

**CLEARANCE OF AMYLOID-BETA IN
ALZHEIMER'S DISEASE**

**To understand the pathogenesis and develop potential
therapies in animal models**

**A THESIS SUBMITTED IN TOTAL FULFILMENT
OF THE REQUIREMENTS OF
THE DEGREE OF DOCTOR OF PHILOSOPHY
BY**

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TABLE OF CONTENTS

THESIS SUMMARY	VI
DECLARATION	VIII
SCHOLARSHIPS SUPPORTING THE PHD STUDY	IX
PERSONAL PUBLICATIONS AND CONFERENCE PRESENTATIONS	X
ACKNOWLEDGEMENTS	XII
CHAPTER 1	1
Literature review: Clearance of Amyloid-beta in Alzheimer's Disease	
INTRODUCTION	2
RECEPTOR-MEDIATED Aβ TRANSPORT ACROSS BLOOD-BRAIN BARRIER (BBB)	4
Efflux of A β from CNS to plasma	4
LRP-mediated A β efflux	4
P-glycoprotein mediated A β efflux	6
Influx of A β from plasma to CNS	6
RAGE-mediated A β influx	7
gp330/megalin-mediated A β influx	8
ENZYME-MEDIATED Aβ DEGRADATION	10
Neprilysin	10
Insulin degrading enzyme (IDE)	11
Other enzymes associated with A β degradation	12
NATURAL ANTI-Aβ AUTOANTIBODIES	14
THERAPEUTIC CLEARANCE OF Aβ	15
Immunotherapy-mediated A β clearance	15
Active immunotherapy	15
Passive immunotherapy	16
Mechanisms of A β clearance by immunotherapy	17
Adverse effect of immunotherapy	18
Improvement of vaccine	20
Modification of anti-A β antibody	22
Anti-A β single chain antibody (scFv)	22

Targeting A β oligomers	23
A β binding substance-mediated A β clearance	25
CONCLUSIONS	26
CHAPTER 2	27
Intramuscular Delivery of a Single Chain Antibody Gene Prevents Brain Aβ Deposition and Cognitive Impairment in a Mouse Model of Alzheimer's Disease	
SUMMARY.....	28
INTRODUCTION	29
MATERIALS AND METHODS	30
Animals	30
rAAV vector construction and production	30
Muscle injection	31
Behavioral test.....	31
Tissue sampling.....	32
Expression of transgenes	33
Histology and image quantification	33
Quantification of A β peptide levels in the brain and plasma by ELISA.....	35
Quantification of inflammatory cytokines in the brain and plasma by ELISA..	35
ELISA assay for antibodies against scFv in mice after intramuscular delivery of rAAV-scFv.	36
Statistical analysis	36
RESULTS	36
Expression of scFv gene after intracranial and intramuscular delivery	36
These histological and biochemical data indicate that intramuscular delivery of scFv gene effectively prevents A β accumulation and deposition in the brain...	40
Intramuscular delivery of scFv gene attenuates AD-type pathologies.....	40
Intramuscular delivery of scFv gene prevents amyloid-associated cognitive impairments	41
Intramuscular delivery of scFv gene is well tolerated and does not cause inflammation and microhemorrhage in the injection sites and brain	41
ScFv has low immunogenicity and does not induce antibodies.....	42
DISCUSSION	43
CONCLUSIONS	46

CHAPTER 3	48
Grape Seed Derived Polyphenols Attenuate Amyloid-beta Neuropathology in the Brain of Alzheimer’s Disease Mice	
SUMMARY.....	49
INTRODUCTION	50
MATERIAL AND METHODS	51
Transgenic mouse model.....	51
HPLC analysis of polyphenols in GSE	52
Diets.....	52
Tissue sampling.....	53
AD-type pathology and quantitative image analysis.....	54
Quantification of A β peptide levels in the mouse brain and plasma by ELISA	55
Western blot for APP and BACE expression.....	55
Quantification of TNF α , IL-1 β and IFN- γ in the mouse plasma by ELISA.....	56
Assessment of toxicity of polyphenol from grape seeds.....	56
Statistical analysis	56
RESULTS	57
Chemical analysis of polyphenols in GSE	57
GSE is well tolerated in APPSwe/PS1dE9 transgenic mice	57
GSE reduces brain and serum A β levels and prevents A β deposition in APPSwe/PS1dE9 transgenic mice.....	58
GSE does not change the expression of APP and BACE1 in the brain of APPSwe/PS1dE9 transgenic mice.....	60
GSE prevents AD-type neuropathology in APPSwe/PS1dE9 transgenic mice .	60
Plasma and brain levels of inflammatory cytokines after GSE consumption	61
DISCUSSIONS	62
CONCLUSIONS	66
CHAPTER 4	68
Deletion of P75NTR Reduces Aβ Production But Exacerbates Aβ Pathology by Increasing Aβ Deposition in an Alzheimer’s Disease Mouse Model	
SUMMARY.....	69
INTRODUCTION	70

