Novel Approaches for the Treatment of Alzheimer's Disease

Literature Seminar

2020/06/17

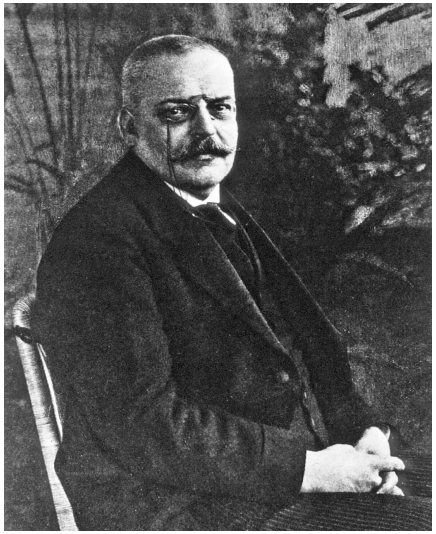
M1 Atsushi Iwai

Contents

Introduction

Alzheimer's Disease

- **Symptoms**
  - Impairment of life functioning
  - Disorientation
  - Memory impairment
  - Speech impediment
  - Visuospatial cognitive impairment
  - Executive dysfunction
  - Psychological symptoms



Aloysius Alois Alzheimer

- **Pathology**
  - Degenerative loss of neurons and associated cerebral atrophy
  - Multiple senile plaques
  - Multiple neurofibrillary tangles

Introduction

Social issues of Alzheimer's disease

- **Number of patients**
  - 47.5 million (2015)
  - Over 9.9 million new cases of AD-related dementia are diagnosed every year.

- **Social costs**
  - Direct medical costs (e.g. nursing home care)
  - Direct nonmedical costs (e.g. in-home day care)
  - Indirect costs (e.g. lost productivity of both patient and caregiver)
  - Dementia costs worldwide have been calculated around $818 billion (2015)
  - The most costly diseases for society in developed countries

World Alzheimer Report 2015: The Global Impact of Dementia.

Introduction

Three main hypothesis

- **Cholinergic hypothesis**

  AD is caused by reduced synthesis of the neurotransmitter acetylcholine.

- **Amyloid hypothesis**

  Extracellular amyloid beta (Aβ) deposits are the fundamental cause of the disease.

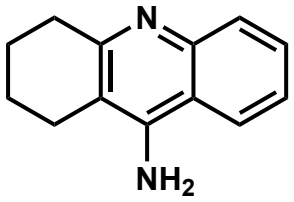
- **Tau hypothesis**

  Tau protein abnormalities initiate the disease cascade.

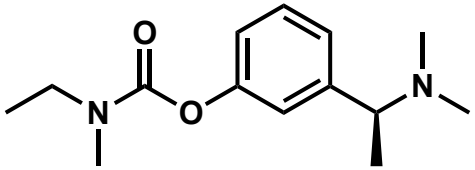
Introduction

Existing drugs

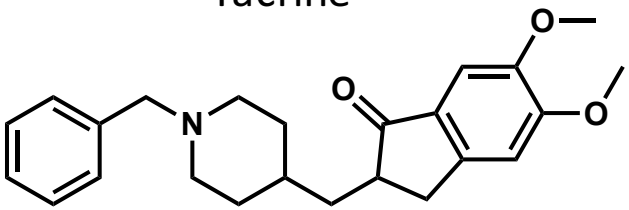
- acetylcholinesterase inhibitor



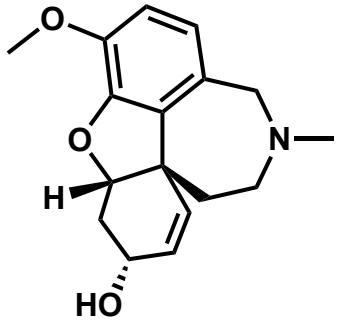
Tacrine



Rivastigmine

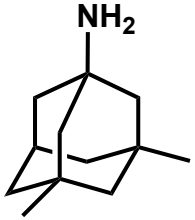


Donepezil



Galantamine

- NMDAR antagonist



Memantine

Introduction

Examples of failed clinical trials of anti-Ab drugs

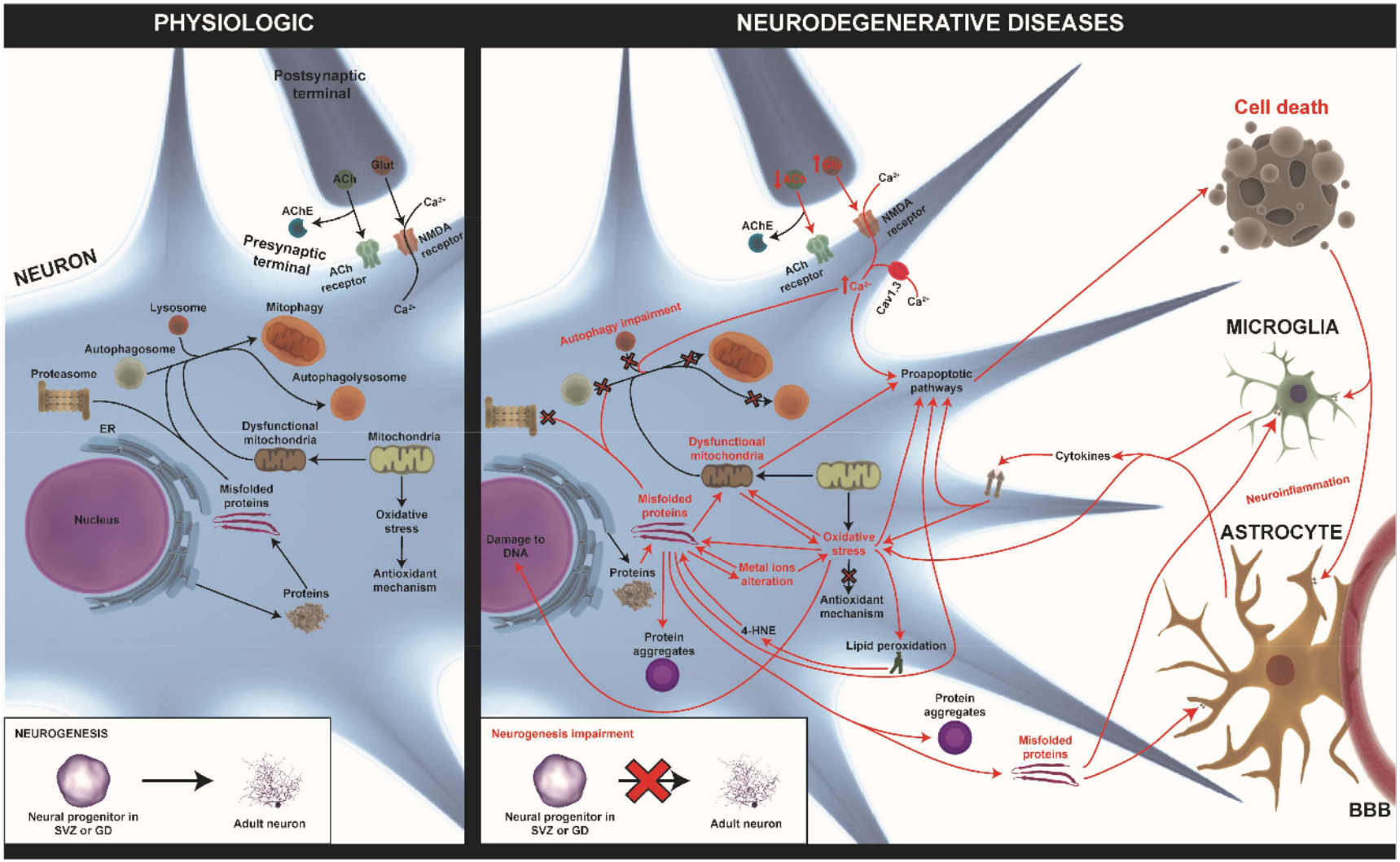
Name	Mode of Action	Sponsor Involved in the Clinical Trials
Solanezumab	Monoclonal antibody	Eli Lilly
Crenezumab	Monoclonal antibody	Roche- Genetech
Gantenerumab	Monoclonal antibody	Roche- Genetech
Aducanumab	Monoclonal antibody	Biogen
Verubecestat	BACE1 inhibitor	Merck
Lanabecestat	BACE1 inhibitor	Astra, Eli lilly
Atabecestat	BACE1 inhibitor	Janssen

Nurul Husna Ibrahim, Mohamad Fairuz Yahaya, Wael Mohamed, Seong Lin Teoh, Chua Kien and Jaya Kumar, *Front. Pharmacol.*, **2020**, *11*, 261.

Contents

AD pathology

The general pathways involved in neurodegenerative diseases



Van Bulck M, Sierra-Magro A, Alarcon-Gil J, Perez-Castillo A, Morales-Garcia JA, *Int. J. Mol. Sci.*, **2019**, *20*, 719.

