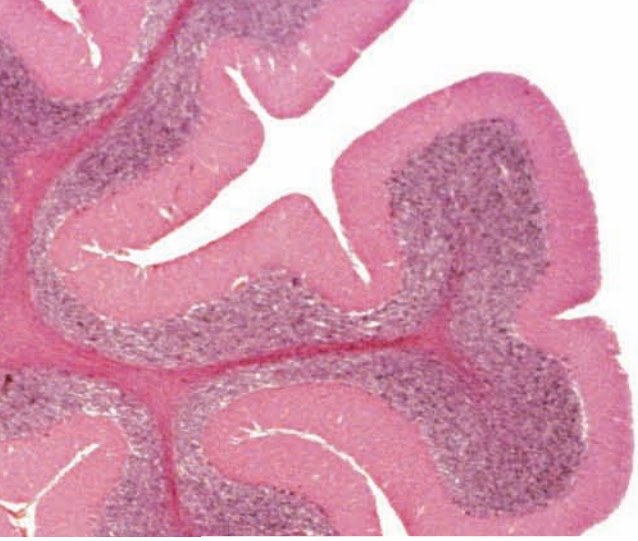

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Advancing Clinical Research in Alzheimer's Disease

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Executive Summary

Significant advances in basic science and clinical research over the past 2 decades have led to the recent re-evaluation of diagnostic criteria for Alzheimer's disease and the development of novel therapeutic strategies. There is now a clear desire to treat patients much earlier in the course of the disease, ideally before the first typical signs and symptoms begin to manifest, and to prevent the progression of the disease.

In this paper, Roza Hayduk, Lynne Hughes, and Amir Kalali evaluate the latest research findings on the diagnosis, treatment, and preventative care of patients with Alzheimer's disease and provide their insights into the impact of the findings on future clinical trials and medical practice.

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Introduction

Alzheimer's disease (AD) represents one of the most active areas of medical research with reportedly the largest drug-development pipeline compared with any other neurological disorder with the exception of pain.[1]

This flourishing arena for research is exemplified by data presented at the Alzheimer's Association International Conference on Alzheimer's Disease (ICAD 10), held July 10–15, 2010 in Honolulu, Hawaii.

Unifying themes of the research presented were:

- *The need to unravel the complexity of AD biology, with the hope that greater understanding of disease mechanisms will lead to earlier, preventative, and disease-modifying treatment options*
- *The identification of patients with preclinical or asymptomatic AD and reclassification of the disease*
- *The importance of an accurate diagnosis, with predictive genes, biomarkers, and improved imaging likely to play increasing roles in the future*
- *The development of novel, targeted therapies that will hopefully result in better patient outcomes*

Unraveling the biological complexity of AD

The neuropathology of AD is somewhat heterogeneous. While much has been learned about the possible underlying pathobiological causes of the disease over the years, the exact mechanisms responsible for the progressive deterioration in neurofunctioning remain elusive, and better understanding of the disease and its heterogeneity are, therefore, still required.[2]

To date, the most popular hypothesis under evaluation has centered on the role that beta-amyloid (Aβ) may play in the pathogenesis of AD[3] and there has been significant speculation about the mechanism by which Aβ may exert toxic effects.[4] The mechanisms underlying the production, transport, and clearance of Aβ have all been considered as potential drug targets. In particular, there has been growing interest in the role of β-secretase (BACE1) and γ-secretase in plaque formation, and inhibitors or modulators of these enzymes are in clinical development.[5]

However, considerable evidence now suggests that AD is most likely a multimodal and multi-component disease. With the failure, in development, of several drugs based on the amyloid hypothesis, it is likely that potential alternative drug targets will increasingly receive greater attention.[2] For example, hyperphosphorylation of the protein tau, and the development of neurofibrillary tangles are thought to be associated with neuronal cell death in AD, although the precise mechanisms remain unknown.[6,7] Several agents blocking tau are currently in development.[3]

In preclinical models of disease, the translocator protein (TSPO) has also been reported to cause neurotoxic inflammation and may be important.[8] Neurotoxic inflammation involves multiple factors, however, with many of these yet to be discovered.

With greater knowledge of the underlying disease mechanisms and the identification of further novel therapeutic drug targets, perhaps in specific populations, the goal of earlier and truly preventative treatment for this devastating neurological disease may ultimately be achieved.

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Identification of preclinical and asymptomatic AD

Aβ plaques are present in asymptomatic elderly individuals.

There is a growing consensus that people at risk of developing AD should be identified as early as possible, and ideally at least 10–15 years before any symptoms develop. This approach may allow the use of disease-modifying therapies at an earlier stage in the disease course than at present, when their use is likely to be most effective. Identifying patients earlier in the preclinical or asymptomatic stage is not without its difficulties, but may be possible in the near future considering Aβ plaques are present in asymptomatic elderly individuals, some of whom will go on to develop clinical AD.

