Dementia disorders are characterized by clinicopathological criteria. Molecular understandings of these disorders, based on immunohistochemical studies, biochemical investigations, genetic approaches, and animal models, have resulted in advances in diagnosis. Likewise, translational research has allowed us to apply our increasing basic scientific knowledge of neurodegeneration to the rational development of new investigational therapies based on our current understanding of disease pathogenesis. This review discusses the application of translational research to both diagnosis and treatment of dementia disorders. The development of biomarkers has yielded imaging and biochemical methods that assist the physician more than ever in the diagnosis of neurodegenerative dementias, especially Alzheimer disease. New diagnostic criteria for disease are based on these molecular-based techniques. And these biomarkers are of potential use in monitoring disease activity during therapeutic trials. Translational investigations likewise have led toward new avenues in targeted dementia research. This is particularly so in the development and testing of disease-modifying treatments that might slow or deter progressive deterioration. Recent clinical trials have not been based on empirical trials of established drugs but, rather, on trials of drugs shown, through experiments in biochemical, cell culture, and animal models, to interfere with known elements of the pathogenetic cascade of Alzheimer disease.

Dementia is defined as a disorder manifest by loss of mental capacity affecting a person’s ability to function. Dementia affects more than 6 million Americans today, most of whom are elderly. Dementing disorders were at one time viewed as of psychiatric origin in the younger population and of “senile” derivation (ie, a consequence of aging) in the elderly. There was little hope in treating either of these. Translational research has emerged as a dominant driving force in both diagnostic and therapeutic advances in dementia. Multidisciplinary research efforts allow for basic knowledge, whether obtained in the laboratory through in vitro investigation, experimental animal science, or neuropathological studies, to be applied to the development of diagnostic techniques or disease-directed specific therapies. Translational research is bidirectional, with clinical data often informing or influencing basic studies, and allowing in turn further development based on basic research of clinically applied methods.

Categorization of the dementias as clinicopathological disorders started in earnest in the early 20th century with modern neuropathology, in conjunction with careful clinical studies. Neurodegenerative diseases include Alzheimer disease (AD), Lewy body dementia, frontotemporal dementia (FTD), corticobasal degeneration, progressive supranuclear palsy,
vascular dementia, Huntington disease, and Creutzfeldt-Jakob disease. Clinical neuropathology, with classical staining techniques, did provide the original basis for identifying these disorders. However, our increasing molecular understanding has sharpened the differentiation of these diseases. The use of immunochemical assays has allowed us to categorize dementias by molecular typology (Table 1). This has been supplemented by the identification of genes leading to specific dysfunctions. Alzheimer disease is most uniquely characterized biochemically by the accumulation of Aβ in plaques and vessels, with concomitant intracellular accretions of tau. Lewy body dementia shares with Parkinson disease the accumulation of abnormal α-synuclein aggregates. About half of the cases of FTD, together with cases of progressive supranuclear palsy and corticobasal degeneration, may be grouped as disorders marked by deposits of abnormal tau. Other degenerative dementias are characterized by abnormalities of TAR DNA-binding protein 43 (TDP-43), fused in sarcoma protein (FUS), huntingtin protein, prion protein, and other proteins (Table 1). The identification of the specific cellular proteins prominently involved in these neurodegenerative disorders has led to in vitro and rodent models, which have been used for probing disease pathways, and to the promise of directed, rather than empirical, therapeutic trials.