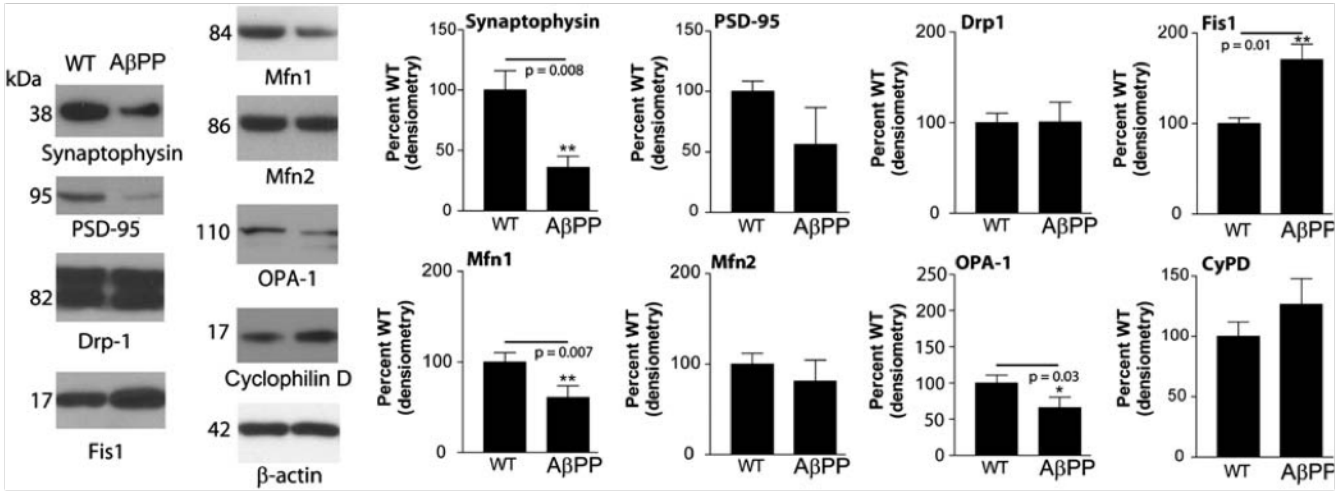
AD pathology

Aβ changes expression level of mRNA and proteins

- **mRNA**

Synaptic		Peroxyredoxins		Mitochondrial dynamics/matrix	
PSD-95	−1.5*	Prx1	−1.3	Fis1	1.5*
Synaptophysin	−2.0*	Prx2	−1.1	Drp1	1.1
Synapsin1	−1.5**	Prx3	−1.3	Mfn1	−1.6*
Synapsin2	−1.4**	Prx4	−1.2	Mfn2	−1.1
Synaptobrevin1	−1.3*	Prx5	−1.1	OPA-1	−1.3
Synaptobrevin2	−1.3*	Prx6	1.0	CypD	1.6**
GAP43	−1.2**				
Neurogranin	1.0				
Synaptopodin	−1.1				

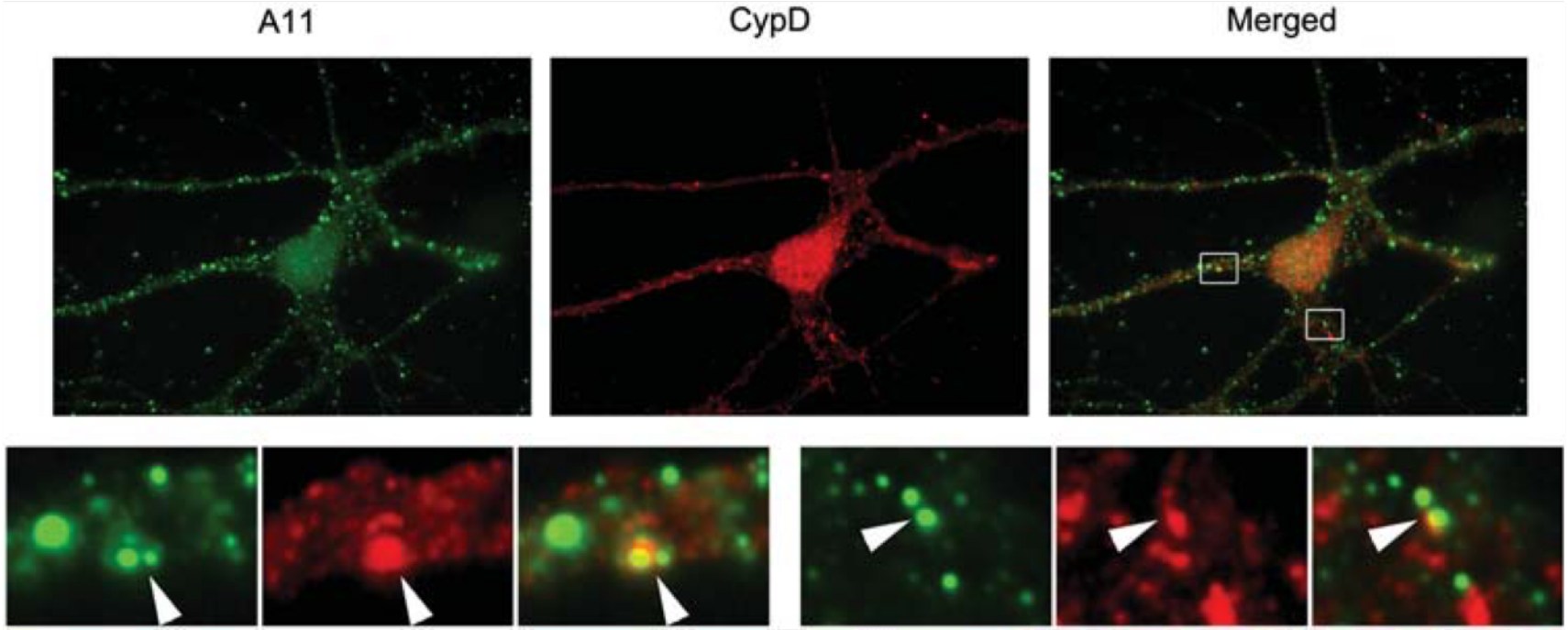
- **Proteins**



Calkins MJ, Manczak M, Mao P, Shirendeb U, Reddy PH., *Hum. Mol. Genet.*, **2011**, *20*, 4515.

AD pathology

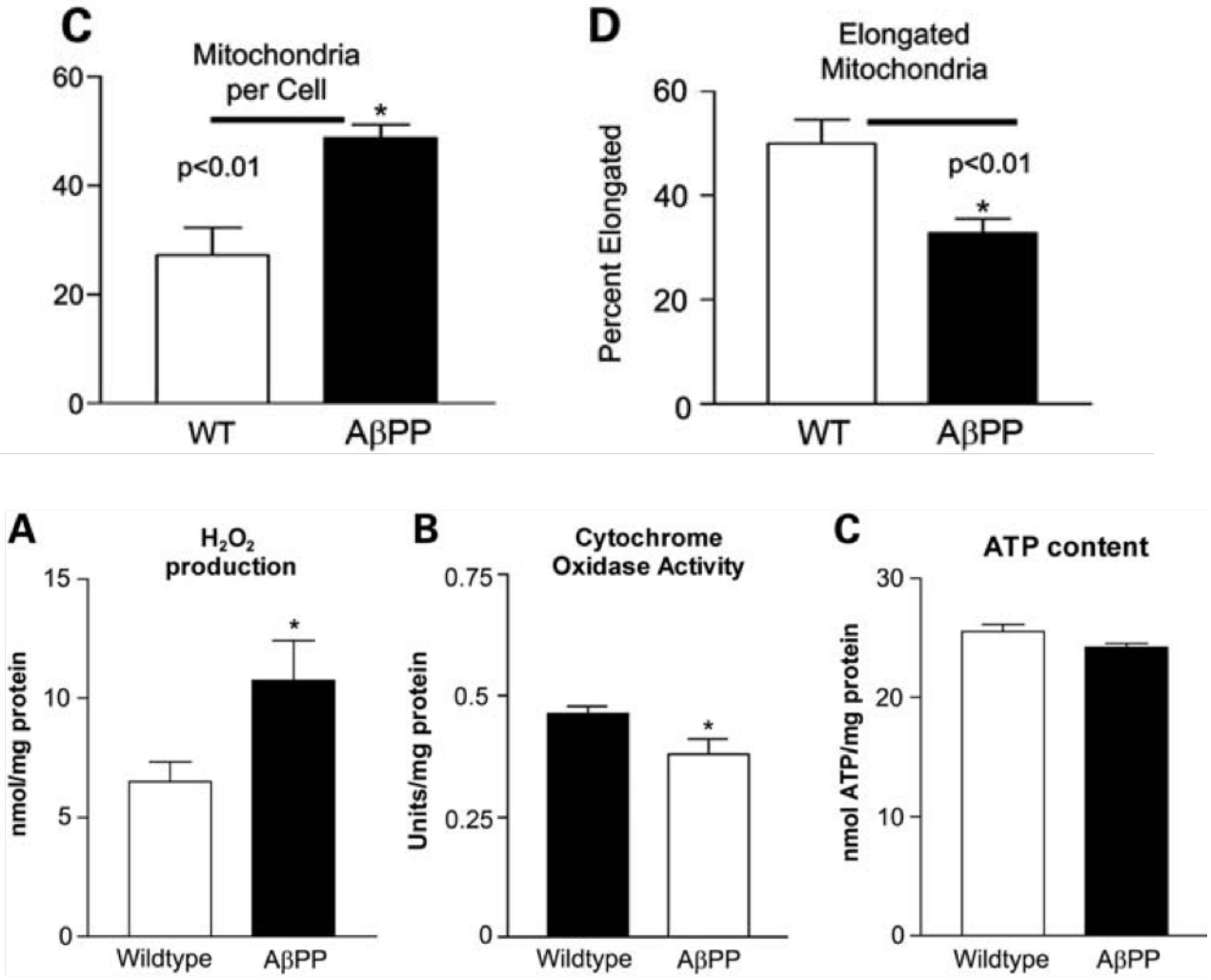
Aβ oligomer localizes in mitochondria



Calkins MJ, Manczak M, Mao P, Shirendeb U, Reddy PH., *Hum. Mol. Genet.*, **2011**, *20*, 4515.