Rate of decline in asymptomatic individuals with amyloid burden

Assessment of Aβ-positive and Aβ-negative normal elderly controls (NEC) (as assessed by imaging and CSF Aβ) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort has shown correlations between Aβ deposition and the rate of cognitive and functional decline. In a proof-of-concept, randomized study, Donohue and colleagues found that the rate of change in volumetric magnetic resonance imaging (vMRI) in both the hippocampus and entorhinal cortex at 2 years was highly significant in Aβ-positive versus Aβ-negative NEC.[9] Changes in cognitive and functional assessments were also significantly correlated with Aβ deposits.[9]

These data provide insight into the numbers of subjects that would be required to participate in a hypothetical 2-year, randomized, placebo-controlled study to detect at least a 50% reduction in amyloid-specific decline in Aβ-positive individuals with 80% power. According to the authors, 613 patients per arm would be required to detect changes using the Functional Assessment Questionnaire (FAQ), 279 per arm for the Mini-Mental State Exam (MMSE), and 187 per arm for vMRI.[9] This knowledge will be useful in the design of future proof-of-concept studies of disease-modifying agents in AD.

Genetic risk and screening for AD

Apolipoprotein (Apo) E4, the major known genetic risk factor for AD, is associated with a poor prognosis and rapid disease progression. The genetic basis of AD in up to 50% of individuals is unknown. However, numerous other genes have been identified and are under investigation. Many of these are already listed within the Alzheimer Research Forum AlzGene database (www.Alzgene.org), which provides a regularly updated repository for genetic association study data in AD.

Additional genes that may be associated with AD risk include *TOMM40* and *FTO. TOMM40* encodes a protein involved in the transport of proteins into mitochrondria and has been linked to the development of late-onset disease. Johnson and colleagues reported the findings of an imaging study looking at a variable-length poly-T repeat polymorphism (rs10524523) of *TOMM40* in 70 asymptomatic individuals at risk for AD.[10] Compared with shorter poly-T lengths, the presence of longer poly-T lengths was associated with lower gray matter volumes in regions of the brain typically affected early in the course of late-onset AD.

Further findings from the group, involving 726 middle-aged, symptomatic subjects, showed that the rs10524523 polymorphism was also associated with memory and learning capabilities.[11] These results suggest that it may be possible to use *TOMM40* allelic variations to stratify individuals according to their AD risk, at least in a clinical trial setting. Further research is required to confirm these early observations, and to determine the likely interplay between *TOMM40* and *ApoE4*.

The obesity-related gene *FTO* may also help to identify early those at risk of AD, according to research reported by Graff and colleagues.[12] They found that the *FTO* A-allele increased the risk for AD and, in subjects with *ApoE4,* the risk was doubled. Their data suggest that metabolic dysregulation is important in the development of AD.

Genetic testing, most likely for ApoE4 in the first instance, will no doubt become more useful as preventative treatments based on genetic risk status are developed.

While genetic screening for *ApoE4, TOMM40, FTO,* and perhaps other yet-to-be-discovered AD-risk genes may be useful in the future, no treatment options based on an individual's genetic risk for AD currently exist. Genetic testing, most likely for *ApoE4* in the first instance, will no doubt become more useful as preventative treatments based on genetic risk status are developed. The genetic testing of individuals at risk of AD raises various regulatory and ethical issues in some countries, however, which will need to be addressed before genetic screening for the disease could reach its full potential.

Re-evaluation of diagnostic criteria

Distinguishing between preclinical or asymptomatic AD and overt Alzheimer's dementia was a hot topic for discussion at ICAD 10 due to the recent re-evaluation of the 1984 NINCDS-ADRDA* criteria by the National Institute on Aging (NIA) and the Alzheimer's Association.[13] While these existing criteria have stood the test of time, advances in the field, such as improved understanding of the genetic risks, imaging methods, and neuropsychological techniques, have led to the need to review existing diagnostic recommendations.

Improved understanding of the genetic risks, imaging methods, and neuropsychological techniques has led to the need to review existing diagnostic recommendations.

The NIA and Alzheimer's Association convened three workgroups to look specifically at AD dementia, MCI due to AD, and the new category of preclinical AD (see box on next page), which reflects the recognition of the various disease states and need for the much earlier diagnosis and subsequent treatment of AD. First drafts of the groups' recommendations require further expert input before publication in a peer-reviewed journal and subsequent validation in a clinical trial setting. Currently, the revised criteria should be considered for research purposes only.

