

## **Title: Trend of Toxic Amyloid $\beta$ Oligomer Hypothesis**

### INDEX

1. Current AD Drug and IVD Development
2. Neurotoxic Amyloid $\beta$  Oligomer Hypothesis (On-pathway / Off-pathway)
3. Toxic Conformer Amyloid $\beta$  Hypothesis and Development of the Specific Antibody
4. Potential of Anti- Amyloid $\beta$ E22P (24B3) Monoclonal Antibody
5. IBL with AD research

### **1. Current AD Drug and IVD Development**

Alzheimer's disease (AD) was named by Dr. Aloisius Alzheimer, a German psychiatrist who first reported the case in 1906 and Amyloid $\beta$  was identified as the main structural component of plaque stained in brain tissue around 1985. Since the first AD report was made by Dr. Aloisius Alzheimer, Amyloid $\beta$  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](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 Amyloid $\beta$  peptides or passive immunization – administration of anti- Amyloid $\beta$  antibody) have mostly focused on anti-Amyloid $\beta$  treatment.

Many reports have been made regarding the efficacy of antibody drugs (administration of anti-Amyloid $\beta$  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 Amyloid $\beta$ 42 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 Amyloid $\beta$ 42 has not.

It has been considered that decreasing Amyloid $\beta$ 42 is because of accumulating Amyloid $\beta$  in brain. Currently available measurement tools of Amyloid $\beta$ 42 as an assistant of AD diagnosis mainly detects Amyloid $\beta$ 42 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 Amyloid $\beta$ 42 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 Amyloid $\beta$ 42 oligomers since it is considered that oligomers easily aggregate and are more neurotoxic.

### **2. Neurotoxic Amyloid $\beta$ Oligomer Hypothesis (On-pathway / Off-pathway)**

It is known that Amyloid $\beta$  is accumulated in the brain of AD patients. and Insoluble fibrils made by aggregated Amyloid $\beta$  form plaques inducing nerve cell mutations to develop AD and is called the "Amyloid Hypothesis". However, a recent new hypothesis called "low molecular weight Amyloid $\beta$  toxic oligomer hypothesis" is more widely accepted. The hypothesis is that soluble and low molecular weight Amyloid $\beta$  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 Amyloid $\beta$  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 Amyloid $\beta$  oligomers and (2) the timing was too late for administration of antibody drug for AD patients.

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

### **3. Toxic Conformer Amyloid $\beta$ Hypothesis and Development of the Specific Antibody**

A Kyoto University research group led by Prof. Irie identified that Amyloid $\beta$  toxic conformer (turned at 22-23 aa) is more toxic and easily aggregated while Amyloid $\beta$  non-toxic conformer (turned at 25-26 aa) is much less toxic and not much aggregated in Amyloid $\beta$ 42 aggregation. Since Amyloid $\beta$ 42 tends to aggregate and more is more toxic compared to Amyloid $\beta$ 40, the focus is on Amyloid $\beta$ 42 in research surrounding the toxic conformer (22-23 turn structure) Amyloid $\beta$  hypothesis.

The new hypothesis was developed that the Amyloid $\beta$  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 Amyloid $\beta$  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 Amyloid $\beta$  to become fibrils considered as stable and weak toxicity oligomerization. The Off-Pathway was defined as the process of Amyloid $\beta$  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 Amyloid $\beta$  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  \$\beta\$ . Kazuhiro Irie et al. Biosci Biotechnol Biochem. 2020 Jan;84\(1\):1-16.](#)

More related publications are also available [here](#).

### **4. Potential of Anti- Amyloid $\beta$ E22P (24B3) Monoclonal Antibody**

The research group has successfully developed the monoclonal antibody (clone: 24B3) that specifically detects Amyloid $\beta$  toxic conformer (turned at 22-23aa) defined above and the sandwich ELISA with Amyloid $\beta$  N-term specific monoclonal antibody (clone: 82E1). It has been also suggested that the monoclonal antibody (clone:24B3) suppresses oligomerization of Amyloid $\beta$ 42 and E22P- Amyloid $\beta$ 42 in neurotoxicity test of the following publication and cell survival rate was significantly improved compare to Amyloid $\beta$  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  \$\beta\$ 42 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 Amyloid $\beta$  related research products with academic collaborators in the AD field since Amyloid $\beta$  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 Amyloid $\beta$  available. IBL was one of the pioneers for entering the market and supplying Amyloid $\beta$  ELISA kits. We have continued to research and supply various antibodies and ELISA that can detect AD biomarkers such as APP, Amyloid $\beta$ , Tau and the aging biomarker  $\alpha$ -Klotho.

Immuno-Biological Laboratories Co., Ltd. / Aging,  
Neurodegenerative IBL Global Sales Network

Distributed by:



Immuno-Biological Laboratories, Inc. Toll-Free: 888-523-1246  
8201 Central Ave NE, Suite P Email: info@IBL-America.com  
Minneapolis, MN 55432 Web: www.IBL-America.com