The dementing disorders of adults are age-dependent, with generally increasing incidence in the later decades of life. The 3 most frequent pathologies are AD, Lewy body dementia, and vascular disease abnormalities. Two or more of these pathologies commonly coexist in the same individual. It is unclear whether this is simply coincidental, evidence of a shared diathesis, or indicative of an interaction between the pathobiologic cascades of these diseases. In addition to those millions of Americans with dementia, there are larger numbers of individuals who have cognitive impairment of insufficient severity, extent, or functional consequence to meet criteria for dementia. This state is most often called mild cognitive impairment (MCI). Most of these persons are actually experiencing the earliest stages of one of the dementia disorders already mentioned, most commonly AD, and thus this is also called “prodromal AD.” There are also those persons who have no symptoms at all but who may be at risk of developing MCI and dementia. These asymptomatic persons have preclinical disease and can be called pre-MCI. They would only be identifiable by biomarkers suggesting that, even without any symptoms, they show the earliest pathological molecular, cellular, or radiological changes suggesting the beginning stages of a dementing disorder that has not become symptomatic. Recent consensus work groups, sponsored jointly by the National Institute on Aging of the US National Institutes of Health and the Alzheimer Association, have utilized the increasing body of knowledge on molecular disease markers to formulate important new criteria, not only for AD but also for MCI and presymptomatic or preclinical disease. These criteria should allow for better definition of individuals who might be in the MCI or preclinical phases of dementia. The use of amyloid imaging to ascertain amyloid deposition in living persons and the use of a cerebrospinal examination to ascertain abnormalities in amyloid, tau, and phosphorylated tau are key techniques in the process. It is possible that the earlier identification of disease during prodromal periods may allow for more effective therapeutic intervention because the disease process could be prevented, interrupted earlier, or attacked before the onset of more irreversible changes such as neuronal cell loss. This review will principally focus on AD dementia and its precursor stage MCI, because AD is responsible for more than 80% of cases of dementia in the elderly.

Major advances in dementia over the past decade have transpired involving both diagnostic and therapeutic areas. These advances spring from the increasingly diverse number of biochemical and microscopic techniques, genetic analyses, and ensuing cell culture, mice, or other model systems. Diagnostic accuracy has increased through the translation of knowledge of molecular pathogenesis to the development of biomarkers and genetic markers assisting in diagnosis, even prior to symptoms. The number of therapeutic trials have increased rapidly because the elucidation of the biochemical pathways, together with the ability to test interventions in model systems, has led to rational drug trials, rather than nonspecific or more arbitrarily chosen empirical trials of established substances, that have had an effect on accumulating disease burden. Herein, we will discuss the advances in transla-

Table 1. Molecular Classification of Dementing Disordersa

<table>
<thead>
<tr>
<th>Clinical Disorder</th>
<th>Protein</th>
<th>Term</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>β-Amyloid</td>
<td>β-Amyloidopathy</td>
<td>PSEN1, PSEN2, APP, APOE, others</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>Tau</td>
<td>Tauopathy</td>
<td>MAPT</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>Tau</td>
<td>Tauopathy</td>
<td>MAPT</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>TDP-43</td>
<td>TDP-43-opathy</td>
<td>TARDP, PGN, C9ORF72</td>
</tr>
<tr>
<td>Lewy body dementia</td>
<td>α-Synuclein</td>
<td>α-Synucleinopathy</td>
<td>GBA</td>
</tr>
<tr>
<td>Parkinson disease dementia</td>
<td>α-Synuclein</td>
<td>α-Synucleinopathy</td>
<td>SNCA, LRRK2, GBA</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>Prion protein</td>
<td>Prionopathy</td>
<td>PRNP</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>Huntingtin</td>
<td></td>
<td>Htt</td>
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</tbody>
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Abbreviation: TDP-43, TAR DNA-binding protein 43.

aNeurodegenerative dementing disorders are characterized by derangements in particular proteins, with characteristic deposition of abnormal proteins in neurons, glia, or brain extracellular space. In some diseases, there are co-pathologies. For example, Alzheimer disease is marked by abnormal deposits of both β-amyloid and tau. Various genes have been shown to be involved in these disorders, either through mutations with autosomal dominant or recessive inheritance, or through risk factors of polymorphisms or mutations.
Brain Atrophy as a Feature of Dementia