*NINCDS, National Institute of Neurological and Communicative Disorders; ADRDA, Alzheimer's Disease and Related Disorders Association (now the Alzheimer's Association).

Hot topic at ICAD 10: Diagnostic criteria redefined

Workgroup on AD dementia

> *The workgroup is revising existing criteria to include possible biomarkers and other assessments that may aid diagnosis.*

Workgroup on MCI due to AD

> *The workgroup is refining current criteria for MCI in AD, which will help indicate cognitive change before dementia and better differentiate MCI from AD. Biomarkers that may signal early cognitive deterioration and imaging methods are being evaluated for their ability to predict progression to AD.*

Workgroup on Preclinical AD

> *The workgroup aims to identify assessment methods that may help predict risk for developing AD. Biomarkers and other clinical assessment tools to identify early cognitive decline are being investigated to establish the presence of brain changes in asymptomatic individuals and identify those who may go on to develop AD.*

Further information available at http://www.alz.org/research/diagnostic_criteria/
Source: NIA/Alzheimer's Association

The definition of AD is important in clinical research. Regarding the new diagnostic criteria, Dr. Guy McKhann, Chair of the workgroup on AD dementia, stated that the workgroup has essentially retained the three categories, although the definitions have been modified (below).

> **Pathologically proved AD dementia,** *a diagnosis that requires patients to meet clinical and cognitive criteria for AD dementia during life and then have proven AD by pathological examination.*

> **Probable AD dementia,** *which includes patients who meet the clinical and cognitive criteria for dementia and do not have evidence of an alternative diagnosis (particularly cerebrovascular disease). In these cases, probability can be enhanced by a documented longitudinal decline, evidence of AD mutation, or positive evidence from biomarkers.*

> **Possible AD dementia,** *including those who meet clinical or cognitive criteria but for whom information on the course of progression is lacking (atypical course) or who are negative for biomarkers, or those who have a mixed presentation.*

> **Not AD dementia,** *defined as patients who do not meet clinical and cognitive criteria and who have sufficient evidence of an alternative diagnosis not concomitant with AD.*

Clinical research trials usually only include patients with probable AD, as defined above.

In clinical practice, diagnosis of AD is not 100% accurate and is therefore currently confirmed post mortem; this is likely to remain the case for the immediate future. With the identification of new predictive genes, biomarkers, and further refinement to imaging modalities, however, more accurate antemortem diagnosis may be possible.

Biomarkers for AD

The NIA–Alzheimer's Disease workgroups recognize the importance of biomarkers and that they may aid a diagnosis of AD. They broadly group biomarkers into the following four categories:

- *Biomarkers of Aβ pathology, such as the detection of amyloid via Pittsburgh compound B (PIB) positron emission tomography (PET) imaging. 18F-AV-45 also shows promise in phase III clinical development as a novel amyloid tracer in PET imaging.*
- *Biomarkers of neuronal injury, including levels of cerebrospinal fluid (CSF) tau and phospho-tau.*
- *Biomarkers of neuronal dysfunction, such as the decreased uptake of fluorine-18 fluorodeoxyglucose (FDG) on PET scans.*
- *Biomarkers of neurodegeneration, including the detection of brain atrophy on structural MRI scans, such as vMRI of the hippocampal and medial temporal lobe volume.*

Of these, data on the use of vMRI measurement of hippocampal and medial temporal lobe volume are increasingly compelling, with evidence that early, preclinical changes are indeed present in the brains of individuals at risk of AD. Biomarkers currently under evaluation for the diagnosis of AD are listed in Table 1.

Data on the use of vMRI measurement of hippocampal and medial temporal lobe volume are increasingly compelling.

Table 1. Biomarkers under investigation for AD diagnosis

Molecular neuropathology	> CSF Aβ-42 > CSF tau/phospho-tau > PET amyloid imaging
Downstream measures of structural change	> Hippocampal volume or medial atrophy volumetric measures or visual rating > Rate of brain atrophy > Diffusion tensor imaging, voxel-based, and multivariate measures*
Downstream measures of functional or metabolic change	> FDG-PET > SPECT perfusion imaging > fMRI activation studies, resting BOLD functional connectivity, MRI perfusion, MR spectroscopy
Associated biochemical change	> Inflammatory biomarkers > Oxidative stress (isoprostanes) > Other markers of synaptic damage and neurodegeneration (e.g. cell death)

*Less well validated than other biomarkers. CSF, cerebrospinal fluid; SPECT, single photon emission computed tomography; fMRI, functional magnetic resonance imaging; BOLD, blood oxygenation-dependent.
Source: NIA/Alzheimer's Association

Improved therapies for improved outcomes

Effective and earlier interventions in appropriately assessed and accurately diagnosed, pre-symptomatic individuals are required to improve patient outcomes in AD beyond what can already be achieved. The Aβ hypothesis of AD remains the central theme for the majority of current drug research, with novel immunotherapies, monoclonal antibodies, γ-secretase inhibitors or modulators (GSI/GSM), and vaccines under clinical investigation.