AD pathology

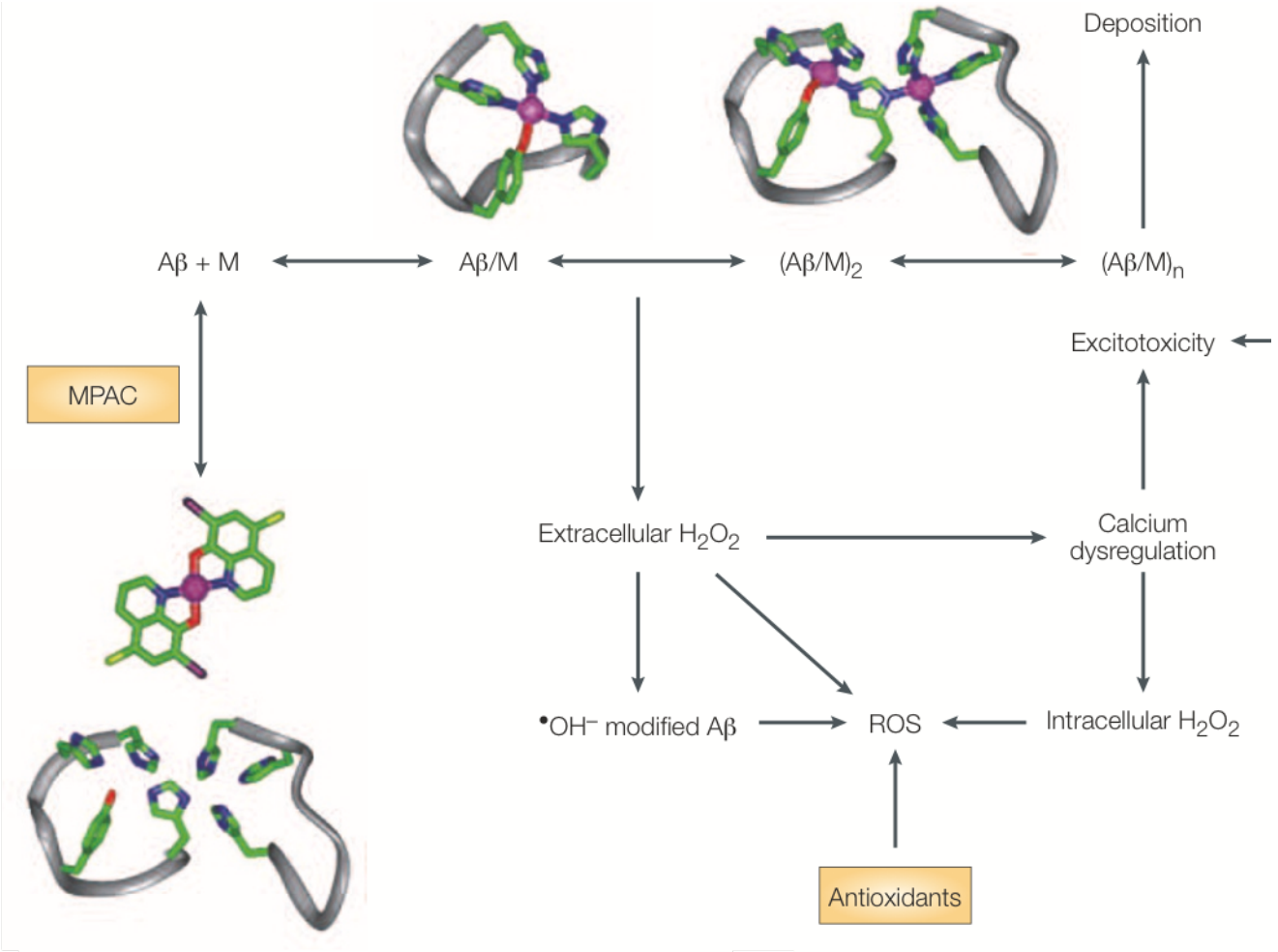
Effects on mitochondria



Calkins MJ, Manczak M, Mao P, Shirendeb U, Reddy PH., *Hum. Mol. Genet.*, **2011**, *20*, 4515.

AD pathology

Aβ coordinates metal ions



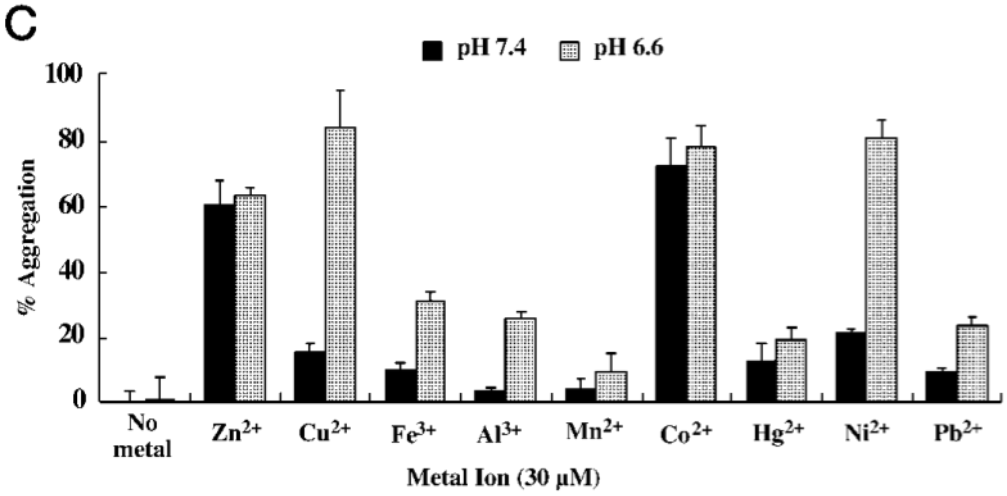
Barnham, K.J.; Masters, C.L.; Bush, A.I., *Nat. Rev. Drug Dis.*, **2004**, *3*, 205.

AD pathology

Metal ions promote Aβ aggregation

	Copper (μg/g) Mean±S.E.M.	Iron (μg/g) Mean±S.E.M.	Zinc (μg/g) Mean±S.E.M.
SP Rim	22.7±6.5[a]	52.4±14.5[a]	67.0±13.0[a]
SP Core	30.1±11.0[b]	53.1±13.7[a]	86.8±21.0[a]
Total SP	25.0±7.8[a]	52.5±13.7[a]	69.0±18.4[a]
AD Neuropil	19.3±6.3[b]	38.8±9.4[b]	51.4±11.0[c]
Control Neuropil	4.4±1.5	18.9±5.3	22.6±2.8

[a] $P<0.05$ (Plaque values vs. AD neuropil).
[b] $P\leq0.08$ (AD Neuropil vs. control neuropil).
[c] $P<0.05$ (AD Neuropil vs. control neuropil).



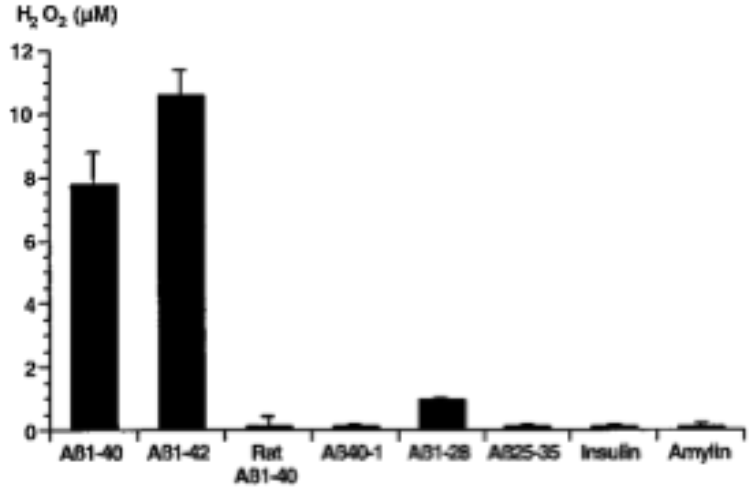
Lovell, M. A., Robertson, J. D., Teesdale, W. J., Campbell, J. L. & Markesbery, W. R., *J. Neurol. Sci.*, **1998**, *158*, 47.

