alzheimer's research&therapy

MEETING REPORT

A diverse portfolio of novel drug discovery efforts for Alzheimer's disease: Meeting report from the 11th International Conference on Alzheimer's Drug Discovery, 27–28 September 2010, Jersey City, NJ, USA

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Abstract

While Alzheimer's disease researchers continue to debate the underlying cause(s) of the disease, most agree that a diverse, multi-target approach to treatment will be necessary. To this end, the Alzheimer's Drug Discovery Foundation (ADDF) recently hosted the 11th International Conference on Alzheimer's Drug Discovery to highlight the array of exciting efforts from the ADDF's funded investigators.

Given the escalating worldwide socioeconomic burden of Alzheimer's disease (AD), there is a strong impetus for better therapeutics. Currently, there are approved symptomatic drugs but very few disease-modifying agents capable of slowing down or reversing disease progression.

As the Alzheimer's Drug Discovery Foundation (ADDF) executive director Howard Fillit (ADDF, New York, NY, USA) pointed out in his opening remarks, major issues include the difficulty in drugging central nervous system targets and the predictability of AD animal models. Preclinical trials have so far demonstrated hundreds of 'cures', yet the track record for translating these treatments to the human disease is lackluster, as evidenced by the recent spate of high-profile failures.

Alzheimer's disease biomarkers

An overarching theme of the conference was disease prevention and early treatment before AD manifests significant cognitive decline, when it is probably too late to reverse the substantial neural pathology. To create preventative treatments, however, we first need accurate and reliable biomarker diagnostics to identify prodromal AD (mild cognitive impairment and even earlier).

As Holly Soares (Bristol-Myers Squibb, New York, NY, USA) pointed out, biomarkers are also critical for patient selection and monitoring treatment efficacy in AD clinical trials. The Alzheimer's Disease Neuroimaging Initiate has proposed cerebrospinal fluid amyloid-β (Aβ) levels and amyloid positron emission tomography imaging as good biomarkers for early detection. Dawn Matthews (Abiant, Inc., Grayslake, IL, USA) expanded on the use of neuroimaging techniques as diagnostic tools. For example, fluorodeoxyglucose positron emission tomography imaging can sensitively detect changes in various brain regions, even in pre-mild cognitive impairment, and follows cognitive decline in AD. Quality control in data acquisition, processing, and analysis is critical, however, for the successful use of neuroimaging methods as diagnostics.

In addition to neuroimaging and cerebrospinal fluid analyses, there is a need for simpler, less invasive tests. Rima Kaddurah-Daouk (Duke University Medical Center, Durham, NC, USA) discussed metabolomics as a minimally invasive technique that allows the examination of global biochemical signatures. In AD, several pathways are disturbed, including those for norephinephrine and ceramides, indicating that metabolites from these pathways could be useful in diagnostic analyses. Stephen Johnston (Arizona State University Foundation, Tempe, AZ, USA) presented another new non-invasive diagnostic technique – immunosignatures – which is based on screening the antibody population of an individual on random peptide sequence arrays. Dr Johnston demonstrated in preliminary tests the ability to detect distinct immunosignatures in AD samples, which are not due to

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Aβ-specific antibodies. Future validation with Alzheimer's Disease Neuroimaging Initiate samples will determine whether this approach holds promise for early-AD detection.

In addition to AD, there are several related dementias that overlap heavily, including dementia with Lewy bodies and frontotemporal dementia (FTD), which also require better biomarker tests to aid diagnosis. Lawrence Honig (Columbia University, New York, NY, USA) proposed that a combination of biomarkers can differentiate dementia with Lewy bodies, including the use of glucocerebrosidase as a genetic marker, neuroimaging, and cerebrospinal fluid analyses. For example, although cerebrospinal fluid Aβ levels are similar to those found in AD, tau and phospho-tau levels are relatively normal. Linda Kwong (University of Pennsylvania School of Medicine, Philadelphia, PA, USA) discussed biomarker diagnostics for FTD and presented her preliminary data demonstrating that ELISA screening of plasma TDP-43 levels may differentiate between FTD-tau and FTD-TDP.

Targeting amyloid-β linked pathologies

A well-publicized drug discovery approach in AD is the manipulation of Aβ metabolism by the modulation or inhibition of the β-secretase and γ-secretase enzymes that process amyloid precursor protein (APP). Tae-Wan Kim (Columbia University, New York, NY, USA) presented his work on indirect, small-molecule BACE1 modulators that can reduce secreted Aβ levels in neuronal cultures and in transgenic APP mice. Dr Kim is currently working on identifying the cellular targets and mechanisms of action.

