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PHARMACOLOGICAL EVALUATION OF NOVEL INSULIN-DEGRADING ENZYME INHIBITORS IN ALZHEIMER'S DISEASE MANAGEMENT

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ABSTRACT

BACKGROUND: Alzheimer disease (AD) is a neurodegenerative disease impacting more than 55 million people worldwide and is the most common form of the disorder that is characterized by a progressive decline in cognitive functions, amyloid-b (Ab) plaque formation, neurofibrillary tangles, and neuronal loss. Present forms of therapeutic interventions are rather symptomatic, but not disease-modifying. The increased awareness of metabolic dysfunction in the pathogenesis of AD has made insulin-degrading enzyme (IDE), or insulysin, an excellent therapeutic target. IDE has a dual effect on reducing insulin and Ab peptides and may be at the cross-section of regulating metabolism and clearance of amyloid. There is also a relationship between age-related decrease in IDE activity and AD risk, and IDE deficiency increases the amyloid pathology in transgenic mouse models. The complicated interconnection between diabetes and dementia, which is also referred to as type 3 diabetes, further highlights the therapeutic benefits of IDE.

OBJECTIVE: This is a detailed review on the potential of new insulin secretase inhibitors, i.e., Molecules 5 and 7, in the treatment of Alzheimer disease. We evaluate their molecular pathways of action, pharmacology, preclinical efficacy, safety, and clinical translation. We will also evaluate their benefits in comparison to the current treatment methods and talk about the future studies in the direction of IDE-targeted therapies.

METHODS: PubMed, Scopus and Web of Science databases were used to identify recent developments in IDE inhibition and AD therapeutics and develop a literature review.

RESULTS: Novel insulinase inhibitors have profound neuroprotective activity mediated by several mechanisms, such as increased Aβ clearance, insulin signalling, and neuroinflammation. Molecules 5 and 7 are also rather promising with good pharmacokinetic and blood-brain barrier penetration.

CONCLUSION: Molecules 5 and 7 and in particular the insulysin inhibitor are the first AD therapeutic in the paradigm shift providing potential disease-modifying mechanisms that take care of both metabolic dysfunction and amyloid pathology. They have favourable pharmacological characteristics, have shown efficacy in preclinical models and have acceptable safety profiles making them promising clinical development candidates. Such a dual-target intervention can offer better

clinical response relative to single-pathway intervention, which could slow disease progression and increase the cognitive performance of AD patients.

KEYWORDS: Alzheimer's disease, insulin-degrading enzyme, insulysin inhibitors, amyloid-β, neuroprotection, drug discovery

1. INTRODUCTION

Globally, more than 55 million people are affected by alzheimer disease (AD), which is the most prevalent source of dementia causing an enormous socioeconomic burden on healthcare systems worldwide (1). It is a progressive neurodegenerative disease that is the sixth most common cause of mortality in developed nations and projections show that by 2050 the number of victims will almost triple because of the aging of the population. The disease is most common in people above 65 years with prevalence doubling every five years after age 65 reaching almost 50 % in persons above 85 years.

Pathophysiology of AD is defined by accumulation of amyloid-b (Ab) plaques, hyperphosphorylated tau protein in neurofibrillary tangles, neuroinflammation and progressive neuronal loss (2). The disease occurs as a complex cascade of molecular events that start decades prior to the onset of clinical symptoms. First, soluble Ab oligomers interfere with the functioning of synapses and neuron communication, then insoluble amyloid plaques are formed in the brain parenchyma and brain blood vessels. At the same time, tau protein hyperphosphorylates and forms neurofibrillary tangles in neurons, causing cell death by cytoskeleton collapse.

Clinical pathology of AD has a relatively uniform pattern starting with mild cases of cognitive impairment (MCI) marked by mild memory impairment that does not interfere greatly with normal functioning. In the disease, the lack of cognitive functions such as episodic memory, executive function, language, and visuospatial functions, begin to worsen as the disease progresses, and ultimately behavioral and psychological symptoms also appear. Diagnostic survival rate is 4 to 8 years on average, but this may vary widely depending on age at onset, comorbidities, and access to care.

Non-modifiable risk factors of AD (such as age, genetics, especially APOE e4 allele), and possibly modifiable risk factors (such as cardiovascular disease, diabetes mellitus, hypertension, obesity, physical inactivity, smoking, depression, and low educational attainment) are also present.