Neuropathological studies have shown that the losses of neurons, synapses, and white matter are accompaniments of dementia. These observations have translated into in vivo structural neuroimaging studies for the diagnosis and follow-up of dementia. Structural imaging, originally performed using computed tomography and then supplanted by MRI, has shown the value of measuring brain loss in dementia. Brains incur detectable volume losses due to synaptic and neuronal degenerative losses. These amount to a 1% to 2% change per year using various global measures of brain volume or ventricular volume, with somewhat greater volumetric changes in specific regional measures of hippocampal volume. Large-scale detailed longitudinal data from many hundreds of subjects have emerged as a result of the Alzheimer’s Disease Neuroimaging Initiative. These data have provided us with a much better understanding of the rates of structural atrophy and of how these relate to normal aging, the conversion of MCI to AD, and the progression of AD. It is now commonplace for local radiologists to include the diagnostic possibility of AD after reviewing images with marked mesiotemporal atrophy. For clinical trials, longitudinal measurements of brain volumes are now frequently incorporated because of their potential use in monitoring the effects of drug treatment.

Regional Variations in Clinical and Neuropathological Changes

Neuropathological and clinical changes are not diffuse, but are variably distributed in different dementias. Functional measures of brain activity have been valuable in the differential diagnosis. These include the nuclear medicine techniques of SPECT and PET. These methods have provided imaging of brain function through the measurement of functional surrogate agents mapping blood perfusion, and oxygen and glucose metabolism. These nuclear medicine studies provide “pattern” biomarkers allowing for a better distinction between disorders primarily affecting temporoparietal cortices (AD), parieto-occipital cortices (Lewy body dementia), and frontotemporal regions (FTD). Alzheimer disease prominently affects temporal cortices but also causes decreased activity in association cortices in frontal and parietal regions. Frontotemporal dementias typically are marked...
by decreased brain activity in frontal and anterior temporal regions. Lewy body dementia is often accompanied by significant decreases in brain activity in parieto-occipital regions, with lesser affliction of frontal and temporal regions. These patterns may correlate with the clinical symptomatology, but have added biomarker value for assisting in the differential diagnosis of dementing disorders. However, there remains uncertainty regarding the interpretation and specificity of these imaging patterns. Functional MRI (fMRI) may provide even less invasive measures of brain function than nuclear medicine imaging.

**Imaging of Specific Molecular and Neurochemical Changes**

Specific molecular and neurochemical changes mark each dementia, and, in a revolutionary fashion, neuroimaging can identify such changes through use of specific ligands. In the research sphere, the use of Aβ-binding agents has provided the means to visualize early evidence of plaques in the living brain. The first agent to be widely used, the carbon 11–radiolabeled agent BTA or Pittsburgh Compound B, has been handicapped by the need for a cyclotron near the PET imaging center, but fluorine 18–radiolabeled agents, including flurbetapir (AV-45), flurbetaben (BAY-949172 or AV-1), and flutemetamol, have now achieved wide use in research studies. The Alzheimer’s Disease Neuroimaging Initiative studies, funded through a partnership between the National Institutes of Health and industry, have shown the ability, even in different centers using different imaging instruments, to reliably detect amyloid binding. A very high percentage of cases of clinical AD, and essentially 100% of cases of pathologically proven AD, show amyloid binding through PET imaging techniques using these agents. Similarly, persons with MCI who progress to AD generally show evidence of amyloid deposition by amyloid PET imaging. However, amyloid binding seen on PET scans also occurs in a moderate percentage (20%-40%) of persons with normal cognition, depending on age. The favored implication of this finding is that persons with such ligand binding are at the beginning, asymptomatic, stage of AD, which might become manifest at some later age. Imaging findings have now been incorporated into the new clinical criteria for AD, MCI, and presymptomatic AD. Because clinical drug trials are aimed at interrupting AD at the earliest stage, these trials may increasingly demand evidence of amyloid binding by PET as an eligibility criteria to increase the homogeneity and accuracy of diagnosis. In one recent European trial that did not use amyloid binding as an eligibility factor, nearly 20% of subjects entering the trial with clinically probable AD had no significant amyloid binding, which suggests a likely erroneous diagnosis of AD in those cases.