MATERIALS AND METHODS	72
Generation of APPSwe/PS1dE9 transgenic mice with deletion of p75NTR gene	72
Behavioural test.....	73
Tissue sampling.....	74
AD-type pathology and quantitative image analysis.....	74
Quantification of A β peptide levels by ELISA	76
APP proteolytic processing and α , β , γ -secretase activities.....	77
Western blot analysis.....	78
Primary cortical neuron culture.....	79
Effects of p75NTR extracellular domain on A β oligomerization and fibrillation	79
Hippocampus injection of p75/Fc and A β plaque analysis.....	81
Statistical analysis	81
RESULTS	82
Expression pattern of p75NTR in the brain of APPSwe/PS1dE9 transgenic mice	82
Deletion of p75NTR exacerbates A β -related pathologies	83
Deletion of p75NTR increases insoluble A β but decreases soluble A β levels in the brain.....	84
Deletion of p75NTR does not affect APP proteolytic processing.....	86
Deletion of p75NTR decreases A β production <i>in vitro</i>	87
Deletion of p75NTR does not affect A β degrading enzymes in the brain	87
Recombinant extracellular domain of p75NTR inhibits the formation of A β fibrils	88
Deletion of p75NTR exacerbates other AD type pathologies.....	89
Deletion of p75NTR does not lessen memory deficits till nine months of age..	90
DISCUSSION	90
CONCLUSIONS	95
CHAPTER 5	96
Future Directions	
1. INTRAMUSCULAR DELIVERY OF A SINGLE CHAIN ANTIBODY GENE PREVENTS BRAIN Aβ DEPOSITION AND COGNITIVE IMPAIRMENT IN A MOUSE MODEL OF AD..	97

(1) What is the mechanism underlying the A β reducing effect of the scFv?	98
(2) How to improve the therapeutic effect of the scFv?.....	98
(3) Whether the scFv is able to inhibit A β oligomerization and block the neurotoxicity of A β	99
2. GRAPE SEED DERIVED POLYPHENOLS ATTENUATE AMYLOID-BETA NEUROPATHOLOGY IN THE BRAIN OF AD MICE	100
(1) What are the mechanisms of the A β reducing effect of grape seed derived polyphenols?.....	100
(2) Which components of GSE are active in reducing A β in the brain?.....	101
(3) Are grape seed derived polyphenols also able to treat other protein misfolding diseases?.....	101
3. DELETION OF p75NTR REDUCES Aβ PRODUCTION BUT EXACERBATES Aβ PATHOLOGY BY INCREASING Aβ DEPOSITION IN AN AD MOUSE MODEL	102
(1) What is the mechanism for promotion of A β production by p75NTR?	102
(2) What are the roles of p75NTR in the neuronal degeneration in AD?	103
(3) Development of novel therapies targeting p75NTR	104
SUMMARY.....	104
BIBLIOGRAPHY	106

THESIS SUMMARY

Alzheimer's disease (AD) is the most common cause of dementia. No strong disease-modifying treatments are currently available. Amyloid-beta peptide ($A\beta$) appears to play a pivotal role in the pathogenesis of AD. We focused our interest on revealing the pathogenesis of the disease and developing novel therapeutic modalities. The thesis consists of three projects:

1. Prevention of AD by intramuscular delivery of an anti- $A\beta$ single chain antibody (scFv) gene

Immunotherapy is effective in removing brain $A\beta$, but was associated with detrimental effects. In the present study, the gene of an anti- $A\beta$ scFv was delivered in the hind leg muscles of APPSwe/PS1dE9 mice with adeno-associated virus at three months of age. Six months later, we found that brain $A\beta$ accumulation, AD-type pathologies and cognitive impairment were significantly attenuated in scFv-treated mice relative to enhanced green fluorescence protein (EGFP)-treated mice. Intramuscular delivery of scFv gene was well tolerated by the animals. These findings suggest that peripheral application of scFv is effective and safe in preventing the development of AD, and would be a promising non-inflammatory immunological modality for prevention and treatment of AD.

2. Prevention of AD with grape seed derived polyphenols

Polyphenols extracted from grape seeds are able to inhibit $A\beta$ aggregation, reduce $A\beta$ production and protect against $A\beta$ neurotoxicity *in vitro*. We investigated the therapeutic effects of a polyphenol-rich grape seed extract (GSE) *in vivo*.