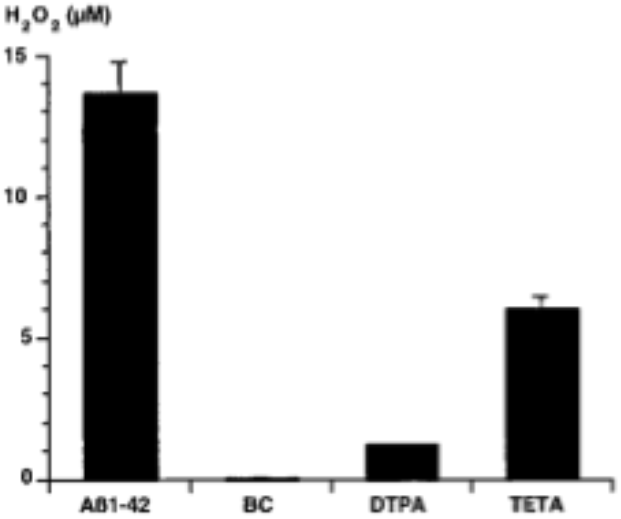
Atwood, C. S., Moir, R. D., Huang, X., Scarpa, R. C., Bacarra, N. M. E., Romano, D. M., Hartshorn, M. A., Tanzi, R. E., Bush, A. I., *J. Biol. Chem.*, **1998**, *273*, 12817.

Appendix

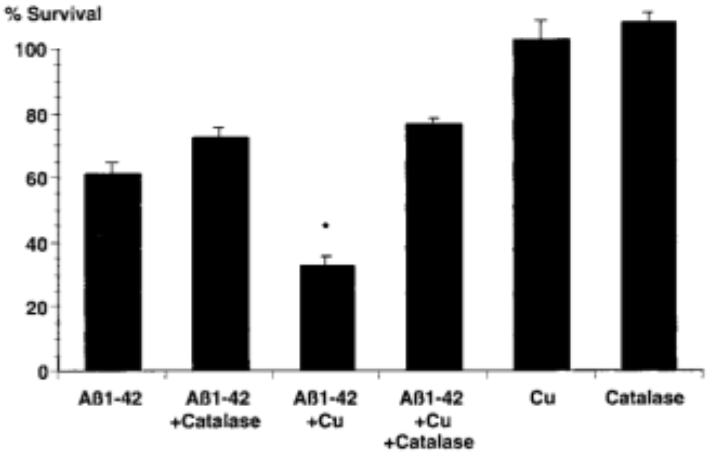
Cu & Aβ promote H_2O_2 production

H_2O_2





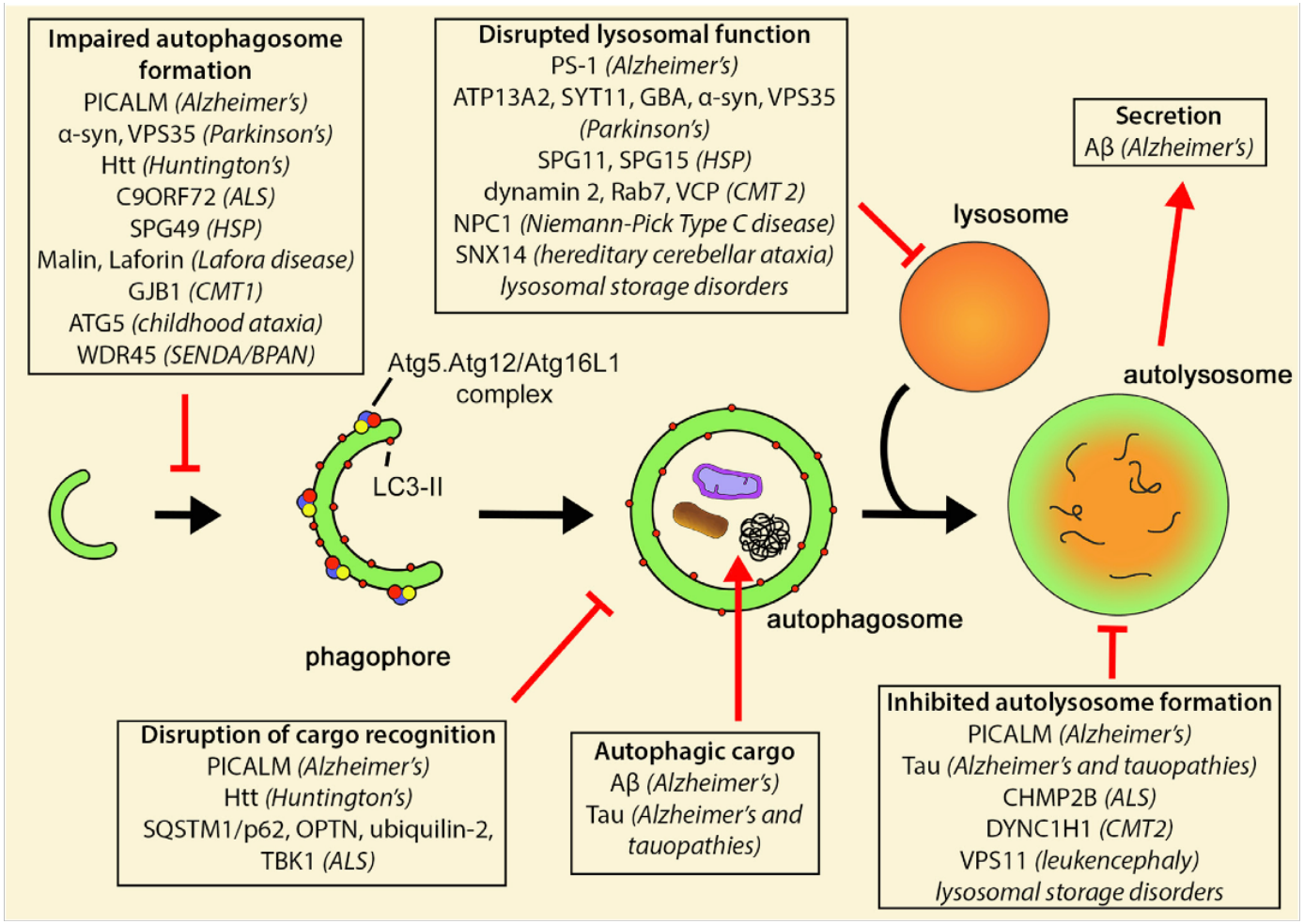
cell survival



Bush A. I. *et al.*, *J. Biol. Chem.*, **1999**, *274*, 37111.

AD pathology

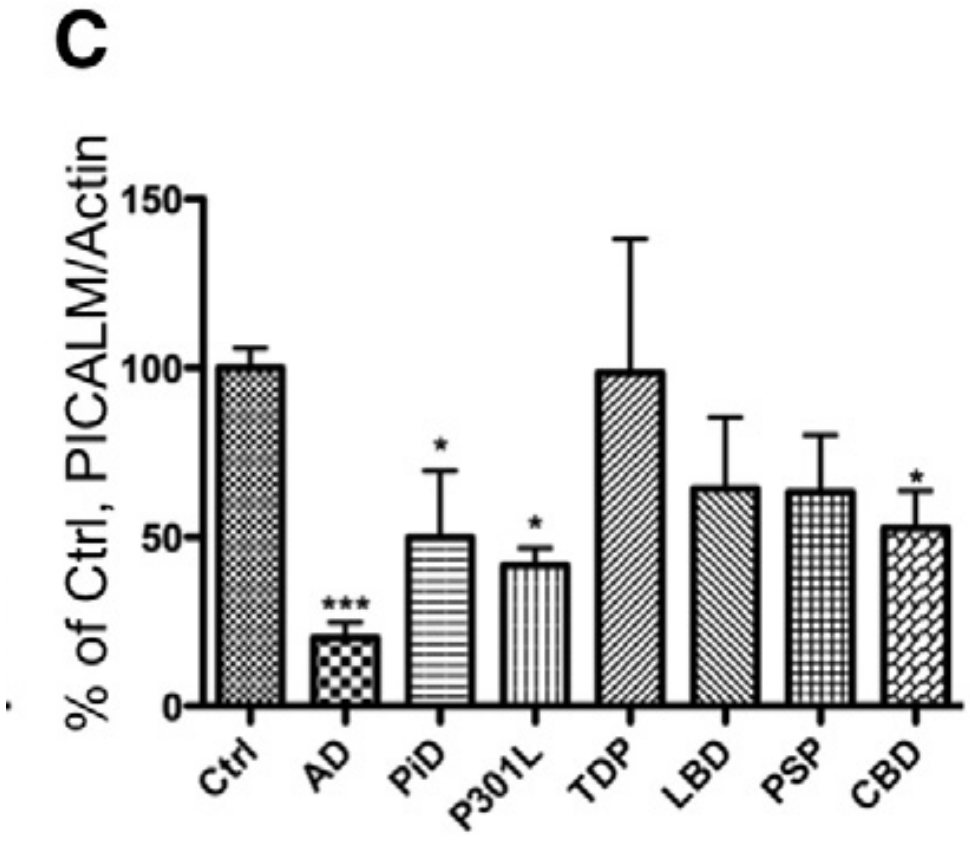
Aβ inhibits autophagy



Menzies, F.M.; Fleming, A.; Caricasole, A.; Bento, C.F.; Andrews, S.P.; Ashkenazi, A.; Füllgrabe, J.; Jackson, A.; Jimenez Sanchez, M.; Karabiyik, C.; et al., *Neuron*, **2017**, *93*, 1015.