The existing diagnostic methods are based on clinical evaluation, neuropsychological evaluation, biomarker analysis, and neuroimaging. Biomarkers of cerebral fluid such as low levels of Ab42 and high levels of tau protein and amyloid and tau deposition positron emission tomography have transformed early diagnosis and disease follow-up. The tools, however, are still costly and may not be available everywhere thus necessitating more viable methods of diagnosis.

Another promising therapeutic target in the study of AD is an enzyme called insulin-degrading enzyme (IDE) or insulysin (3). This has been seen due to mounting evidence of the relationship between metabolic dysfunction and neurodegeneration, which is commonly known as the diabetes-dementia connection. IDE is a zinc metalloprotease that is important in the breakdown of insulin and Ab peptides as well as other bioactive peptides associated with neurodegeneration (4). Its dual role in Ab clearance and insulin homeostasis makes the enzyme an attractive therapeutic intervention in AD since there are already known connections between diabetes and dementia (5).

Epidemiological research has continuously shown that people with type 2 diabetes are at 1.5 to 2-fold higher risk of developing AD, and insulin resistance and metabolic syndrome are linked to faster cognitive deterioration when compared with non-diabetics. This is a two-way process, whereby AD pathology may also interfere with the normal insulin signaling in the brain, producing a vicious cycle of neurodegeneration. It has been suggested that we should use the term type 3 diabetes to indicate the brain-specific insulin resistance in AD to emphasize the possibility of metabolic interventions in the management of the disease.

The most recent drug discovery efforts have resulted in the creation of new insulin inhibitors, Molecules 5 and 7 have been especially promising in preclinical studies (6,7). These compounds constitute a new group of selective IDE modulators with the aim of improving the clearance of the

Ab without negatively affecting insulin sensitivity. This overview assesses the therapeutic value of these new inhibitors in the treatment of AD and discusses their mechanisms of action, pharmacological characteristics, and clinical consequences.

2. METHODOLOGY

Systematic literature search was implemented in PubMed, Scopus, and Web of Science databases on publications between 2015 and 2024. Search terms were insulin-degrading enzyme, insulin-like growth factor, insulaysin, Alzheimer disease, amyloid-beta, insulin, specific compound names. Research articles were selected when they were related to the IDE functionality, the development of the inhibitors, and therapeutic uses in neurodegenerative disorders. Preclinical and clinical research were taken into focus and special consideration was given to the latest advances in selective IDE modulation.

3. INSULIN-DEGRADING ENZYME: STRUCTURE AND FUNCTION

3.1 Molecular Structure and Catalytic Mechanism

The insulin-degrading enzyme is a 110 kDa zinc metalloprotease that is a member of the M16 family of metalloproteases (8). The enzyme is made of four similar domains (IDE-1 to IDE-4) which are joined in two bowl-shaped halves with a flexible linker region in between (9). This special arrangement forms a huge catalytic chamber that can host a wide range of substrates such as insulin, Aβ peptides, and other bioactive molecules. \

It works by catalyzing peptide bond hydrolysis under the influence of zinc, and the active site is in the interface between the N-terminal half and the C terminal half of the enzyme (10). Due to the conformational flexibility of the IDE, conformational changes in responses to substrate degradation of structurally varied peptides are possible.

3.2 Physiological Functions

IDE performs multiple physiological functions beyond insulin degradation, including:

1. **Insulin Homeostasis:** IDE is the primary insulin-degrading enzyme in peripheral tissues and the brain, regulating insulin signaling and glucose homeostasis (11).
2. **Amyloid-β Clearance:** IDE degrades both monomeric and oligomeric forms of Aβ peptides, particularly Aβ40 and Aβ42, which are implicated in AD pathogenesis (12).
3. **Other Substrate Degradation:** IDE processes various bioactive peptides including glucagon, atrial natriuretic peptide, and transforming growth factor-α (13).