APP^{Swe}/PS1^{dE9} transgenic mice were fed with normal AIN-93G diet (control diet), AIN-93G diet with 0.07% curcumin, or diet with 2% GSE beginning at 3 months of age for 9 months. Total phenolic content of GSE was 592.5 mg/g dry weight, including gallic acid, catechin, epicatechin and proanthocyanidins. Long-term feeding of GSE diet was well tolerated. The A β levels in the brain and serum of the mice fed with GSE were reduced by 33% and 44% respectively compared with the mice fed with the control diet. Amyloid plaques and microgliosis in the brain of mice fed with GSE were also reduced by 49% and 70% respectively. In conclusion, polyphenol-rich GSE is promising to be a safe and effective drug to prevent the development of AD.

3. Roles of p75^{NTR} in the development of AD

P75^{NTR} has been suggested to mediate A β induced neurotoxicity. However, its role in the development of AD is undetermined. APP^{Swe}/PS1^{dE9} transgenic mice were crossed with p75^{NTR} knockout mice to generate APP^{Swe}/PS1^{dE9} mice with p75^{NTR} gene deleted. P75^{NTR} mainly expressed in the basal forebrain neurons and degenerative neurites in neocortex and hippocampus. Genetic deletion of p75^{NTR} gene in APP^{Swe}/PS1^{dE9} mice reduced soluble A β levels, but increased the insoluble A β accumulation and A β plaque formation in the brain. P75^{NTR} deletion decreased A β production of cortical neurons *in vitro*. Recombinant extracellular domain of p75^{NTR} attenuated the oligomerization and fibrillation of synthetic A β ₄₂ peptide *in vitro*, and reduced local A β plaques after hippocampus injection *in vivo*. Our data suggest that p75^{NTR} plays an important role in AD development and may be a valid therapeutic target for the treatment of AD.

DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

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Yan-Jiang Wang

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SCHOLARSHIPS SUPPORTING THE PHD STUDY

1. International Postgraduate Research Scholarship. Federal Government of Australia, 2005-2009
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PERSONAL PUBLICATIONS AND CONFERENCE PRESENTATIONS

Refereed journal articles

1. **Wang YJ**, Wang X, Li QX, Sun Y, Liu XH, Gao CY, Yang M, Lim Y, Evin G, Zhong JH, Masters C, Zhou XF. p75NTR regulates Abeta deposition by increasing Abeta production but inhibiting Abeta aggregation (In submission).
2. **Wang YJ**, Gao CY, Yang M, Pollard A, Valadares D, Liu XH, Dong XY, Wu XB, Zhong JH, Zhou HD, Zhou XF (2010). Intramuscular delivery of a single chain antibody gene prevents brain Abeta deposition and cognitive impairment in a mouse model of Alzheimer's disease. *Brain Behav Immun* (in revision).
3. Wong I, Liao H, Bai X, Zaknic A, Zhong J, Guan Y, Li HY, **Wang YJ***, Zhou XF*(2010). ProBDNF inhibits infiltration of ED1+ macrophages after spinal cord injury. *Brain Behav Immun* (in press, * Co-corresponding author)
4. **Wang YJ**, Valadares D, Sun Y, Wang X, Zhong JH, Liu XH, Majd S, Chen L, Gao CY, Chen S, Lim Y, Pollard A, Aguilar E, Gai WP, Yang M, Zhou XF (2010) Effects of proNGF on neuronal viability, neurite growth and amyloid-beta metabolism. *Neurotox Res* 17: 257-67.
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1. **Wang YJ**, Thomas P, Zhong JH, Bi FF, Kosaraju S, **Pollard A**, Fenech M, Zhou XF. (2008) Consumption of polyphenol-rich grape seed extract prevents amyloid deposition and suppresses inflammation in the brain of a transgenic mouse model for AD. Society for Neuroscience (SfN) 38th annual meeting, Washington DC, US, Nov19 (Symposium talk)
2. **Wang YJ**, Thomas P, Zhong JH, Bi FF, Pollard A, Kosaraju S, Fenech M, X.F. Zhou. Polyphenols of grape seeds prevents amyloid deposition in the brain of Alzheimer's mice. 3rd Asia-Pacific conference on Nutrigenomics, Melbourne, Australia, May 5-8. (Oral presentation)
3. **Wang YJ**, Pollard AN, Zhou HD, Zhong JH, and Zhou XF. (2006) Characterization of an AD Mouse Model Bearing Mutant Genes of Amyloid Precursor Protein and Human Presenilin 1. Australian Neuroscience Society (ANS) 26th annual meeting, Sydney, Australia, Jan 31-Feb 3. (Poster presentation)

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A handwritten signature in black ink, reading "Yan-Jiang Wang". The signature is written in a cursive, flowing style.

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