AD pathology

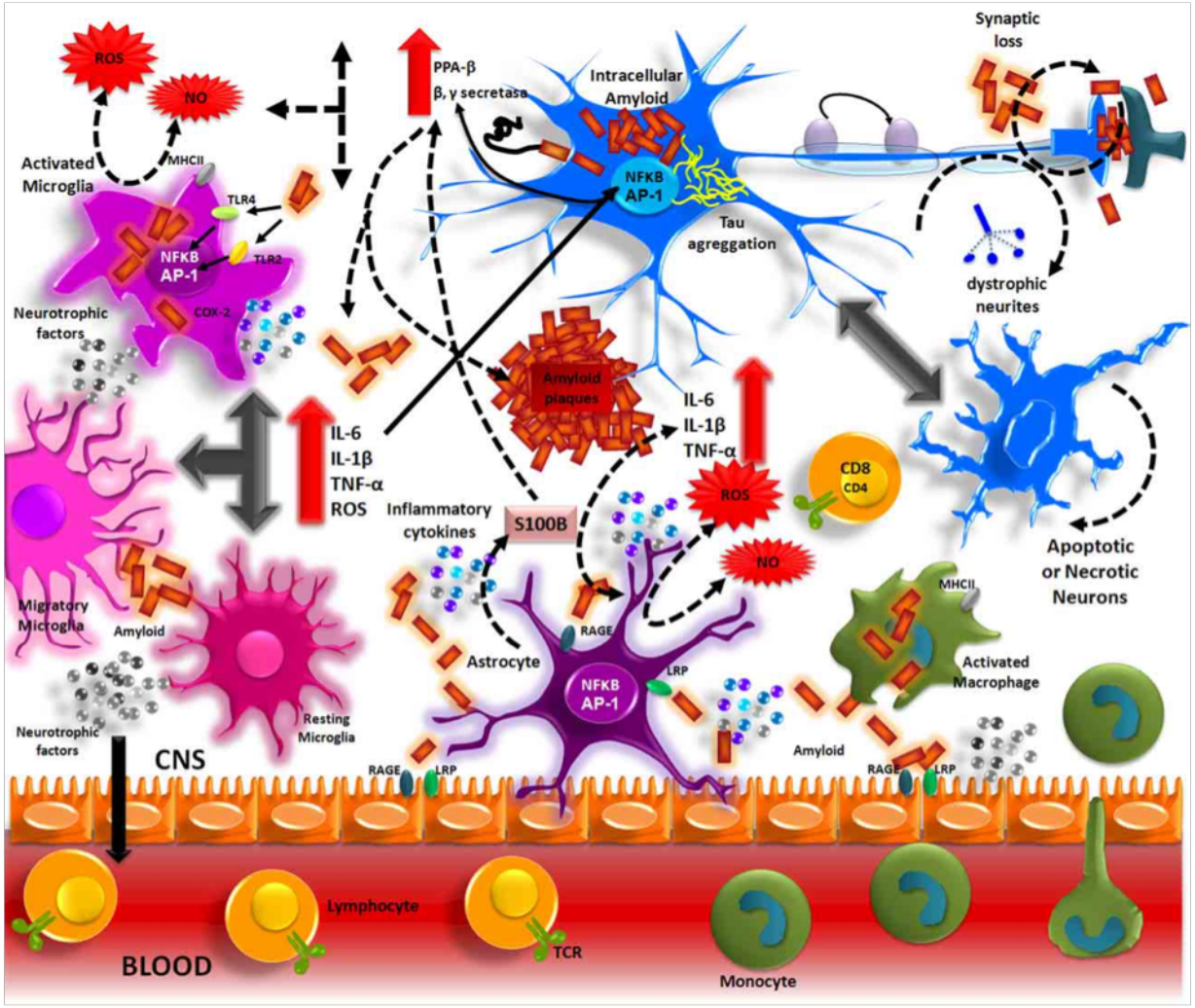
PICALM is low in AD patients



Ando K, Tomimura K, Sazdovitch V, et al. *Neurobiol Dis*. **2016**, *94*, 32

AD pathology

Neuro-inflammation



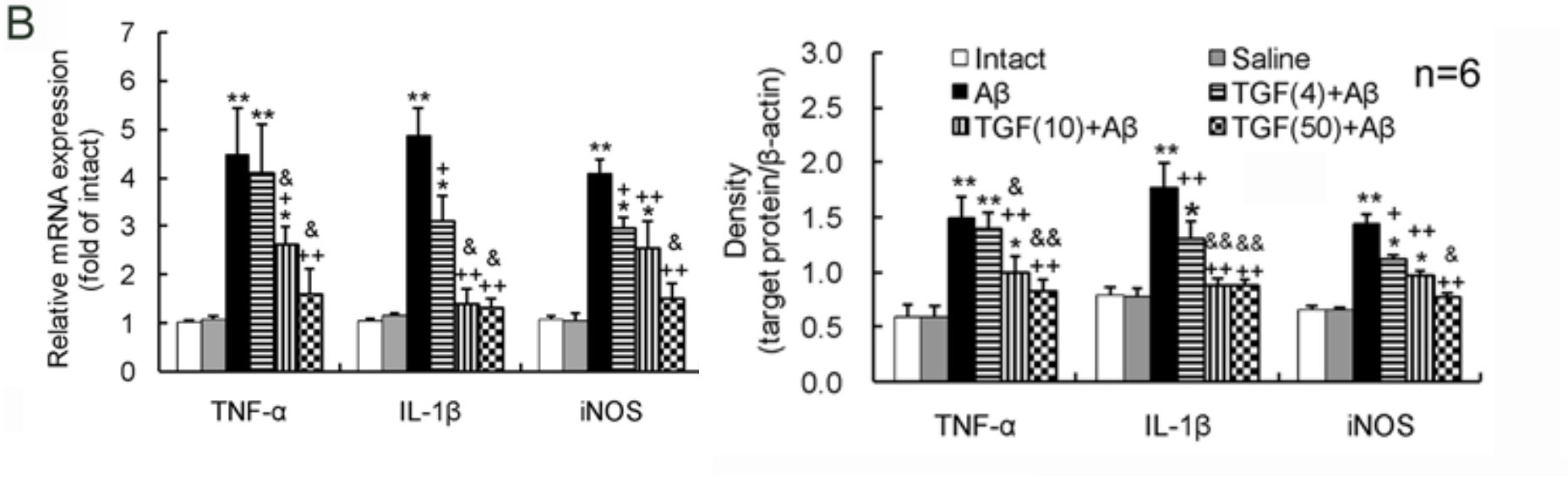
Meraz-Ríos, M. A., Toral-Rios, D., Franco-Bocanegra, D., Villeda-Hernández, J., Campos-Peña, V., *Front. Integr. Neurosci.*, **2013**, *7*, 59.

AD pathology

Aβ increases levels of TNF-α & IL-1β

mRNA

protein



Loftis JM, Huckans M, Morasco BJ, *Neurobiol Dis.*, **2010**, *37*, 519.

