognition abnormal
Function normal	Function normal	Subtle functional decline	Function abnormal
Full approval: Longer study shows effects on sensitive cognitive measures (those used in Stage 2)	Persuasive effect on cognitive measures; large magnitude effects or effects on multiple measures making the observations more compelling	Single clinical outcome approvable; effects on clinical and functional aspects of a composite need to be shown	Dual outcomes – cognition plus function or cognition plus global – required
Accelerated approval: Effect on characteristic pathophysiologic changes of AD thought reasonably likely to predict clinical benefit; pattern of effects across multiple biomarkers increases the persuasiveness of the putative effect	Cognitive effects reasonably likely to predict clinical benefit; plus effect on characteristic pathophysiologic changes of AD to add support for accelerated approval	Conventional strategies required (not accelerated)	Conventional strategies required (not accelerated)

Figure 1.3 FDA stages of Alzheimer's disease.

by even the most sensitive measures; Stage 2 individuals have positive biomarkers and cognitive symptoms that are detectable with very sensitive measures; Stage 3 is characterized by positive biomarkers, abnormal cognition and functional deficits detectable with only the most sensitive measures (this stage is traditionally known as MCI); Stages 4–6 are mild, moderate, and severe AD dementia. The FDA staging creates a framework for assessing treatments in very early AD with outcomes on sensitive measures (biomarkers or clinical assessments) or impact on progression to the next stage.

1.2.6.2 Biomarkers in Phase 3 Trials

Biomarkers are used in Phase 3 to diagnose participants, support disease-modifying activity, and to monitor ARIA in mAb studies. Biomarker evidence of less degeneration and more neuroprotection by the active agent suggests that the drug is a DMT [9, 51]. Biomarkers currently considered as indicative of disease modification in AD include volumetric MRI, FDG PET, CSF NfL chain and total tau, and blood NfL and total tau [52, 53]. Changes on Aβ PET, tau PET, or CSF or blood measures of Aβ protein or p-tau may contribute to the weight of evidence informing the understanding of drug activity and building a narrative for how the agent is achieving disease modification. Aβ and p-tau protein abnormalities are mediators of cell death and changes in these intermediate biomarkers are supportive but not definitive evidence of disease modification.

1.2.6.3 Clinical Outcomes in Phase 3 Trials

The standards for trials of patients with mild-to-moderate AD were created when tacrine – the first agent approved for the treatment of AD – trials were conducted, and these approaches have remained highly influential. The approval process is based on draft guidelines from the FDA of 1990 [54]. These guidelines require that anti-dementia agents show improvement on the core symptoms of AD – memory and cognition – and that the effect is clinically meaningful as shown by a significant drug–placebo difference on a global or a functional rating. Dual outcome requirements are the standard for both DMTs and cognitive enhancer trials for AD dementia trial populations.

New instruments have been added to the repertoire of tools available to assess different trial populations (Table 1.1). The CDR and CDR-sb are composites of cognitive and functional items that have become the standard global outcome for DMT trials [33]. In trials of prodromal AD, the CDR-sb may serve as a single outcome although regulatory authorities consider the contribution

Table 1.1 Clinical assessments commonly used in AD clinical trials

Population	Domain	Instruments
Preclinical (normal cognitive function)	Cognition	Preclinical Alzheimer's Cognitive Composite (PACC)
		API Preclinical Composite Cognitive (PCC) Test Battery
		DIAN-TU Cognitive Composite
	Function	Amsterdam Instrumental ADL scale
	Behavior	Neuropsychiatric Inventory (NPI)
		Mild Behavioral Impairment (MBI) Checklist
Prodromal	Global	Clinical Dementia Rating – sum of boxes (CDR-sb)
	Cognition	Neuropsychological Test Battery (NTB)
		Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
	Function	Amsterdam Instrumental ADL scale
		ADCS ADL scale (MCI version)
	Behavior	NPI
		MBI checklist

Table 1.1 (cont.)