Early attempts at immunotherapy

The negative results from a trial of AN1792 (and others) raise the question as to whether the Aβ hypothesis constitutes the correct target for therapeutic intervention.

AN1792 was the first immunotherapy designed to provide active immunization against Aβ plaques. A subset of patients with raised antibodies to Aβ showed evidence that amyloid (and tau from cell processes) was removed from the brain when compared with control subjects with no Aβ antibody titers. However, there was no major impact on clinical progression of Alzheimer's dementia in these patients compared with the control arm, and AN1792-treated patients progressed and died at the same rate as controls.[14-16] A number of patients who were given the immunotherapy developed meningoencephalitis, which led to the subsequent discontinuation of this agent.[17]

The negative results from this trial raise the question as to whether Aβ constitutes the correct target for therapeutic intervention, or if the changes in Aβ content constitute manifestations after neurological damage is done. Nevertheless, other agents that target Aβ are in late-stage development, which may provide further insights as to whether this longstanding target should be re-evaluated, or perhaps targeted in combination with other factors.

New generation of anti-Aβ therapeutics

Solanezumab

Eli Lilly's solanezumab is a humanized monoclonal antibody targeted at the mid-domain epitope of the Aβ peptide. Currently in phase III development as a passive immunization treatment to slow the progression of AD by binding and clearing soluble Aβ, solanezumab is expected to have a good safety profile as very little, if any, of the drug is thought to cross the blood-brain barrier and the drug does not activate complement or cause encephalitis in the small number of patients exposed to the agent thus far. It is hoped that the intravenous immunotherapy will provide proof of concept for the Aβ hypothesis in patients with mild-to-moderate AD.

Two posters were presented on solanezumab at ICAD 10. Goto and colleagues reported data from a small (n=33), phase II, multicenter, randomized, open-label trial that showed solanezumab was well tolerated in Japanese patients, which is consistent with findings of a US study involving Caucasian and African-American subjects.[18] In the Japanese trial, patients with mild-to-moderate AD were randomized to 8 weeks of intravenous treatment with solanezumab 400 mg given once a week, once every 4 weeks, or once every 8 weeks. There were no on-study deaths reported, or treatment-emergent effects leading to discontinuation, and no evidence of meningoencephalitis or other serious adverse events related to the treatment. Most treatment-related effects, which included nasopharnygitis, diarrhea, and increased blood creatine phosphokinase, were mild to moderate.

Other data on solanezumab, reported by DeMattos and colleagues, highlighted the heterogeneity of amino-terminally truncated Aβ peptides in the brain and quantified a series of amino-terminally truncated Aβ42 peptides that accumulate in plasma after solanezumab treatment.[19] This opens the door for patterns of truncated or modified Aβ proteins to serve as a 'fingerprint' of AD central pathology.

Bapineuzumab

Another monoclonal antibody targeted at the Aβ peptide, this time at the N-terminal region, showing promise is bapineuzumab (Janssen/Pfizer). Phase II study results in 234 subjects suggested a possible effect of the drug in non-*APOE4* carriers. Bapineuzumab is currently in phase III development.[20,21]

lgVL2-t2E6 and lgVL-t5D3

Degradation of the Aβ plaque may be achieved by multiple mechanisms, and recent progress in immunotherapy has led to the development of catalytic antibodies that are targeted at Aβ degradation.[22] These antibodies exhibit proteolytic activity only when bound to Aβ and result in approximately 95% degradation of the peptide, in either its monomeric or aggregated forms. It is hypothesized that degradation of the peptide chains will be associated with an improved safety profile, attributable to the neutral effect the degradation has on existing cerebral amyloid angiopathy. Two antibodies that show particular promise at this stage are IgVL2-t2E6 and IgVL-t5D3. *In vivo* data suggest that these catalytic antibodies also prevent Aβ aggregation as well as degradation of pre-formed fibrils. *In vitro* findings suggest they have a significant effect on plaque clearance and Aβ degradation.

Ponezumab

Ponezumab (PF04360365) is another humanized IgGΔ2A monoclonal antibody that, like solanezumab, reduces Aβ burden in the brain by sequestering the peptide in the periphery (the peripheral sink hypothesis of plaque dissolution). However, unlike solanezumab, ponezumab targets the C-terminus of the Aβ1-40 peptide; thus, it will be interesting to see if the drug will cause encephalitis.