Contents

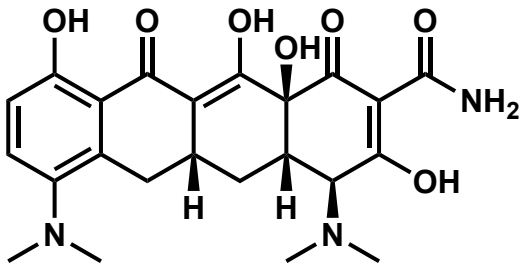
AD pathology-based therapeutic target

Novel treatment strategies for AD

1. Minocycline
2. 4-(1-benzylpiperidin-4-yl)thiosemicarbazone
3. Diethyl (3,4-dihydroxyphenethylamino) (quinolin-4-yl)methylphosphonate
4. Oligomannate

Targeting Neuroinflammation

Minocycline



Minocycline

Tetracycline antibiotics

In animal models

- Alzheimer's disease (Garcez et al. 2017)
- Traumatic brain injury (Hanlon et al. 2016)
- Multiple sclerosis (Giuliani et al. 2005)
- Cerebral ischemia (Yrjänheikki et al. 1999)
- Huntington's disease (Chen et al. 2000)
- Parkinson's disease (Du et al. 2001)
- Stroke (Lampl et al. 2007)
- Anxiety-related behaviors (Majidi et al. 2016)
- Schizophrenia (Chaudhry et al. 2012)
- Anti-depressant effect (Amorim et al. 2017)

Targeting Neuroinflammation

Clinical trial of minocycline

Success example of depression

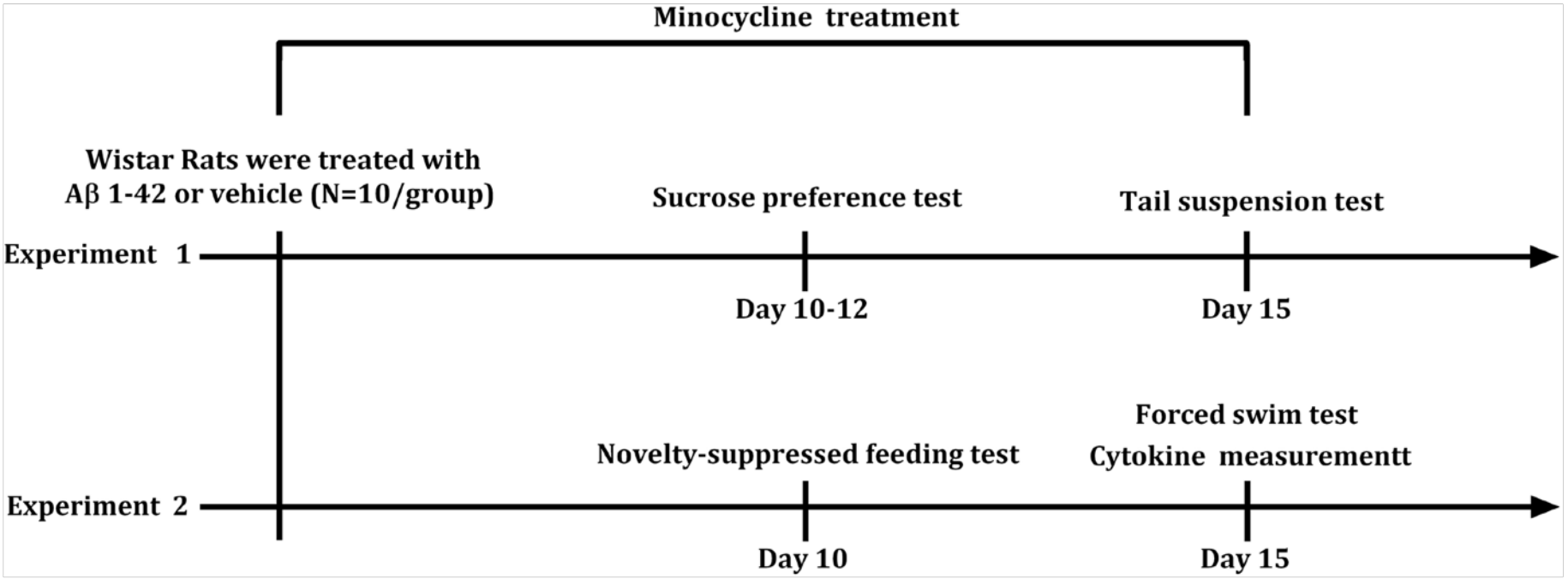
- Mild-to-moderate depression in HIV patients (Emadi-Kouchak et al. 2016)
- Major depressive disorder (Dean et al. 2017)
- Bipolar depression (Soczynska et al. 2017)

In Alzheimer's disease

- “Minocycline did not delay the progress of cognitive or functional impairment in people with mild AD during a 2-year period.” (Howard et al. 2020)

Targeting Neuroinflammation

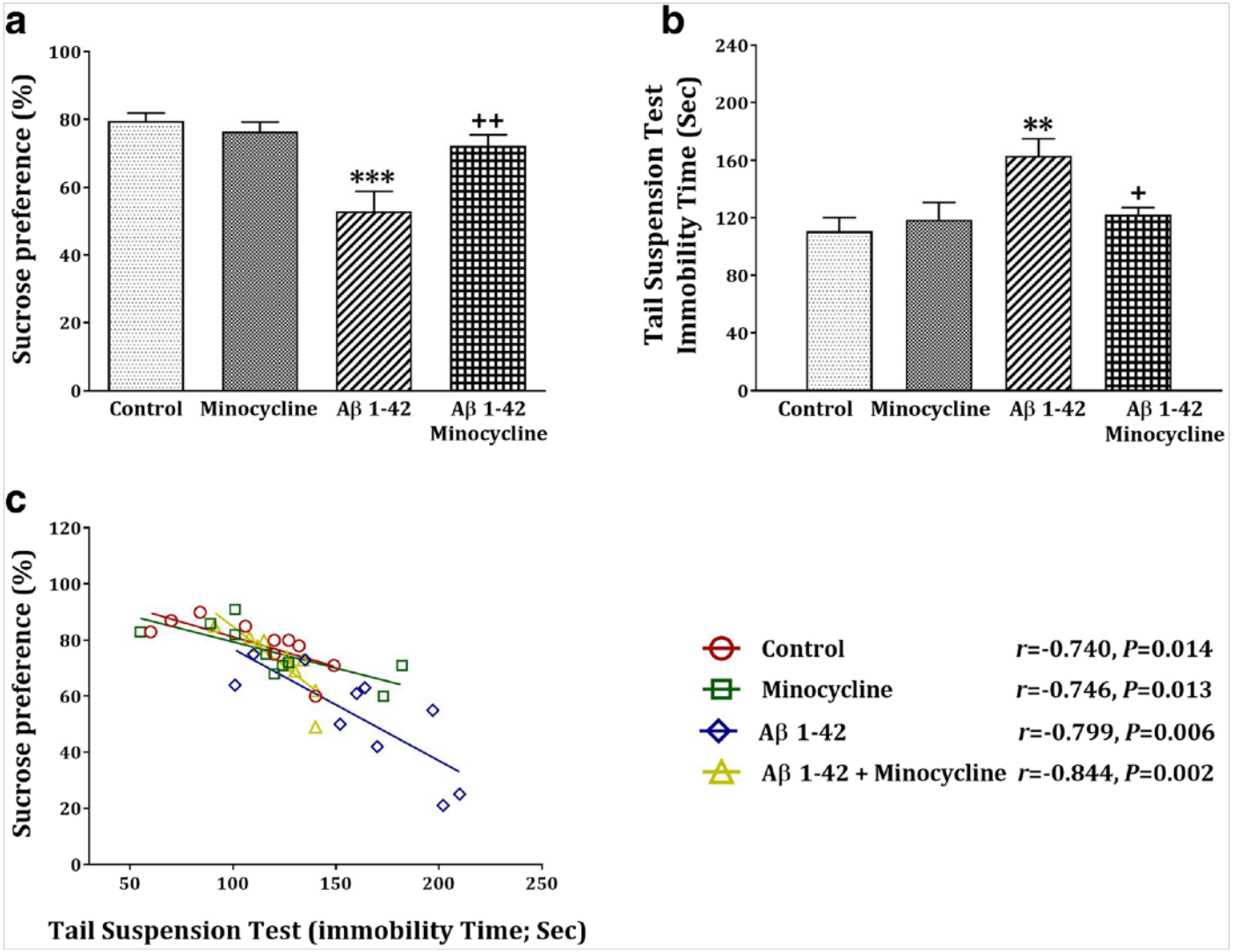
Experimental design of minocycline treatment



Amani,M.;Shokouhi,G.;Salari,A.A., *Psychopharmacology*, **2019**, *236*, 1281.