Population	Domain	Instruments
Mild-to-moderate AD dementia	Global	CDR-sb
		Clinical Global Impression of Change (CGIC)
	Cognition	NTB
		ADAS-cog
	Function	Amsterdam Instrumental ADL Scale
		ADCS ADL scale
	Behavior	NPI
Severe AD dementia	Global	CDR-sb
		CGIC
	Cognition	Severe Impairment Battery (SIB)
	Function	ADCS ADL scale (severe)
	Behavior	NPI

ADCS – Alzheimer's Disease Cooperative Study; ADL – activities of daily living; API – Alzheimer's Prevention Initiative; DIAN-TU – Dominantly Inherited Alzheimer Network Treatment Unit; MCI – mild cognitive impairment.

of changes in cognition and changes in function to the total score change. The Neuropsychological Test Battery (NTB) has been shown to work well as an as an alternative to the ADAS-cog [55]. The Severe Impairment Battery (SIB) is most commonly used to assess cognition in patients with severe dementia [56]. The Neuropsychiatric Inventory (NPI) is the tool most commonly used to assess behavioral changes in trials of AD and other neurodegenerative disorders. Function is assessed with the Alzheimer's Disease Cooperative Study (ADCS) activities of daily living (ADL) scale [57] or the Amsterdam Instrumental ADL scale [58]. In some trials the Clinical Global Impression of Change (CGIC; or one of its variants) is used as a global measure instead of or in addition to the CDR. Measures of caregiver burden [59], quality of life [60], and resource utilization [61] are commonly included as outcome measures in Phase 3 trials in anticipation of payer discussions.

The emergence of prevention trials involving participants with normal cognitive function requires the use of tools that are very sensitive to small changes in cognition in older adults. Tools in this category include the Preclinical Alzheimer's Cognitive Composite (PACC) [62], Preclinical Composite Cognitive (PCC) Test Battery used in the Alzheimer's Prevention Initiative (API) [63], the Cognitive Composite of the Dominantly Inherited Alzheimer Network Treatment Unit (DIAN-TU) [64], and the European Prevention of AD (EPAD) Neuropsychological Examination (EPE) [65].

1.2.7 Phase 4 Clinical Trials and Post-marketing Studies

Phase 4 studies occur after a drug has been approved by the FDA or other regulatory agency and is available on the market. Regulatory agencies may request a risk evaluation and mitigation strategy to assess safety after marketing approval. Phase 4 studies may be used to extend treatment to a new indication or can be used to extend an indication within the same disease [66, 67]. These strategies comprise life-cycle management of an asset once it is approved. Phase 4 studies may be required to confirm efficacy in agents marketed on the basis of accelerated approval and effects on a biomarker.

1.3 Organization and Funding of the Alzheimer's Disease Drug-Development Ecosystem

1.3.1 Drug Discovery

No agent progresses from discovery in the laboratory to approval for marketing under the stewardship of a single individual or team. The skills sets

are too diverse and the financial infrastructure required too complex to be accommodated without a mosaic of stakeholders in an ecosystem of support [68].

Target identification begins with study of the neuropathology of AD where the key pathological aspects of AD are evaluated [69]. This type of research is typically conducted in university settings funded by the NIA of the NIH. Philanthropists and advocacy organizations with funding capacity such as the Alzheimer's Association play important roles in supporting basic research directed at the biology of AD. Within the pathology of AD, there are an array of possible drug targets. These are captured in the Common Alzheimer's Disease Research Ontology (CADRO) (https://iadrp.nia.nih.gov/about/cadro) (Table 1.2).

Once a target has been identified, assays are developed, and libraries screened for "hits" that begin the process of developing a candidate agent. This type of screening is done in academic laboratories, biotechnology companies, and pharmaceutical companies. Over the past 10–15 years there has been a shift in pharmaceutical company strategy away from being vertically organized, end-to-end discovery-to-marketing organizations to focusing more on late-stage compounds and Phase 3 opportunities. This shift has been accompanied by an increased emphasis on partnering with academic medical centers (AMCs) and biotechnology companies [70–72]. Products of value in collaborations between biopharmaceutical companies and AMCs include information exchange and intellectual growth, drug candidates, new technology and laboratory processes, data, and biomarker development. Clinical trials are often conducted in AMCs and provide another conduit for collaboration. Academic trainees become familiar with the pharmaceutical industry, an experience that diversifies career choices for them [73]. Independent confirmation and validation of studies performed in academic laboratories are required before investments are made in a promising agent. The Academic Drug Discovery Consortium (ADDC) (www.addconsortium.org) facilitates information exchanges among AMCs with drug discovery programs [74].

Table 1.2 CADRO summary of possible therapeutic targets or treatment of AD

Amyloid beta	Tau	ApoE, lipids, and lipoprotein receptors
Neurotransmitter receptors	Neurogenesis	Inflammation
Oxidative stress	Cell death	Proteostasis/ proteinopathies
Metabolism and bioenergetics	Vasculature	Growth factors and hormones
Synaptic plasticity/ neuroprotection	Gut–brain axis	Circadian rhythm
Environmental factors	Epigenetic regulators	Multi-target
Unknown target	Other	

Source: https://iadrp.nia.nih.gov/about/cadro.