Molecular Brain Changes Reflected in CSF

Molecular brain changes are also discernible through analysis of CSF. Obtained through generally painless lumbar puncture, CSF contains brain proteins that are shed into the surrounding fluid and that are increasingly the subject of analysis. Alzheimer disease is associated with certain hallmark changes in the CSF, including reduction of Aβ42. It has been proposed that there is a lower concentration of Aβ42 in the CSF of patients with AD owing to deposition in the brain parenchyma; however, there is a decreased level of Aβ42 in various other non-AD disorders. An alternative explanation of low CSF levels is that a decreased level of Aβ42 relates to decreased brain synaptic activity. Tau protein is elevated in the CSF of patients with AD, but this finding is non-specific. An increased CSF tau level presumably reflects increased neurodegeneration, with the release of this intraneuronal cytoskeletal protein. An increased CSF phosphorylated tau (P-tau; particularly, tau phosphorylated at the 181 position) is a more specific hallmark of AD, related to increased phosphorylation of tau in AD. Because each of these biomarkers in isolation is not highly specific, combinations of biomarkers, such as ratios of Aβ42 to tau or other indices (such as the amyloid tau index, ATI = Aβ42/[240 + (1.18 × tau)]), have had particular utility in diagnosis. Cerebrospinal fluid biomarkers have now been incorporated into the new clinical criteria for AD, MCI, and presymptomatic AD. Blood plasma or serum tests are increasingly sought and might ultimately provide the least invasive measure, but, to date, there has been less clear success in measurements of blood, whether by measures of specific markers, such as Aβ40 and Aβ42, or by changes in clusters of proteins, as revealed by proteomic analysis. Like amyloid-imaging, CSF biomarker profiles can be used to select individuals with molecular characteristics of AD for clinical trials and, potentially, may be used to monitor therapeutic efficacy. Decreased CSF levels of tau might be evidence of a decreased degree of neurodegeneration, and preliminary data in some drug trials (eg, bapineuzumab) have shown such change.

**Genetic Factors**

Genetic factors were discovered in the epidemiologic search for risk factors for dementia. Early-onset AD can be caused by genetic mutations in APP, the gene coding
for the β-amyloid precursor protein, or in PSEN1 or PSEN2, the genes involved in the γ-secretase–mediated cleavage of APP to Aβ42 (Table 1). Late-onset AD is associated with the presence of the APOE gene ε4 allele, which conveys significant risk for AD: about a 2-fold risk for 1 copy and a more than 4-fold risk for 2 copies of this allele compared with individuals with no ε4 alleles. Overall, for persons aged 55 to 75 years in the US population, only about one-third of the general population has an ε4 allele, but about two-thirds of those with AD have 1 or more ε4 alleles. Although the presence of an ε4 allele has not been proven to alter disease course or prognosis, it is increasingly clear that there may be differential sensitivity to drug therapy efficacy or side effects in those with vs without an ε4 allele. Several studies have suggested an effect of ε4 allele on efficacy (eg, on donepezil in MCI), although this may relate to diagnosis, on rosiglitazone in AD (although subsequent studies have not confirmed any effect of this drug), and on bapineuzumab in AD, although this may relate more to side effects. Although definite effects of APOE are not proven in efficacy data, it is reasonably clear that having the APOE ε4 allele is a risk factor for the adverse effect of amyloid-reducing therapy; this adverse effect was originally called \textit{vasogenic edema} but is now called ARIA, standing for \textit{amyloid-related imaging abnormality}. There is a markedly increased risk of this radiologic brain change, which may or may not be symptomatic in persons with APOE ε4 alleles. This observation is responsible for the protocol in which treatment is stratified by genetic background in the bapineuzumab phase 3 studies, in which individuals without ε4 alleles are eligible for higher doses of drug than those with ε4 alleles.

The results of recent genetic analytic studies have shown that there is an increasing number of gene families for which polymorphisms might increase the genetic risk of late-onset “sporadic” AD. These genes include members of protein processing, membrane or cholesterol production, and immune/inflammatory pathways (\textit{SORL1}, \textit{CR1}, \textit{PICALM}, \textit{CLU}, \textit{MS4A4}, \textit{CD2AP}, \textit{CD33}, and \textit{EPHA1}). Although variations in these genes appear to be responsible for only small fractions of the risk of AD, the genetic findings make it likely that newly identified pathways could be addressed by drug treatment strategies.