Targeting Neuroinflammation

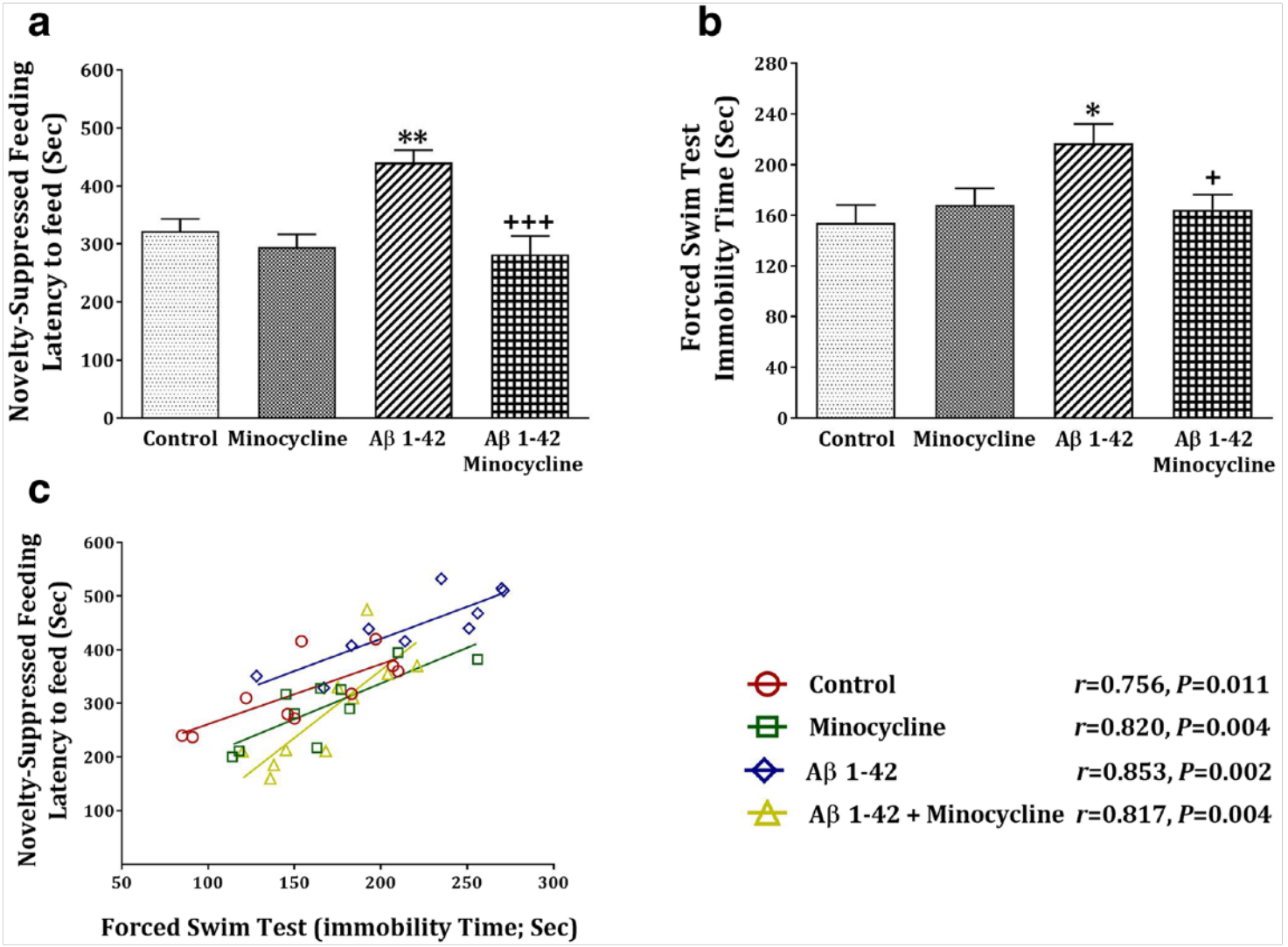
Result of experiment 1



Amani,M.;Shokouhi,G.;Salari,A.A., *Psychopharmacology*, **2019**, *236*, 1281.

Targeting Neuroinflammation

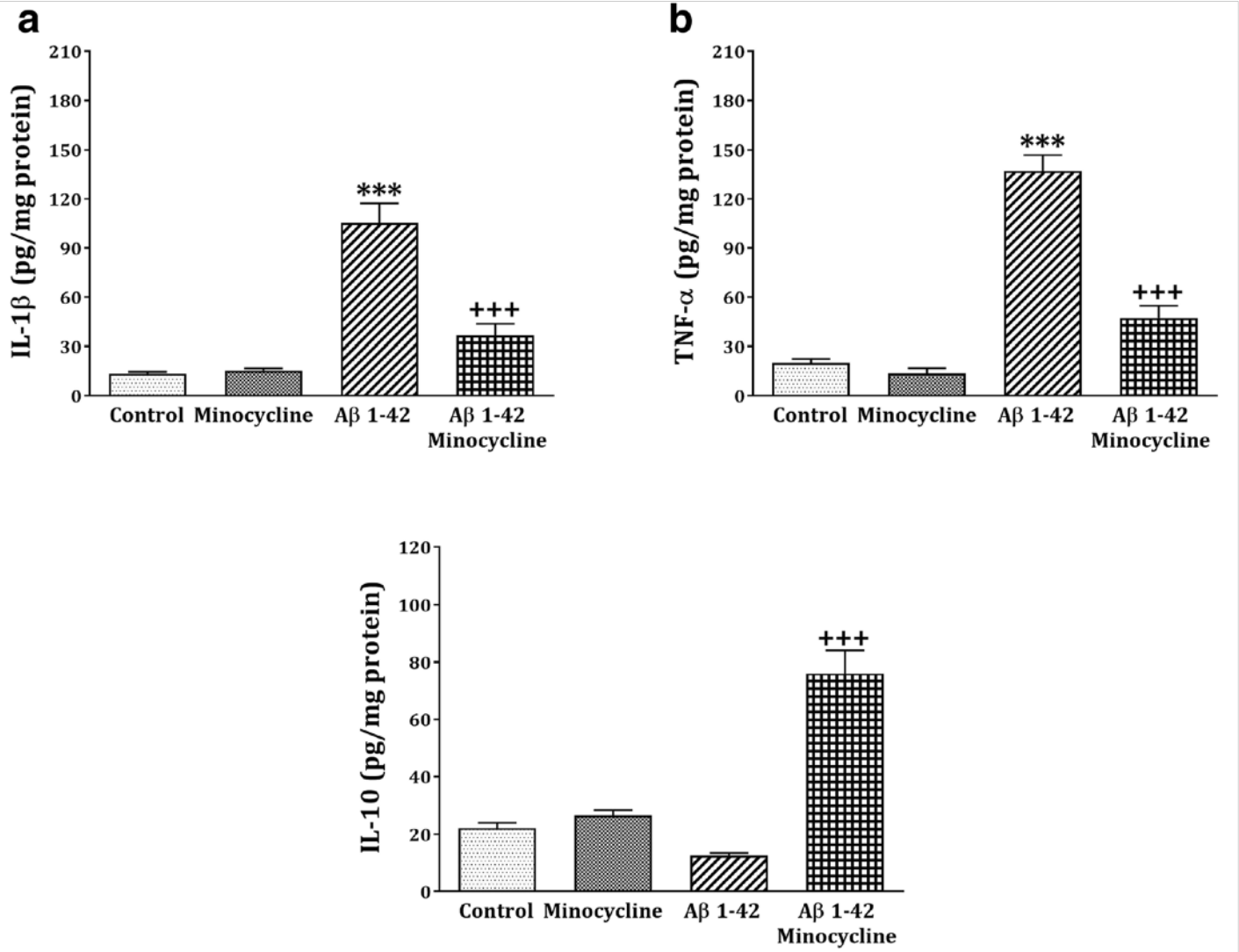
Result of experiment 2



Amani,M.;Shokouhi,G.;Salari,A.A., *Psychopharmacology*, **2019**, *236*, 1281.

Targeting Neuroinflammation

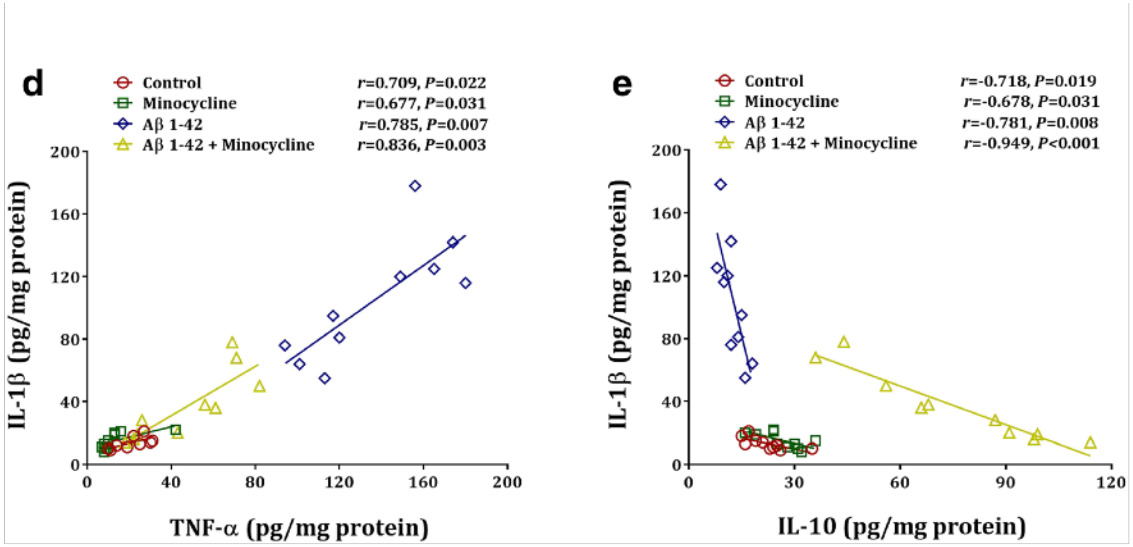
The level of Cytokines



Amani,M.;Shokouhi,G.;Salari,A.A., *Psychopharmacology*, **2019**, *236*, 1281.

