Title: Trend of Toxic Amyloidβ Oligomer Hypothesis

INDEX

1. Current AD Drug and IVD Development

Alzheimer's disease (AD) was named by Dr. Aloysius Alzheimer, a German psychiatrist who first reported the case in 1906 and Amyloidβ was identified as the main structural component of plaque stained in brain tissue around 1985. Since the first AD report was made by Dr. Aloysius Alzheimer, Amyloidβ has been extensively researched worldwide for decades as one of the major targeted proteins to cure AD. A definitive drug for curing AD has not been established yet. The number of dementia patients including those diagnosed with AD has been continuously increased. According the WHO (World Health Organization), the current number of dementia patients is approx. 50 MIL people and it is predicted to be reached around 152 MIL people (3 times bigger) in 2050 in the world. It is also reported that the global expenditure for taking care of dementia patients is approx. 818 BIL (USD) which is equivalent to 1.1% of world GDP.

References: Risk reduction of cognitive decline and dementia: WHO guidelines ISBN 978-92-4-155054-3
https://cdn.prod-carehubs.net/n1/802899ec472ea3d8/uploads/2019/05/Dementia-Guidelines_30042019-Final-embargoed.pdf

Global researchers have been aggressively working on AD drug development. Secretase inhibitors and immune therapy (active immunization – administration of Amyloidβ peptides or passive immunization – administration of anti- Amyloidβ antibody) have mostly focused on anti-Amyloidβ treatment.

Many reports have been made regarding the efficacy of antibody drugs (administration of anti-Amyloidβ antibody). However, the most of clinical trials initiated by global pharmaceutical companies failed at phase III due to its side effects and the lack of efficacy of the drugs. We are still struggling to develop disease modifying drugs to completely cure AD and it is still considered that AD treatment is an unmet medical need.

Regarding AD diagnosis, the guideline is different from country to country but it is well known that Amyloidβ42 is decreased and Total Tau and phosphorylated Tau (pTau) are increased in CSF of AD patients. In Japan, measurement of pTau in CSF has been subjected for reimbursement with the purpose of an assistive tool in AD diagnosis while measurement of Amyloidβ42 has not.

It has been considered that decreasing Amyloidβ42 is because of accumulating Amyloidβ in brain. Currently available measurement tools of Amyloidβ42 as an assistant of AD diagnosis mainly detects Amyloidβ42 monomers and/or fibrils that are considered less toxic due to the specificity of antibodies used in the measurement assay system. This has led to some concern about the risk of "over diagnosis of AD".

As fibrosis of Amyloidβ42 is found in early stage of AD, there are also some voices for the requirement of developing a diagnostic tool using specific antibodies can detect Amyloidβ42 oligomers since it is considered that oligomers easily aggregate and are more neurotoxic.

2. Neurotoxic Amyloidβ Oligomer Hypothesis (On-pathway / Off-pathway)

It is known that Amyloidβ is accumulated in the brain of AD patients. and Insoluble fibrils made by aggregated Amyloidβ form plaques inducing nerve cell mutations to develop AD and is called the "Amyloid Hypothesis". However, a recent new hypothesis called "low molecular weight Amyloidβ toxic oligomer hypothesis" is more widely accepted. The hypothesis is that soluble and low molecular weight Amyloidβ oligomer intermediate products produced during oligomerization process have more synaptic dysfunction causing decreased cognitive function and eventually the development of AD.

There are some points of view with regard to main reasons for failure of anti Amyloidβ antibody drug development for curing AD at the final stage. The reasons could be (1) lack of optimizing an antibody that can specifically detect toxic Amyloidβ oligomers and (2) the timing was too late for administration of antibody drug for AD patients.

Actually, it has been observed that Amyloidβ oligomers increased in the brain of AD patients compared to healthy normal control, however, as Amyloidβ oligomer is not well understood yet, Amyloidβ oligomers have been gathering a lot of interest from AD researchers as research target of anti- Amyloidβ antibody drugs.

3. Toxic Conformer Amyloidβ Hypothesis and Development of the Specific Antibody

A Kyoto University research group let by Prof. Irie identified that Amyloidβ toxic conformer (turned at 22-23 aa) is more toxic and easily aggregated while Amyloidβ non-toxic conformer (turned at 25-26 aa) is much less toxic and not much aggregated in Amyloidβ42 aggregation. Since Amyloidβ42 tends to aggregate and more is more toxic compared to Amyloidβ40, the focus is on Amyloidβ42 in research surrounding the toxic conformer (22-23 turn structure) Amyloidβ hypothesis.

The new hypothesis was developed that the Amyloidβ toxic conformer (turned at 22-23 aa) is fixed at the turn structure by Proline mutation at 22 amino acid position. The fixed form tends to be more aggregated to be more toxic. Moreover, the research group has also developed the hypothesis with regard to the pathway of Amyloidβ oligomerization. They have defined two pathways called On-Pathway and Off-Pathway.

The On-Pathway was defined as the pathway which involving the process of Amyloidβ to become fibrils considered as stable and weak toxicity oligomerization. The Off-Pathway was defined as the process of Amyloidβ to becoming soluble intermediate oligomers (ADDL ~24mer, Annulus ~50mer, and Amylospheroid ~ 150mer) without forming fibrotic oligomers. The hypothesis has been continuously researched for revealing more detailed Amyloidβ oligomerization processes.

Please refer to the following publication for further details about the hypothesis.
New Diagnostic Method for Alzheimer's Disease Based on the Toxic Conformation Theory of Amyloid β. Kazuhiro Irie et al. Biosci Biotechnol Biochem. 2020 Jan;84(1):1-16.
More related publications are also available here.

4. Potential of Anti- AmyloidβE22P (24B3)Monoclonal Antibody

The research group has successfully developed the monoclonal antibody (clone: 24B3) that specifically detects Amyloidβ toxic conformer (turned at 22-23aa) defined above and the sandwich ELISA with Amyloidβ N-term specific monoclonal antibody (clone: 82E1). It has been also suggested that the monoclonal antibody (clone:24B3) suppresses oligomerization of Amyloidβ42 and E22P- Amyloidβ42 in neurotoxicity test of the following publication and cell survival rate was significantly improved compare to Amyloidβ N-term specific antibody or control group.

Please refer to the following publication for more details of the study.
Monoclonal antibody with conformational specificity for a toxic conformer of amyloid β42 and its application toward the Alzheimer's disease diagnosis. Murakami K et al. Sci Rep. 2016 Jul 4;6:29038

5. IBL with AD research

IBL has been developing, manufacturing and supplying in-house developed antibodies and ELISAs over 37 years since IBL was established in 1982. IBL has continuously researched and developed Amyloidβ related research products with academic collaborators in the AD field since Amyloidβ drug discovery researches become more active in 1995 (almost 25 years ago). Back in those days, there were no many ELISA kit which enable to accurately and quantitatively measure Amyloidβ available. IBL was one of the pioneers for entering the market and supplying Amyloidβ ELISA kits. We have continued to research and supply various antibodies and ELISA that can detect AD biomarkers such as APP, Amyloidβ, Tau and the aging biomarker α-Klotho.

IBL-America Amyloid Beta Toxic Oligomer

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