For Parkinson disease, there are likewise genes that are relatively informative of inherited disease, whether autosomal dominant (eg, \textit{SNCA} and \textit{LRRK2}) or recessive (eg, \textit{PARK2}, \textit{PARK7}, and \textit{PINK1}), and those that may convey risk (\textit{UCHL1}, \textit{SNCAIP}, and \textit{GBA}). In particular, GBA may provide risk of dementia in Parkinson disease or Lewy body dementia. There are now several autosomal dominant genes known to convey risk of FTD, including \textit{MAPT} (tau), \textit{GRN}, \textit{CHMP2B}, \textit{VCP}, and \textit{C9orf72} (Table 1 and Table 2).

**TRANSLATIONAL RESEARCH IN THERAPY FOR AD**

Therapies for dementia may be divided into symptomatic therapies for secondary symptoms, disease-specific symptomatic therapies, and disease-modifying therapies. Secondary symptoms of dementia are clinically important and include agitation, aggression, hallucinations, delusions, depression, and incontinence. Although these symptoms can be refractory to present treatments, the neurotransmitter-based medications, including neuroleptics, antidepressants, anxiolytics, and antispasmodic drugs, have been valuable; however, the adverse effects are sometimes limiting.

**Symptomatic Therapies for AD**

These were first developed after the recognition of the particular cholinergic deficit in AD. Drugs causing increased brain acetylcholine, through acetylcholinesterase inhibition, were studied. The first such drug was tcarine hydrochloride, which became available in 1993. Three additional cholinesterase inhibitors have been developed successfully for clinical use. Donepezil hydrochloride, galantamine hydrobromide, and rivastigmine tartrate have been shown to be of modest symptomatic benefit in AD. Following the development of these drugs, memantine, an activity-dependent glutamatergic N-methyl-D-aspartate receptor antagonist, was demonstrated to have modest symptomatic benefit in persons with moderate to severe AD. However, none of these 5 neurotransmitter-based drugs, labeled by the US Food and Drug Administration for use in AD (four acetylcholinesterase inhibitors and one N-methyl-D-aspartate glutamatergic receptor antagonist), provide more than a modest symptomatic benefit for patients with AD. And these drugs do not appear to modify the molecular pathology or clinical course of patients with AD. Investigations of other drugs that involve different neurotransmitter systems, as well the use of intranasal insulin, are ongoing.

**Disease-Modifying Therapies**

Because established therapies do not actually modify disease course, the strongest focus of drug discovery for dementing disorders is investigations into agents that might alter disease progression through affecting basic disease pathophysiology. A variety of empirical trials of existing medications or natural substances, including various vitamins, fish oils, botanical compounds (eg, Gingko biloba), hormones (eg, estrogen), HMG-CoA reductase inhibitors, and anti-inflammatory agents, have suggested possible utility, but subsequent studies have proven inefficacy in the treatment of AD. Hence, it is translational medical science that most likely will provide advances in treatment of AD and the other dementing disorders (Table 3).

Pathological studies show that AD is marked by accumulation of β-amyloid protein in the brain in the form of plaques and by accumulation of hyperphosphorylated tau in the brain in the form of tangles. In vitro, animal model, and human genetic evidence all point to a centrality of β-amyloid in the pathophysiological cascade causing AD. Thus, many drugs in development have mechanisms of action based on either decreasing β-amyloid production (through inhibition of β-secretase or γ-secretase), increasing β-amyloid clearance (through active or passive immunization), or decreasing β-amyloid aggregation/fibrillization (Table 3).
INHIBITORS OF β-AMYLOID PRODUCTION IN AD