Pharmaceutical companies have active landscape surveillance teams searching for promising emerging compounds that can be licensed, purchased (the compound or the company), partnered, or acquired through merger [75]. Some biotechnology companies specialize in performing assay and screening activities and may create libraries of compounds that can be purchased for further development. Some larger biotechnology companies can escort a compound from early-stage development to later-stage trials. Biopharmaceutical "deals" consist of upfront payment and have risk reduction strategies such as milestone payments that depend on satisfactory progress of the asset. Shared governance is common with assumption of some degree of oversight of the biotech by the pharmaceutical partner with participation in the board of the biotechnology company. Biotechnology companies may be able to take advantage of the partner's expertise in regulatory, legal, commercialization, operations, manufacturing, clinical and medical affairs, and drug safety and pharmacovigilance.

Biotechnology companies typically begin as "spin-offs" from academic programs. The "start-up" focuses on a single product and accesses federal funding through the Small Business Innovation Research (SBIR) program, angel investors, philanthropists, or friends and family investors. Success may attract venture capital that allows the development of the asset to the level where it may attract interest from another biotech, a pharmaceutical company, or larger-scale venture capital investments. Venture capital may come from general funds, funds that specialize in biomedical and life science areas, or dementia-specific funds that specialize in dementia-related investments (e.g.,

Dementia Discovery Fund, Dolby Ventures, LSP Dementia Fund).

Compounds may languish from lack of support in the early stages of development. Once a compound has been shown to be efficacious in animals, its promise can by explored and eventually realized only if it can be tested in humans. The cost of Phase 1 studies is substantial (~$1,000,000 to $2,500,000) per agent. The studies are typically conducted in healthy volunteers and focus on safety, tolerability, and PK. The information gained in Phase 1 is essential for advancing an agent further, but because it tends to be "recipe like" and does not provide information on treatment of a diseased population, it is often difficult to fund. This creates the "valley of death," where promising agents may not be advanced because of lack of funding, expertise, and infrastructure [76, 77]. Difficulty with fundraising may extend to early Phase 2 testing prior to the generation of disease-related information and beginning clarification of the commercial promise of the agent. Funding agencies have realized and responded to this challenge and support for very early-stage development is increasingly available through the NIA, National Center for Advancing Translational Science, and philanthropic organizations such as the Alzheimer's Drug Discovery Foundation (ADDF) [78, 79].

1.3.2 The Alzheimer's Disease Neuroimaging Initiative

The Alzheimer's Disease Neuroimaging Initiative (ADNI) began in 2004 as a public–private partnership between the NIA and more than 30 private (e.g., pharmaceutical) and not-for-profit enterprises. ADNI has a trial-like structure and was designed to collect brain imaging and biomarker data that could be used to understand the natural history of AD and to model trajectories relevant to planning clinical trials. ADNI has enrolled approximately 325 cognitively normal controls, 425 participants with MCI, and 215 participants with mild AD dementia. Biomarkers collected at 6-month intervals include MRI (structural, diffusion, perfusion, resting state), amyloid PET, tau PET, FDG PET, and genetic and autopsy data. CSF (for measures of Aβ, tau, p-tau, and other proteins) is collected annually. All participants have cognitive and clinical assessments with commonly used clinical trials instruments (Mini-Mental State Examination [MMSE], ADAS-cog, CDR, Everyday Cognition [Ecog], NPI Questionnaire [NPI-Q], and others). Data are collected at 60 participating sites and added to a publicly available database in real time. Trial-like site monitoring and data management ensure data quality.

Among its most important contributions has been ADNI's provision of data to trials sponsors which can be used to model clinical trials and determine necessary sample sizes. Sample sizes for different populations using different clinical instruments have been calculated [80], and the utility of biomarkers, genetic assessments, and MRI atrophy measures in identifying patients with MCI likely to progress to AD dementia has been demonstrated [81–83].

ADNI has worldwide collaborators including ADNI-like organizations in Europe, Japan, Australia, Korea, and Argentina [84]. The similarity of the participants recruited in different global regions has been assessed and the feasibility of using data from different regions shown [85]. Most late-stage trials require globally distributed sites to achieve adequate recruitment, and the baseline features of participants in non-Western countries vary [86, 87] making global data valuable for trial planning.

1.3.3 The Dominantly Inherited Alzheimer's Network – Treatment Unit

The DIAN is an international multi-site study characterizing early clinical and biomarker changes occurring in persons inheriting autosomal-dominant AD (ADAD) mutations. All subjects in the DIAN are either affected by or known to be at 50% risk for inheriting pathogenic presenilin 1 (*PSEN1*), amyloid precursor protein (*APP*), or presenilin 2 (*PSEN2*) mutations. Washington University (St. Louis, Missouri, USA) is the lead site (John Morris, Principal Investigator) and there are 19 participating sites in eight countries recruiting and assessing ADAD participants.