Several presentations on ponezumab, which is currently in phase II clinical development by Pfizer to delay disease progression in patients with mild-to-moderate AD, were made at ICAD 10 (abstracts O3-07-05, P1-440, P1-454, P1-459, P3-450).[23-27] These showed that pharmacokinetic and pharmacodynamic parameters have good dose proportionality across a 0.1 to 10mg/kg range, and that there is a dose-dependent effect on pharmacodynamic markers such as Aβ in the cerebrospinal fluid.

Semagacestat

Semagacestat (LY450139) is a GSI originally developed by Eli Lilly and Elan. No new data on this agent were reported at ICAD 10, although at the time of the meeting patient accrual into the IDENTITY (Interrupting Alzheimer's Dementia by EvaluatiNg Treatment of amyloId paThologY) and IDENTITY 2 phase III, randomized, double-blind, placebo-controlled clinical trials had been completed. In a recent announcement on August 17, 2010, Eli Lilly indicated that they will halt the development of semagacestat because preliminary results from these two trials have shown that the drug did not halt disease progression and was associated with worsening clinical measures of cognition and the ability to perform activities of daily living.

BMS708163

BMS 708163 (Bristol-Myers Squibb) is an oral, small molecular GSI that selectively inhibits Aβ synthesis relative to Notch and is in phase II development. Phase I data reported at ICAD 10 by several authors showed that the novel agent is well tolerated by healthy subjects, with good pharmacokinetic and pharmacodynamic profiles (abstracts P3-289, P3-298, P3-303, P3-318, O3-07-07).[28-32] Furthermore, no difference between Japanese and non-Japanese subjects was observed. This agent is thought to have a better side-effect profile and may be slightly more tolerable than other agents currently under investigation.

ELND006

ELND006 (Elan) is an amyloid precursor protein (APP)-selective GSI in phase I development. Data show that the novel therapeutic is between 15 and 70 times more selective for inhibiting γ–secretase-mediated cleavage of APP than Notch cleavage (abstracts P3-320, P3-321, P3-322).[33-35] Preclinical data also show a reduction of Aβ-related pathologies. These early results with ELND006 complement those seen with another of Elan's neurodegenerative disease products, ELND0005, which is now entering phase III clinical trials.

EVP-0015962

Another γ–secretase-targeting agent, now in preclinical development, is EVP-0015962. This is a modulator rather than an inhibitor of γ-secretase and had been proposed to result in the production of less toxic Aβ peptides, such as $A\beta_{x-38}$.

Rogers and colleagues reported data from a study in Tg2576 mice showing that the GSM improves cognitive defects and that this is associated with concomitant decreases in Aβ42.[36]

V950

Merck is currently undertaking a new immunological strategy, with development of several AD 'vaccines' that recognize multiple, mid-domain epitopes of the Aβ peptide. These vaccines will potentially be able to target all forms of Aβ including those that are the most neurotoxic. Merck's lead molecule is V950, which has been shown to cause significant delays in Aβ aggregation. Indeed, V950 elicits a strong anti-sera response to all forms of Aβ without T-cell activation. This molecule is scheduled to complete phase I studies in the fall of 2010.

Agents in development

- *Bapineuzumab*
- *BMS708163*
- *ELND005/ELND006*
- *EVP-0015962*
- *IgVL2-t2E6 and IgVL-t5D3*
- *Ponezumab (PF04360365)*
- *Solanezumab (LY2062430)*
- *MABT5102A*

While many agents in current development target Aβ or tau, other agents such as the histaminergic and serotonergic agent, Dimebon (latrepirdine), have also undergone considerable evaluation. However, the phase III data of Dimebon in patients with mild-to-moderate AD did not replicate the positive phase II clinical results. As such, further development of Dimebon is unlikely.

As the understanding of the disease pathways grows, new therapeutic targets are being identified. One example is the insulin signaling pathway, which Craft and colleagues looked at in a randomized, double-blind, placebo-controlled pilot trial.[37] Their research suggests that intranasal insulin could be a possible therapeutic option for patients with MCI and AD. Other intriguing new targets under investigation include glycogen synthase kinase-3 (GSK3) (abstract S4-01-04),[38] the β1 adrenergic receptor (abstract P4-120), and the receptor for advanced glycation end-products (RAGE) (abstracts P1-167, P2-348).[39,40]

Preventing AD

Obtaining proof of concept and confirmatory evidence for a disease-modifying drug in a successful pivotal phase III AD trial will not only lead to providing a much needed treatment option for patients with AD, but may also provide the impetus to embark on long-term trials to prevent this devastating disease. The phase III Continued Safety Monitoring of Solanezumab in Alzheimer's Disease (EXPEDITION EXT) trial may provide proof of concept in this regard, although this trial is being conducted in patients with mild-to-moderate AD; it will be interesting to see if solanezumab could prevent the accumulation of amyloid in the brain earlier in the disease process (e.g. in preclinical or asymptomatic AD).[41]