Aβ42 production can be inhibited by reduction of γ-secretase or β-secretase activities or by enhancement of α-secretase activity (Figure). Tarenflurbil (Flurizan; Myriad Pharmaceuticals, Inc), otherwise known as R-flurbiprofen, acts in vitro as a selective inhibitor of Aβ42 production both in vitro and in mouse models.39 This drug recently showed no effect on any efficacy or harm in a large phase 3 double-blind randomized placebo-controlled trial involving more than 2000 subjects.39 It is unclear whether this was because of a differing action in humans than mice, whether there was simply an insufficient dose or inadequate penetration into the central nervous system, or whether the putative mechanism of action did not occur in humans. Semagacestat (LY450139) is an inhibitor of γ-secretase that showed evidence of having an effect on amyloid production in vitro, in mice, and, demonstrably, in humans.36 However, a large phase 3 double-blind randomized placebo-controlled trial was recently stopped upon interim review because of evidence that subjects treated with the drug were doing less well cognitively than those treated with placebo.37 The reasons for these unexpected findings are unclear but might possibly relate to the changed balance of amyloid products, to insufficient overall inhibition of γ-secretase, or to “off-target” effects of this inhibitor on other cellular processes. Other γ-secretase inhibitors are under development, notably including avagacestat (BMS-708163), for which a phase 2 trial (http://www.dementiatoday.com/?p=3565) has been completed, and phase 3 development is reportedly planned. Inhibition of β-secretase also results in decreased Aβ42 production in animal models,38 and inhibitors of this enzymatic activity are under development. Enhancement of α-secretase activity by etretinate has been reported, and limited clinical trials of this agent have started.

THERAPIES TO INCREASE β-AMYLOID CLEARANCE IN AD

Active Immunization

Injection with β-amyloid peptide is efficacious in mouse models of AD: Aβ deposits in the brain are reduced,39 and memory function is improved in maze tasks.38 The first drug with this mechanism of action tried in humans was AN-1792, for which a phase 2 trial38 was halted prematurely owing to the occurrence of meningoencephalitis, which was symptomatic in about 5% of treated patients. Limited clinical data obtained from this study39 did not show efficacy, although a follow-up study40 did seem to show possible evidence suggestive of efficacy. Postmortem studies43,44 of some immunized individuals showed apparent evidence that immunization may have had the intended effect in those treated. Individuals who had a serological antibody response did show successful clearance of amyloid,43 and immunized individuals may have shown beneficial changes in abnormal neurites.44 The possibility that amyloid clearance was successful but was still accompanied by lack of clinical improvement or clinical deterioration has raised the issue of whether Aβ-removing strategies will indeed be successful.45 However, with such small numbers, with the lack of clarity as to the influence of subclinical adverse effects in treated patients, and with the lag from treatment to autopsy, it is not possible to reach any conclusions at this time. It is likely that the severe inflammatory symptoms from AN-1792 were related significantly to the immunological adjuvant. Experimental laboratory studies have led to the introduction of other forms of Aβ immunization, including different haptens and adjuvants, such as vanutide cridificar (ACC-001) and CAD-106, which are now being used in phase 2 trials. Such trials, as well as passive immunization trials, should result in data that may clarify whether amyloid reduction strategies will be effective in stabilizing, slowing, or, less likely, reversing AD clinical symptoms.

Passive Immunization

Passive immunization with antibodies to β-amyloid peptide has demonstrated efficacy in mouse models of AD. Bapineuzumab (AAB-001) is a humanized mouse monoclonal antibody to the N-terminal portion of β-amyloid. It has undergone a phase 2 trial40 and is now undergoing 2 large multicenter phase 3 trials, with more than 4000 patients being studied. Although the phase 2 trial40 did not meet the efficacy end points, there was clear evidence of radiological adverse effects, including vaso-
genic edema of the brain in apolipoprotein ε4 carriers, and suggestive evidence of a benefit from active treatment, particularly in noncarriers of the apolipoprotein ε4 allele. The phase 3 trial is ongoing in both carriers (at lower dose) and noncarriers of the ε4 allele. A different humanized mouse monoclonal antibody to the midportion of /H9252-amyloid, solanezumab (LY2062430), is also undergoing phase 3 trials, after phase 2 trials and cerebrospinal fluid testing showed encouraging biomarker changes. This antibody may act more to clear soluble /H9252-amyloid, although, secondarily, it may cause plaque clearance. Additional antibodies including crenuzumab and gantenerumab are also undergoing phase 2 trials (Table 3).