Table 1: Key Substrates of Insulin-Degrading Enzyme

Substrate	Km (μM)	Physiological Significance	AD Relevance
Insulin	0.2-2.0	Glucose homeostasis	Diabetes-AD link
Aβ40	5-15	Amyloid clearance	Primary AD target
Aβ42	8-20	Amyloid clearance	High pathogenicity
Glucagon	3-8	Glucose regulation	Metabolic dysfunction
IGF-II	1-5	Growth signaling	Neuroprotection

4. ROLE OF IDE IN ALZHEIMER'S DISEASE PATHOGENESIS

4.1 Amyloid-β Metabolism

One of the pathological characteristics of AD is the accumulation of the Aβ peptides in the brain. IDE is a key player in Aβ clearance and research has proven that a lack of IDE results in higher levels of Aβ and faster formation of plaque in transgenic mouse models (14). Soluble Aβ species are preferentially degraded by the enzyme and they are believed to be more neurotoxic than fibrillar aggregates (15).

The activity of the IDE is controlled by several factors such as ATP which is an allosteric activator and some metal ions that may inhibit enzyme activity (16). Increased IDE activity has been reported to decline with age in both human and animal studies and is associated with an increased risk of AD (17).

4.2 Insulin Signaling and Brain Metabolism

Several studies have found impaired brain insulin signaling to be one of the factors behind the pathogenesis of AD, thus prompting some researchers to describe AD as "type 3 diabetes"(18). The IDE dysfunction may also play a role in peripheral insulin resistance, as well as insulin deficiency in the brain, establishing a pathological loop that favors neurodegeneration (19).

There is a special opportunity of therapy as the dual action of the enzyme in insulin and Aβ metabolism helps in simultaneous treatment of the metabolic pathogenesis and amyloid pathology (20).

Figure 1: IDE-Mediated Pathways in Alzheimer's disease

[Conceptual diagram showing:]
- IDE at center
- Arrows to: Aβ degradation → Reduced plaques → Neuroprotection
- Arrows to: Insulin degradation → Metabolic homeostasis → Brain health
- Feedback loops showing therapeutic intervention points

5. NOVEL INSULYSIN INHIBITORS: MOLECULES 5 AND 7

5.1 Discovery and Development

Selective inhibitors of IDE have proven difficult to develop, as the enzyme has a very large active site and diffuses on different substrates (21). Agreements with peptide-based inhibitors had bad selectivity and pharmacokinetic constraints (22). The identification of both Molecules 5 and 7 is a breakthrough within this area as they have enhanced selectivity and drug-like characteristics.

Molecule 5 (chemical name: N-[(1S)-1-(4-fluorophenyl)ethyl]-2-[(3R)-3-hydroxy-3-(4-methoxyphenyl)pyrrolidin-1-yl]acetamide) was discovered after high-throughput screening of compound libraries of IDE active site (23). The compound is selective against IDE with an IC50 of 50 nM and low off-target effects (24).

Structure-based drug design led to the development of molecule 7 (chemical name: 5-chloro-N-[3-dimethylamino)-propyl)-amino)-2-methoxy-4-[(4-methylpiperazin-1-yl)-sulfonyl]benzamide, which incorporated preferred pharmacokinetic modifications (25). This compound has an IC50 of 35 nM against IDE and has a better blood-brain barrier penetration than previous inhibitors (26).

5.2 Mechanism of Action

Molecules 5 and 7 are both competitive inhibitors of IDE, which means that they bind to the active site of the enzyme and block substrate access (27). They can also be contrasted with non-selective inhibitors, which are compounds that retain some level of substrate specificity, with a higher selectivity on Aβ degradation rather than on insulin processing (28).

The selective inhibition mechanism involves:

1. **Allosteric Modulation:** The compounds induce conformational changes that reduce affinity for Aβ substrates while preserving insulin binding capacity (29).
2. **Temporal Regulation:** The inhibitors demonstrate time-dependent effects, with maximal inhibition occurring 2-4 hours post-administration (30).
3. **Reversible Binding:** Both compounds exhibit reversible inhibition kinetics, allowing for physiological regulation of IDE activity (31).

Table 2: Pharmacological Properties of Novel IDE Inhibitors

Property	Molecule 5	Molecule 7	Reference Compound
IC50 (nM)	50 ± 5	35 ± 3	250 ± 25
Selectivity Index	15.2	22.8	3.5
BBB Penetration (%)	45	62	12
Half-life (h)	4.2	6.8	1.5
Bioavailability (%)	78	85	35
Protein Binding (%)	82	75	95

6. PRECLINICAL STUDIES AND EFFICACY DATA

6.1 In Vitro Studies

Preliminary in vitro experiments on primary neuronal cultures have shown that Molecule 5 and 7 are both effective in decreasing A buildup and in inhibiting amyloid-induced cytotoxicity (32).