The ideal design for a preventative trial would most likely involve individuals who are no older than 55 years at recruitment and who are at high risk of developing AD. High-risk patients could eventually be identified using biomarkers or combinations of biomarkers. Long-term follow-up of patients, for up to 15–20 years, would of course be needed to gauge the true preventative effects of any intervention, and to see if a therapeutic agent delays the onset or reduces the severity of AD. If such a preventative trial were performed, and in turn an agent found that could prevent the progressive deterioration toward Alzheimer's dementia, it could potentially make a huge difference to current treatment practices and the lives of so many patients.

In the absence of such a trial and treatment, ethical considerations with respect to the optimal management of patients with AD will remain. Challenges of current symptomatic treatment approaches include deciding upon the best time to initiate treatment and whether to prolong the period when patients are in a 'twilight zone', caught in a state where they are aware of what is happening to them and are upset with the cognitive changes that impair their ability to apprehend and/or recall important information. A further challenge is not having a complete understanding of when to stop symptomatic treatment that appears to be no longer effective.

Non-pharmacological approaches

Non-pharmacological approaches in managing risk and preventing the progression to AD may prove important as well. Several presentations on the benefits of exercise were given at ICAD 10 (abstracts S4-01-01, P3-033, S1-01-03, O3-04-08).[42-45] Data suggest that aerobic exercise changes insulin sensitivity, Aβ levels, brain-derived neurotrophic factor, along with other factors associated with AD risk. Although aerobic exercise may represent a potentially efficacious preventative strategy to forestall both age-related changes and deleterious neurological processes leading to AD, as yet there are no data from large, well-controlled trials investigating the impact of exercise on AD pathology.

Conclusions

Significant progress is being made in understanding the likely pathogenic mechanisms underlying AD. However, there is still much to be learned with regards to determining how these basic research findings correlate with clinically meaningful outcomes, making the development of novel therapeutic agents somewhat challenging at the present time.

There is increasing recognition of the need to identify and treat patients at risk of AD dementia as early as possible, perhaps 10–15 years before signs and symptoms of cognitive or functional impairment are likely to manifest. Continued improvements in our understanding of AD pathology, the identification of new drug targets, use of potential biomarkers, and the study of a more homogenous population in clinical trials, will drive drug development forward, with a view to achieving the ultimate goal: the preventative treatment of AD.

References

1. *Medicines in Development for Neurological Disorders.* PhRMA, 2008. http://www.phrma.org/medicines_in_development_for_neurological_disorders (accessed September 27, 2010).
2. Hardy J. The Amyloid Hypothesis for Alzheimer's Disease: A Critical Reappraisal. *J Neurochem* 2009;110:1129–1134.
3. AAICAD Press Release: New Research Advances from the Alzheimer's Association International Conference on Alzheimer's Disease 2010. http://www.alz.org/ICAD/2010_release_advances_071410_1230pm.asp (accessed September 27, 2010).
4. Crews L, Masliah E. Molecular Mechanisms of Neurodegeneration in Alzheimer's Disease. *Hum Mol Genet* 2010;19:R12–R20.
5. Arnold CJ, Divan V, Jahja A. DMD Focus Remains on Anti-Amyloid Agents. *Credit Suisse* 2010;4–6.
6. Brunden KR, Trojanowski JQ, Lee VM. Advances in Tau-focused Drug Discovery for Alzheimer's Disease and Related Tauopathies. *Nat Rev Drug Discov* 2009;8:783–793.
7. Metcalfe MJ, Figueiredo-Pereira ME. Relationship Between Tau Pathology and Neuroinflammation in Alzheimer's Disease. *Mt Sinai J Med* 2010;77:50–58.
8. Higuchi M. In Vivo Targeting of Abeta and Tau Amyloidogenesis, Neuroinflammation, Calcium-Mediated Neurotoxicity and Their Interplays. *Alzheimers Dement* 2010;6:S94.
9. Donohue M, Gamst A, Thomas R, et al. Rate of Decline in ADNI Normal Controls with Evidence of Amyloid Burden. *Alzheimers Dement* 2010;6:S126.
10. Johnson SC, La Rue A, Hermann BP, *et al.* Tomm40 Is Associated with Gray Matter Volume in Middle-Aged Persons with Apoe e3/e3 Genotype. International Conference on Alzheimer's Disease (ICAD 10), July 10-15, 2010, abstract O4-03-04.
11. Sager MA, La Rue A, Johnson SC, *et al.* TOMM40 Variable Length Polymorphism is Associated with Memory Function in Asymptomatic Middle-Aged Persons. International Conference on Alzheimer's Disease (ICAD 10), July 10-15, 2010, abstract P4-050.
12. Graff C, Keller L, Xu W, *et al.* The Obesity Related Gene, FTO, Increases the Risk for Incident Alzheimer's Disease in a Prospective Population Based Study. *Alzheimers Dement* 2010;6:S111.
13. McKhann G, Drachman D, Folstein M, *et al.* Clinical Diagnosis of Alzheimer's Disease: Report of the NINCDS-ADRDA Work Group Under the Auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–944.
14. Boche D, Donald J, Love S, *et al.* Reduction of Aggregated Tau in Neuronal Processes but Not in the Cell Bodies After Abeta42 Immunisation in Alzheimer's Disease. *Acta Neuropathol* 2010;120:13–20.
15. Fox NC, Black RS, Gilman S, *et al.* Effects of Abeta Immunization (AN1792) on MRI Measures of Cerebral Volume in Alzheimer Disease. *Neurology* 2005;64:1563–1572.
16. Holmes C, Boche D, Wilkinson D, *et al.* Long-Term Effects of Abeta42 Immunisation in Alzheimer's Disease: Follow-Up of a Randomised, Placebo-Controlled Phase I Trial. *Lancet* 2008;372:216–223.