DIAN-TU leverages the existing infrastructure of the ongoing DIAN longitudinal study and builds on important DIAN baseline and rate-of-change data. DIAN-TU has a platform trial design that can introduce new candidate treatments sequentially as each is shown to be effective and matriculates to other studies or is shown to be ineffective and is discontinued. DIAN-TU is led by Randall Bateman of Washington University. Governance is by a steering committee comprised of clinical trial experts, regulatory advisors, and ADAD family-member

representatives. Funding for the DIAN-TU is provided by the NIA, Alzheimer's Association, and the DIAN Pharma Consortium. The Pharma Consortium was created by the DIAN-TU and collaborating pharmaceutical companies to provide funds, expertise, and drug candidates for the platform [88].

The DIAN-TU platform was initiated as a randomized, blinded, placebo-controlled four-arm trial with a target of 160 asymptomatic to mildly symptomatic mutation carrier participants who are −15 to +10 years of their estimated age at onset of AD dementia [88]. A pooled placebo group derived from the placebo arm for each agent greatly increases efficiency and enhances the participant's likelihood of receiving the active drug compared with traditional designs; this makes participating in the trial more attractive to potential volunteers.

DIAN-TU has introduced innovations including construction of a disease progression model (DPM) to detect changes in cognition with fewer participants, self-administered cognitive testing, a predefined dose escalation algorithm to safely maximize target engagement, adaptive trial design strategies that include both early biomarker and later cognitive interim analyses to inform early efficacy or futility, and novel biomarkers [64].

1.3.4 Alzheimer's Prevention Initiative

The API, led by researchers from Banner Alzheimer's Institute (BAI; Drs. Reiman, Tariot, Langbaum) in partnership with leaders from academia, industry, and other public and private stakeholder organizations was initiated to accelerate the evaluation and approval of prevention therapies. The API ADAD Colombia trial is studying the use of an anti-amyloid treatment – crenezumab – in cognitively normal *PSEN1* mutation carriers and non-carriers from the world's largest ADAD kindred [89]. Mutation carriers are at virtually certain risk for developing AD at young ages. The study is conducted in conjunction with the University of Antioquia in Colombia and Genentech/Roche.

The API Generation Program aims to prevent or delay the onset of symptoms associated with AD in cognitively healthy people with two *APOE-4* alleles, making them at particularly high risk for developing the AD [90]. These studies are part of a collaboration between BAI, Novartis, Amgen, and the NIA. The API has pioneered new cognitive assessments for cognitively normal individuals at risk for AD [91] and developed innovative approaches to genetic counseling [92].

1.3.5 European Prevention of Alzheimer's Disease

The EPAD project, funded by the Innovative Medicines Initiative (IMI), was established to overcome the major hurdles hampering drug development for secondary prevention of AD [65, 93, 94]. EPAD is led by Craig Ritchie at the University of Edinburgh and trial delivery centers throughout Europe participate in the consortium. EPAD incorporates several drug-development innovations: collaborative access to existing European cohorts and registries; development of the EPAD Registry of people at increased risk of developing AD dementia; establishment of the EPAD Longitudinal Cohort Study (LCS) to serve as a trial-ready cohort for POC studies; and establishment of an adaptive, POC trial platform. In addition to providing patients for trials, the LCS provides run-in data for the pre-randomization period in the EPAD POC study, gathers longitudinal data for AD modeling of probability of decline, and generates models that place individuals on the disease probability spectrum [93].

The EPAD POC study emphasizes biomarker effects of candidate agents, but success in the EPAD POC study requires the demonstration of clinical benefit. Drugs deemed successful in the POC study will, therefore, be more likely to achieve clinical and regulatory success in Phase 3. The POC study employs a Bayesian adaptive design that learns from data accrued as the trial progresses. Frequent interim analyses, done in accordance with predefined algorithms and blinded to all trial personnel, allow adaptive randomization of individuals to interventions that appear to show the greatest clinical efficacy, and, potentially, in subpopulations defined by clinical status, biomarkers, or genetics. These interim analyses are used to test for early signals of drug success or futility [93]. The trial design utilizes a shared placebo group to minimize the number of participants assigned to placebo without compromising trial integrity. EPAD has structured involvement of participants as collaborators recognizing the participants' key role [95]. Participant panels establish accountability and transparency between the study goals and the study population, provide an opportunity for researchers to respond to participants' concerns, and create a conduit for