Nonspecific Immunoglobulin Therapy and Other Immunization Strategies

The success in mice of specific anti-β passive immunization prompted small human phase 1 and phase 2 trials of nonspecific human immunoglobulin intravenous therapy. Biochemical experiments have suggested that human intravenous immunoglobulin contains some polyclonal anti-β-amyloid antibody at low levels, and this would be one putative mechanism of action of human immunoglobulin preparations, if they indeed were shown to have beneficial effects in AD. Alternative mechanisms of action include modifying the immune response. A phase 3 trial of human immunoglobulin intravenous therapy is ongoing in mild to moderate AD. An alternative to immunization with protein or passive immunoglobulin administration has been the concept of DNA vaccination, in which injection of specific DNA in mice has led to decreased /H9252-amyloid in the brain.

THERAPIES TO INHIBIT β-AMYLOID AGGREGATION IN AD

Antifibrillation/Antiaggregation Agents

In vitro and animal model experiments have suggested that treatment with agents that might prevent the aggregation of β-amyloid might be effective against AD. The first such agent tested in a phase 3 trial, tramiprosate (also known as homotaurine), failed to show any efficacy in cognitive tests or first-order biomarker tests. The developer of that drug has discontinued the development of the molecule as a drug but has recharacterized it as a "medical food" (Vivimind; Bellus Health) marketed in Canada. However, evidence that it might be effective against AD is lacking. A different agent that appears to show promising preclinical results is ELN D005, also known as scyllo-inositol, which has now completed phase 2 testing and for which phase 3 testing is being planned.
THERAPIES TO PREVENT NEURONAL DEGENERATION IN AD

Agents That Might Inhibit Tau Dysfunction or Support Neuronal Integrity

Given the prominence of neurofibrillary degeneration in AD, it is reasonable to speculate about agents that might prevent the formation of the phosphorylated tau that aggregates into neurofibrillary tangles in the brains of persons with AD. In vitro and animal experiments have suggested that a variety of agents might deter the formation of tangles. Methylene blue (methylthioninium) was tried in a small phase 2 study but showed no clear efficacy. Taxol has been suggested to be of potential utility on the basis of animal studies, but its toxicity will likely preclude human trials. Davunetide, also known as AL-108, has been proposed, based on animal experimentation, to be of potential utility in AD, and a phase 1 trial has been performed. Growth factors might improve neuronal survival. The injection of the nerve growth factor (NGF) gene into the brain has been tried in a limited number of persons in a phase 1, proof-of-concept experiment. Since then, injections of DNA coding for brain-derived neurotrophic factor has been the subject of phase 1 experiments. Neuronal degeneration is marked by a number of final processes, including cell membrane breakdown, calcium influxes, caspase activations, and other cell-death pathways. Research continues on developing agents that might intervene beneficially at these more terminal steps of nervous system injury that occur in common in ischemic and neurodegenerative disease.

NON-AD DEMENTIAS

The biological underpinnings of dementia with Lewy bodies, FTD, progressive supranuclear palsy, corticobasal degeneration, and Creutzfeldt-Jakob disease are reasonably described, but the pathogenetic cascade of these non-AD dementias is less well understood than it is for AD. Thus, advances in diagnosis and therapy are in less advanced stages for these non-AD dementias. For FTD and related disorders, possible medications (including tau-dissruptive or neuronal supportive medications for the tau forms of this disorder) are under consideration, including AL-108, which is being tried in a phase 2 study of progressive supranuclear palsy. Likewise, memantine, which has neuroprotective effects in vitro, is being tried in a phase 2 study of FTD. Quinacrine hydrochloride has shown efficacy in vitro in deterring prion protein aggregation, leading to trials of this agent in Creutzfeldt-Jakob disease; to date, these limited trials have been without success. Even though our understanding of the molecular cascades of AD is limited, it is nonetheless more advanced than our understanding of the molecular pathologic underpinnings of these other neurodegenerative disorders. Thus, translational investigations leading to potential diagnostic or therapeutic methods for the non-AD degenerative disorders are lagging behind those for AD.

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