17. Gilman S, Koller M, Black RS, *et al.* Clinical Effects of Abeta Immunization (AN1792) in Patients with AD in an Interrupted Trial. *Neurology* 2005;64:1553–1562.

18. Goto T, Fujikoshi S, Kazunori U, *et al.* Solanezumab Was Safe and Well-Tolerated for Asian Patients with Mild-to-Moderate Alzheimer's Disease in a Multicenter, Randomized, Open-Label, Multi-Dose Study. *Alzheimers Dement* 2010;6:S308.

19. DeMattos RB, Racke M, Gelfanova V, *et al.* Characterization of Amino-Terminally Truncated Abeta-42 Peptides in Plasma from Alzheimer's Patients Receiving Solanezumab Immunotherapy Treatment. International Conference on Alzheimer's Disease (ICAD 10), July 10-15, 2010, abstract P3-308.

20. Grundman M, Black R. Clinical Trials of Bapineuzumab, a Beta-Amyloid-Targeted Immunotherapy in Patients with Mild to Moderate Alzheimer's Disease. *Alzheimers Dement* 2008;4:T166.

21. Peck P. ICAD: Post Hoc Analysis Finds Silver Lining in Bapineuzumab Failed Trial. *Medpage Today* 2008.

22. Nishiyama Y, Sigurdsson EM, Taguchi H, *et al.* Candidate Therapeutic Antibody with Specific Ability to Catalyze Beta-Amyloid Degradation. *Alzheimers Dement* 2010;6:S141–S142.

23. Zhao Q, Abe S, Miyoshi I, *et al.* Pharmacokinetics of Ponezumab (PF-04360365) Following a Single-Dose Intravenous Infusion in Japanese Patients with Mild-to-Moderate Alzheimer's Disease: Preliminary Results. *Alzheimers Dement* 2010;6:S305.

24. Zhao Q, Landen J, Burstein AH, *et al.* Pharmacokinetics and Pharmacodynamics of Ponezumab (PF-04360365) Following a Single-Dose Intravenous Infusion in Patients with Mild to Moderate Alzheimer's Disease. *Alzheimers Dement* 2010;6:S143.

25. Burstein AH, Zhao Q, Ross J, *et al.* Safety and Pharmacokinetics Following a Single 10-Minute Intravenous Infusion of the Anti-Amyloid mAb Ponezumab (PF-04360365) in Patients with Mild to Moderate Alzheimer's Disease. *Alzheimers Dement* 2010;6:S585.

26. Fujimoto Y, Miyoshi I, Ishibashi T, *et al.* Safety of the Anti-Amyloid Monoclonal Antibody Ponezumab (PF-04360365) Following a Single-Dose Intravenous Infusion in Japanese Patients with Mild-to-Moderate Alzheimer's Disease: Preliminary Results. *Alzheimers Dement* 2010;6:S310.

27. Wood KM, McCush F, Conboy JJ, *et al.* IP/MS Analysis of Human CSF Ab Following a Single Dose of the C-Terminal Anti-Ab Antibody Ponezumab (PF-04360365) to Alzheimer Patients. *Alzheimers Dement* 2010;6:S311.

28. Tong G, Wang J, Sverdlov A, *et al.* The Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Doses of BMS-708163 in Young and Elderly Subjects. *Alzheimers Dement* 2010;6:S539.