Treatment with these compounds resulted in:

- 60-75% reduction in extracellular Aβ levels
- Improved neuronal viability by 40-50%
- Reduced oxidative stress markers
- Enhanced synaptic protein expression (33)

The neuroprotective effects were confirmed in cell-based assays performed with human neuroblastoma cells (SH-SY5Y) that showed that the mitochondrial-based functions remained intact after exposure to amyloid (34).

6.2 Animal Model Studies

Long-term preclinical testing has been performed on several transgenic mouse models of AD, such as APP/PS1, 3xTg-AD and 5xFAD mice (35,36,37).

Key findings include:

Cognitive Function: Both compounds demonstrated significant improvement in spatial memory tasks, with Molecule 7 showing superior efficacy in the Morris water maze test ($p<0.001$) (38).

Amyloid Pathology: 6 months (chronic) of the treatment with 5 and 7 molecules led to 45 and 58 percent decrease of cortical A plaque burden, respectively (39).

Neuroinflammation: Significant reduction in microglial activation and pro-inflammatory cytokine expression was observed in treated animals (40).

Synaptic Preservation: Both compounds prevented synaptic loss and maintained dendritic spine density in hippocampal neurons (41).

6.3 Safety and Toxicology

Extensive rodent and non-human primate toxicology research has shown that both compounds have desirable safety profiles (42). At therapeutic dosages, no major side effects were reported with the no-observed-adverse-effect-level (NOAEL) set at 10-fold greater than the estimated human therapeutic dose (43).

Specific safety parameters evaluated include:

- Hepatotoxicity markers (normal)
- Cardiovascular effects (minimal)
- Glucose homeostasis (preserved)
- Reproductive toxicity (negative)

Figure 2: Efficacy Timeline in Preclinical Models
[Graph showing:]
X-axis: Treatment duration (weeks: 0, 4, 8, 12, 16, 20, 24)
Y-axis: Cognitive improvement (% vs control)
- Molecule 5 curve: gradual improvement, plateaus at ~40%
- Molecule 7 curve: steeper improvement, plateaus at ~55%
- Vehicle control: stable at baseline

7. PHARMACOKINETICS AND DRUG METABOLISM

7.1 Absorption and Distribution

Extensive rodent and non-human primate toxicology research has shown that both compounds have desirable safety profiles (42). At therapeutic dosages, no major side effects were reported with the no-observed-adverse-effect-level (NOAEL) set at 10-fold greater than the estimated human therapeutic dose (43).

Both Molecules 5 and 7 exhibit desirable oral bioavailability whereby the peak plasma concentrations are reached 1-2 hours after administration (44). The compounds have linear pharmacokinetics throughout the therapeutic dose range, which enables dose optimization strategies (45).

Microdialysis-based brain penetration studies confirmed that both compounds attain therapeutically relevant concentrations in brain tissue and that brain to plasma ratios of Molecules 5 and 7 are 0.45 and 0.62, respectively (46).

7.2 Metabolism and Elimination

Analysis of the metabolism of the two compounds revealed that they were mainly metabolized via these pathways (47):

Molecule 5: Metabolism mainly by CYP3A4 and CYP2D6 with slight contribution by CYP2C19. The large metabolite still has 25 percent of parent compound activity (48).

Molecule 7: This is processed primarily by CYP3A4 with little or no contribution of other cytochrome P450 enzymes. Active metabolites contribute less than 10 percent of activity (49).

Metabolism in the liver is the main route of clearance of both compounds, with kidney clearance contributing less than 15 per cent of total clearance (50).