Another approach to lower Aβ in the brain is through the inhibition of RAGE, which transports Aβ across the blood–brain barrier. Rashid Deane (University of Rochester, Rochester, NY, USA) is testing some lead compounds that can block Aβ–RAGE interactions at multiple points across cell types. When tested in Tg2575 transgenic mice, these compounds were able to reduce brain Aβ levels, to improve blood flow, and to ameliorate cognitive decline.

Targeting other pathways disrupted by Aβ could also yield effective therapeutics. For example, there is a significant link between AD and cardiovascular dysfunction. Sidney Strickland (Rockefeller University, Rockefeller, NY, USA) discussed his studies showing that Aβ can bind fibrinogen and alter blood clot structure and dissolution. Reducing fibrinogen pharmacologically or genetically improved learning and memory in AD transgenic mice, indicating that this protein could be a target for AD drug discovery. Looking at another aspect of this process, Chris Schaffer (Cornell University, Ithaca, NY, USA) described a method to induce specific microvascular clots using a laser scalpel to make single micron-size cuts in blood-vessel endothelial cells. He showed that these microvascular clots induce new Aβ deposits locally and increased inflammation.

Since apolipoprotein E (ApoE) is currently the most significant genetic risk factor for late-onset AD, we need to better understand its underlying mechanisms to develop new treatments and aid interpretation of clinical trials that demonstrate differential efficacy depending on the ApoE genotype. Cheryl Wellington (University of British Columbia Hospital, Vancouver, BC, Canada) observed that highly lipidated ApoE is protective in AD, possibly due to the facilitation of Aβ degradation. Dr Wellington is currently screening chemical libraries for compounds that can enhance ApoE lipidation and secretion, with retinoic acid and progestin as preliminary hits.

Eric Schon (Columbia University, New York, NY, USA) found that presenilins – components of the γ-secretase complex that play important roles in Aβ metabolism, among other functions – are enriched in mitochondria-associated membranes. Dr Schon hypothesizes that many aspects of AD pathology arise from mitochondria-associated membrane dysfunction. Cells from presenilin knockout mice as well as from sporadic AD patients have enhanced sensitivity to cinnamycin, which could be used as a possible diagnostic tool for screening mitochondria-associated membrane-targeted compounds.

Neuroprotection and cognitive enhancement:

The primary goal for AD therapeutics is to prevent neuronal damage and improve cognitive function, a goal that is being pursued via many different approaches. Scott Noggle (The New York Stem Cell Foundation, New York, NY, USA) discussed stem cell technology as a way to specify cell types involved in neurodegeneration. In particular, induced pluripotent stem cell lines derived from AD patients could be especially valuable for both basic research and drug discovery screening programs; several familial AD lines are currently in development.

Various compounds that can improve cognition were presented in the rest of this session. Roberta Brinton (University of Southern California, Los Angeles, CA, USA) introduced allopregnanolone, a progesterone metabolite that is able to improve memory and neurogenic defects in 3xTg mice as well as in normally aged wild-type mice. These beneficial effects are only observed in transgenic mice younger than 1 year old, however, with the biggest improvements in young pre-plaque 3-month-old mice, indicating that allopregnanolone should be used as an early preventative treatment. Ottavio Arancio (Columbia University, New York, NY, USA) discussed cAMP responsive element-binding protein, which is a key transcription factor involved in synaptic plasticity that has been shown to be impaired by Aβ. Dr Arancio's laboratory recently demonstrated that sildenafil, an approved phosphodiesterase-5 inhibitor,

improves cAMP responsive element-binding protein phosphorylation, synaptic plasticity, and learning and memory in APP/PS1 transgenic mice. After demonstrating that phosphodiesterase-5 is highly expressed in the human brain, Dr Arancio is working on optimizing lead phosphodiesterase-5 inhibitors.

Klotho, a secreted hormone that acts on multiple pathways in aging and metabolism, was presented as another possible drug target by Carmela Abraham (Boston University School of Medicine, Boston, MA, USA). Dr Abraham discovered that while Klotho knockout mice have an accelerated aging phenotype that includes cognitive impairment, Klotho-overexpressing mice have increased life spans and enhanced resistance to oxidative stress. A high-throughput screen of chemical libraries identified several lead compounds that increase Klotho expression and will be tested for protective effects against Aβ-induced pathology.

High brain levels of striatal enriched tyrosine phosphatase (STEP) are found in several neurological diseases including AD. Paul Lombroso (Yale University, New Haven, CT, USA) found that increased STEP levels can impair synaptic plasticity and memory due to the dephosphorylation and subsequent internalization of glutamate receptors. A high-throughput screen identified STEP inhibitor lead compounds, which rescued behavioral tasks in transgenic mouse models a few hours after treatment, compared with the weeks of treatment necessary with memantine.