29. Dockens R, Karkas J, Zheng M, *et al.* Effect of Concomitant Administration of Multiple Doses of BMS-708163 on Safety, Tolerability, and the Pharmacokinetics of Midazolam, Warfarin, Caffeine, Omeprazole, and Dextromethorphan in Healthy Male Subjects by Administration of a Modified Cooperstown Cocktail. *Alzheimers Dement* 2010;6:S536.

30. Wang J, Castaneda L, Sverdlov A, *et al.* A Placebo-Controlled, Ascending, Multiple-Dose Study to Evaluate the Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) of BMS-708163 in Healthy Young and Elderly Subjects. *Alzheimers Dement* 2010;6:S540.

31. Ono G, Kondo K, Yamahira N, *et al.* The Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single and Multiple Doses of BMS-708163 in Young and Elderly Japanese Subjects. *Alzheimers Dement* 2010;6:S545.

32. Tong G, Castaneda L, Wang J, *et al.* A Study to Evaluate the Effects of Single Oral Doses of BMS-708163 in the Cerebrospinal Fluid of Healthy Young Men. *Alzheimers Dement* 2010;6:S143.

33. Brigham E, Quinn K, Kwong G, *et al.* Pharmacokinetic and Pharmacodynamic Investigation of ELND006, a Novel APP-Selective Gamma-Secretase Inhibitor, on Amyloid- Concentrations in the Brain, CSF and Plasma of Multiple Nonclinical Species Following Oral Administration. *Alzheimers Dement* 2010;6:S546.

34. Brigham E, Quinn K, Motter R, *et al.* Effects of Single and Multiple Dose Oral Administration of ELND006, a Novel APP-Selective Gamma-Secretase Inhibitor, on Amyloid- Concentrations in the Brain and CSF of Cynomolgus Monkeys. *Alzheimers Dement* 2010; 6:S546–S547.

35. Schroeter S, Brigham E, Motter R, *et al.* APP-Selective Gamma Secretase Inhibitor ELND006 Effects on Brain Parenchymal and Vascular Amyloid Beta in the PDAPP Mouse Model of Alzheimer's Disease. *Alzheimers Dement* 2010;6:S546.

36. Rogers K, Leventhal L, Hopp S, *et al.* The Gamma Secretase Modulator EVP-0015962 Improves Cognitive Deficits in Tg2576 Mice Concomitant with Decreases in Ab42. International Conference on Alzheimer's Disease (ICAD 10), July 10-15, 2010, abstract P4-022.

37. Craft S, Baker LD, Montine TJ, *et al.* Intranasal Insulin- and Biomarker-Associated Improvement In Memory And Functional Status In Mild Cognitive Impairment and Alzheimer's Disease: Results of a Randomized, Double-blind, Placebo-controlled Pilot Trial. International Conference on Alzheimer's Disease (ICAD 10), July 10-15, 2010, abstract O4-01-01.

38. del Ser T. Phase IIa Clinical Trial on Alzheimer's Disease with NP12, a GSK3 Inhibitor. *Alzheimers Dement* 2010;6:S147.

39. Fang F, Yan S, Nguyen HL, *et al.* Genetic Deficiency of RAGE Protects Against Ab Accumulation in an Alzheimer Mouse Model via Modulating Beta and Gamma Secretase Activity. *Alzheimers Dement* 2010;6:S224–S225.

40. Luo F, Fox GB, Seifert T, *et al.* Guiding Anti-RAGE Monoclonal Antibody Development for the Treatment of Alzheimer's Disease via Imaging. *Alzheimers Dement* 2010;6:S418.

41. Continued Safety Monitoring of Solanezumab in Alzheimer's Disease (EXPEDITION EXT). http://www clinicaltrials gov/ct2/show/NCT01127633?intr=%22Solanezumab%22&rank=1 (accessed September 22, 2010).

42. Baker LD. Aerobic Exercise as a Therapeutic Strategy: Effects on Cognition & Biomarkers. *Alzheimers Dement* 2010;6:S146–S147.

43. Brewster PWH, Tuokko HA, MacDonald SWS. Physical Exercise Differentially Moderates Cognitive Decline Trajectories in Incident Dementia and Normal Aging. *Alzheimers Dement* 2010;6:S458.

44. Cotman CW. Exercise and Prevention of Dementia. *Alzheimers Dement* 2010;6:S64.

45. Vreugdenhil A, Cannell J, Davies A, *et al.* A Community-Based Exercise Program to Improve Functioning in People with Alzheimer's Disease: A Randomized Controlled Trial. *Alzheimers Dement* 2010;6:S134.

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