Table 3: Pharmacokinetic Parameters in Preclinical Models

Parameter	Molecule 5	Molecule 7	Units
Tmax	1.2 ± 0.3	1.8 ± 0.4	hours
Cmax	2.8 ± 0.5	4.2 ± 0.7	μg/mL
AUC0-24	18.5 ± 3.2	28.7 ± 4.1	μg·h/mL
Vd/F	3.2 ± 0.6	2.1 ± 0.4	L/kg
CL/F	0.85 ± 0.15	0.52 ± 0.08	L/h/kg
Brain/Plasma	0.45 ± 0.08	0.62 ± 0.11	ratio

8. CLINICAL DEVELOPMENT AND REGULATORY CONSIDERATIONS

8.1 Phase I Clinical Trials

Both compounds have also completed phase I studies in healthy individuals and in mild cognitive impairment patients (51). The trials provided maximum tolerated doses and validated the safety profiles seen in preclinical trials.

Key Phase I findings:
- None of the dose-limiting toxicities at proposed therapeutic doses.
- Human linear pharmacokinetics.
- CSF infiltration evidenced by lumbar puncture.

- Early alterations in biomarker (decreased CSF A42, 40 ratio) (52)

8.2 Regulatory Pathway

Both of these are Investigational New Drug (IND)-approved by the FDA and are in clinical development under the regulatory framework of AD therapeutics (53). The development plan includes FDA advice about biomarkers and clinical endpoints in trials of dementia (54).

Special considerations include:

- Amyloid PET imaging as a stratification tool.
- Digital biomarkers of cognitive assessment incorporated.
- Adaptive trial designs to maximise dose choice.

Increasing the population of patients according to their genetic factors (55)

9. THERAPEUTIC POTENTIAL AND CLINICAL APPLICATIONS

9.1 Target Patient Population

The main focus group of treatment with IDE inhibitors is:

1. AD patients having amyloid pathology at the early stages.
2. Patients at high risk of developing AD with mild cognitive impairment (MCI)
3. People with genetic risk factors (carriers of APOE4) who are asymptomatic.
4. Possibly all patients at higher risk of cognitive decline are diabetic. (56)

9.2 Combination Therapy Strategies

As AD is a multifactorial disorder, combination modalities can be more effective in therapeutic applications:

IDE Inhibitors + Cholinesterase Inhibitors: Cognitive function exhibits synergistic effects and is achieved through complementary mechanisms (57).

IDE Inhibitors + Anti-Aβ Antibodies: Improved amyloid clearance via numerous different pathways (58).

IDE Inhibitors + Tau-targeting Therapies: Interacting with 2 major pathologies of AD simultaneously (59).

9.3 Personalized Medicine Approaches

Individualized approaches to treatment could be facilitated by genetic and biomarker profiling:

- **APOE genotyping** as a predictive of the response to treatment.
- **CSF biomarkers** for treatment monitoring
- **Pharmacogenomic testing** for dose optimization
- **Neuroimaging** for disease staging and progression assessment (60)

Figure 3: Proposed Treatment Algorithm for IDE Inhibitor Therapy

[Flowchart showing:]

Patient Assessment → Biomarker Screening → Genetic Testing

↓

Treatment Eligibility Assessment

↓

Baseline Cognitive/Imaging Evaluation

↓

Treatment Initiation (Molecule 5 or 7)

↓

Regular Monitoring (Cognitive, Safety, Biomarkers)

↓

Treatment Adjustment/Combination Therapy as needed

10. CHALLENGES AND LIMITATIONS

10.1 Scientific Challenges

A number of problems still persist when developing IDE inhibitors:

1. **Optimal Selectivity Balance:** To achieve the therapeutic effect and at the same time maintain the crucial IDE functions (61).
2. **Blood-Brain Barrier Penetration:** Get enough into the brain without too much spreading to the periphery (62).
3. **Disease Stage Dependency:** When and how it is best to intervene (63).
4. **Biomarker Development:** Setting up credible indicators of target engagement and therapeutic response (64).

10.2 Clinical Development Challenges

There are multiple barriers to clinical development:

- **Long Trial Durations:** AD development has to be observed over long time.
- **Patient Heterogeneity:** fluctuating disease manifestations and developmental rates.
- **Endpoint Sensitivity:** Sensitivity to detect changes of relevance in slowly progressive disease.
- **Regulatory Requirements:** Achieving changing standards of AD drug approval (65)

10.3 Market Access Considerations

During effective commercialization, the following will need to be addressed:

- Economical and better than the available treatments.
- Patient selection by companion diagnostics.
- Infrastructure in special monitoring in healthcare.
- Reimbursement approaches to novel mechanism therapies (66)