Another mechanism for cognitive dysfunction in AD could be hippocampal hyperexcitability, which is found in mild cognitive impairment patients and suggests that an attenuation of neuronal excitability could be a therapeutic strategy. As detailed by Michela Gallagher (Johns Hopkins University, Baltimore, MD, USA), the α5 subunit of the GABA-A receptor is highly expressed in the hippocampus, and agonists for this subunit, such as levetriacetam, can improve cognition in age-impaired rats; this drug is now being tested in elderly humans for cognition-improving effects.

Instead of targeting a specific pathway disrupted by pathological Aβ signaling, Susan Catalano (Cognition Therapeutics, Inc., Pittsburgh, PA, USA) presented efforts to block Aβ oligomer binding to neurons. Using a membrane trafficking assay, Dr Catalano found several small-molecule compounds that competitively inhibit Aβ oligomer-induced perturbations and can rescue synaptic defects and cognitive impairments in transgenic AD mice. Current studies are underway to test for efficacy as a chronic, preventative treatment.

Tangle pathology and frontotemporal dementia

Beyond Aβ-associated dysfunction, tau pathology also figures prominently in several diseases, including AD and FTD. In these diseases, there is a shift in the dynamic equilibrium between free and microtubule-associated tau, leading to tau aggregation, microtubule destabilization, and disrupted cellular transport. Carlo Ballatore (University of Pennsylvania School of Medicine, Philadelphia, PA, USA) focuses on small-molecule compounds that can prevent or reverse tau aggregation. Using *in vitro* tau fibrillization assays, he identified aminothienoyridazine as a highly selective tau fibrillization inhibitor that prevents tau oligomer buildup without disrupting normal tau function.

Another approach to ameliorating tau pathology is to decrease levels of the tau-4R splice isoform, which aggregates more readily than tau-3R. As discussed by Michael Wolfe (Harvard University, Cambridge, MA, USA), this splicing process is regulated by a stem-loop structure in tau mRNA. To decrease levels of the tau-4R isoform, Dr Wolfe screened for compounds that can bind and stabilize this stem-loop structure and identified a cancer drug, mitoxantrone, as an effective but nonspecific treatment. To increase specificity for tau mRNA, Dr Wolfe is testing the use of an antisense nucleic acid tag conjugated to mitoxantrone to target the compound to the regions flanking the stem-loop structure.

Hyperphosphorylated tau is a significant pathological feature of several dementias. In AD, elevated homocysteine levels can inhibit phosphoprotein phosphatase 2A, which then leads to a buildup of hyperphosphorylated tau. Jeffry Stock (Signum Biosciences, Monmouth Junction, NJ, USA) has found a compound present in coffee, SIG1012, which reduces phosphatase 2A inhibition and tau phosphorylation. *In vivo* tests showed that treatment with the compound delays motor defects and improves survival in the JNPL3 tauopathy mouse model.

Despite relatively high research investments, Aβ immunotherapy does not appear to be effective after the onset of significant cognitive impairments and high plaque load. Since tau deposition correlates better with cognitive decline, Einar Sigurdsson (New York University Langone Medical Center, New York, NY, USA) suggests that tau may be a better target for immunotherapy after the diagnosis of AD. Using tauopathy mouse models, Dr Sigurdsson was able to decrease tau aggregates in the brain and improve motor and cognitive function with both active and passive immunization targeting phospho-tau.

Another way to clear tau aggregates is via macroautophagy, which is a cellular process leading to the sequestration and degradation of dysfunctional organelles and misfolded proteins. Wai Haung Yu (Columbia University, New York, NY, USA) has found two compounds – rapamycin and trehalose – that stimulate autophagy and decrease pathological tau aggregates. Trehalose, which has good blood–brain barrier penetration, was effective as both a therapeutic agent after disease onset as well as a

long-term preventative treatment that improved motor function in the JNPL3 mouse model. Dr Yu's studies point to macroautophagy as a potential drug target for enhancing the clearance of protein aggregates in AD as well as other neurodegenerative diseases.

Conclusion

At this conference, many exciting new strategies and targets for AD drug discovery were presented and will hopefully pioneer effective diagnostic and therapeutic treatments in the near future. We hope you will join us next year for the 12th International Conference on Alzheimer's Drug Discovery, 26–27 September 2011, in Jersey City, NJ, USA.

Abbreviations

Aβ, amyloid-β; AD, Alzheimer's disease; ADDF, Alzheimer's Drug Discovery Foundation; ApoE, apolipoprotein E; APP, amyloid precursor protein; BACE1, β-site of APP cleaving enzyme 1; ELISA, enzyme-linked immunosorbent assay; FTD, frontotemporal dementia; RAGE, receptor for advanced glycation endproducts; STEP, striatal enriched tyrosine phosphatase.

Competing interests

The authors declare that they have no competing interests.

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