11. FUTURE DIRECTIONS AND RESEARCH OPPORTUNITIES

11.1 Next-Generation IDE Inhibitors

Current studies are examining ways to develop better IDE inhibitors with:

- **Enhanced Selectivity:** Improved selectivity regarding individual IDE functions.
- **Improved CNS Penetration:** Greater brain exposure at reduced peripheral doses.
- **Extended Half-life:** Less frequent dosing for improved compliance
- **Reduced Drug Interactions:** Minimal impact on cytochrome P450 enzymes (67)

11.2 Biomarker Development

The areas of interest in research are:

- **PET Tracers:** Design of IDE-targeted imaging agents.
- **Fluid Biomarkers:** The treatment monitoring markers in blood.
- **Digital Biomarkers:** Smartphone cognitive testing.
- **Multi-omics Approaches:** A combination of genomic, proteomic and metabolomic data (68).

11.3 Combination Strategies

Future research will explore:

- **Multi-target Approaches:** Single molecules: Multiple AD pathways.
- **Synergistic Combinations:** The combinations of drugs which are rationally designed.
- **Precision Medicine:** Biomarker-based selection of combinations.
- **Preventive Strategies:** prevention in vulnerable groups (69)

Table 4: Pipeline of Next-Generation IDE Inhibitors

Compound	Development Stage	Key Advantages	Expected Timeline
Molecule 12	Lead Optimization	Enhanced selectivity	Preclinical 2025
Molecule 15	IND-Enabling	Improved PK profile	Phase I 2026
Molecule 18	Discovery	Novel mechanism	Preclinical 2027
Bispecific-1	Lead Generation	Dual target engagement	Discovery 2025

12. ECONOMIC IMPACT AND HEALTHCARE IMPLICATIONS

12.1 Healthcare Economics

The economic effects of a successful IDE-inhibitor are huge:

- **Direct Medical Costs:** The possible decrease in healthcare spending on AD.
- **Caregiver Burden:** Reduced informal care needs.
- **Productivity Losses:** Retained working of the affected people.
- **Long-term Care:** Reduced institutionalization and related expenditure (70)

It has been postulated in economic modeling that a 2-3 year postponement in AD progression would lead to healthcare savings of up to $7.9 trillion during 30 years in the United States alone (71).

12.2 Global Health Impact

Effective development of IDE inhibitors would help to deal with the increasing world dementia burden:

- **Developing Countries:** Low-cost medicine in the developing countries.
- **Healthcare Infrastructure:** Less complex than the use of infusion-based therapies.
- **Population Aging:** Interventions that can be scaled to aging populations throughout the world.
- **Comorbidity Management:** Diabetes and cognitive decline occur together and are treated together. (72)

13. CONCLUSION

Innovations in the design of new insulinase inhibitors, especially Molecules 5 and 7, are a positive developmental breakthrough in the treatment of Alzheimer disease. These compounds have the following benefits over the current treatments:

1. Disease-modifying capability by increased Aβ clearance.
2. Two-fold pathway of action that covers amyloid pathology and metabolic dysfunction.
3. Excellent safety histories recorded during preclinical trials.
4. Oral bioavailability that enables patient compliance.
5. CNS concentrations attained that are therapeutically relevant.

These compounds have extensive preclinical data available, which, in conjunction with positive Phase I clinical findings, indicates that they exhibit high therapeutic potential. Nonetheless, some issues still exist, such as optimization of selectivity profiles, setting the right biomarkers and showing clinical effectiveness in the heterogeneous AD patient group.

The next research should be based on:

- Phase II/III clinical development of existing compounds.
- New generation of better inhibitors.
- Development of biomarker-directed therapy.
- Consideration of combination therapy.
- Discussing both access and economics of healthcare.

The area of IDE inhibition of AD will be a synthesis of decades of fundamental research and contemporary drug discovery technologies. This is an exciting and significant area of further research even though there are still challenges. Achieving success in this effort would give patients and families impacted by AD desired therapeutic choice and would aid in our understanding of neurodegenerative disease pathways.

The translation of laboratory findings to clinical practice is an example of the translational research process that illustrates the potential and challenges associated with the development of treatments to neurodegenerative diseases. In the future, the cooperation between academia, industry, and regulatory bodies should be maintained to achieve the maximum of IDE inhibitors in the treatment of AD.

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