Targeting Neuroinflammation

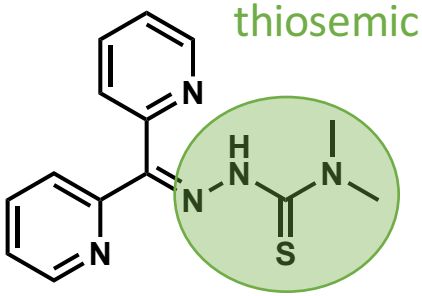
The level of Cytokines



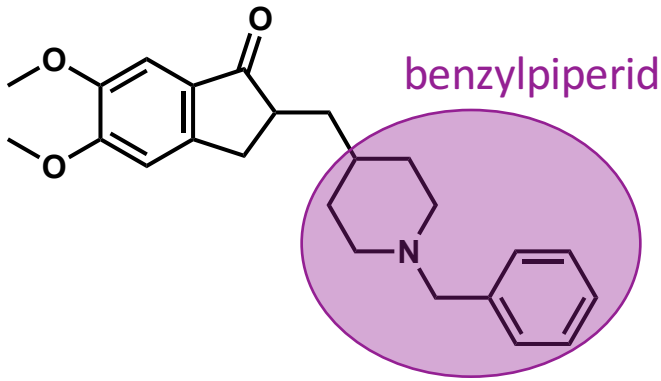
Amani,M.;Shokouhi,G.;Salari,A.A., *Psychopharmacology*, **2019**, *236*, 1281.

Multi-target drug BPT

Design strategy of multi-target drug



Dp44mT

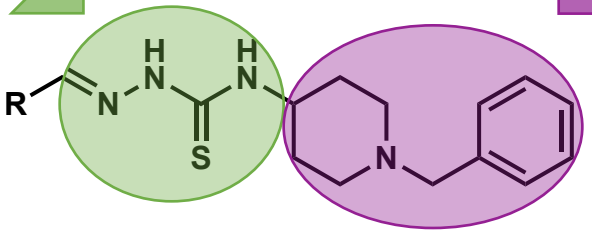


Donepezil

- Chelation of redox-active metals
- Induction of autophagy

- Inhibition of AChE activity

combine pharmacophores



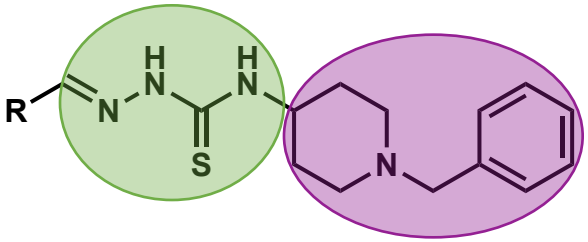
4-(1-benzylpiperidin-4-yl)thiosemicarbazone (BPT)

Palanimuthu, D.; Poon, R.; Sahni, S.; Anjum, R.; Hibbs, D.; Lin, H.Y.; Bernhardt, P.V.; Kalinowski, D.S.; Richardson, D.R., *Eur. J. Med. Chem.* **2017**, *139*, 612.

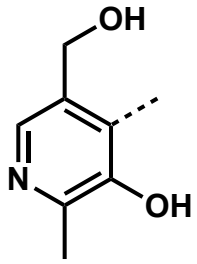
Multi-target drug BPT

BPT series

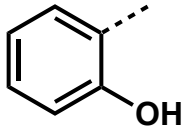
4-(1-benzylpiperidin-4-yl)thiosemicarbazone (BPT)



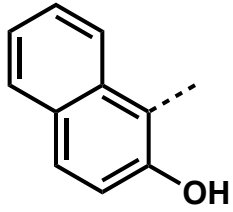
1. Cytotoxicity
2. Inhibition of AChE activity
3. Chelation of redox-active metals
4. Induction of autophagy
5. BBB permeability



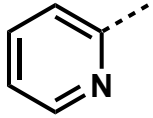
PBPT



SBPT



NBPT



PCBT

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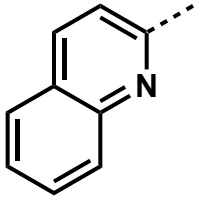
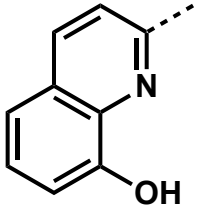
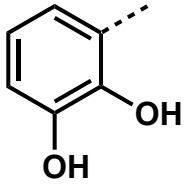


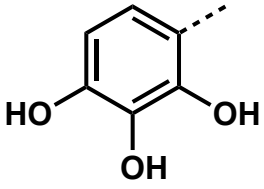
QBPT



8-OH-QBPT



2,3-OH-BBPT



2,3,4-OH-BBPT

Palanimuthu, D.; Poon, R.; Sahni, S.; Anjum, R.; Hibbs, D.; Lin, H.Y.; Bernhardt, P.V.; Kalinowski, D.S.; Richardson, D.R., *Eur. J. Med. Chem.* **2017**, *139*, 612.

Multi-target drug BPT

Anti-proliferative activity

- The anti-proliferative activity against SK-N-MC neuroepithelioma cells

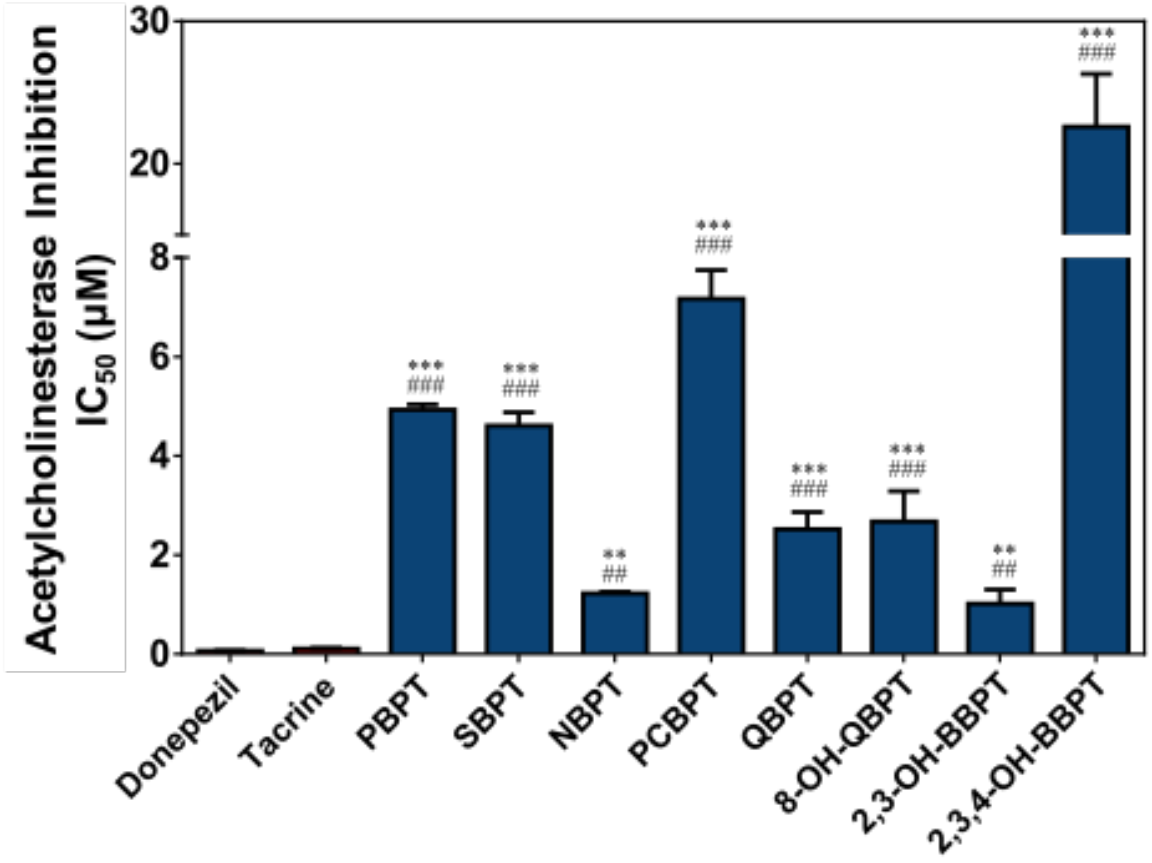
IC_{50} (μM)

Compound	Ligand (L)	$Cu^{II}(L)$	$Fe^{III}(L_2)$
DFO	16.81 ± 3.87	9.83 ± 0.38	>25[b]
Dp44mT	0.013 ± 0.01	0.014 ± 0.01	2.00 ± 0.49
Donepezil	>100	83.33 ± 7.60	>100
PBPT	>100	46.18 ± 7.97	>100
SBPT	34.41 ± 1.24	1.30 ± 0.14	77.99 ± 11.58
NBPT	8.86 ± 0.10	1.81 ± 0.53	52.90 ± 8.34
PCBPT	4.23 ± 1.41	0.43 ± 0.02	1.33 ± 0.11
QBPT	17.71 ± 0.70	3.86 ± 1.28	1.20 ± 0.26
8-OH-QBPT	36.14 ± 3.24	1.87 ± 0.50	>100
2,3-OH-BBPT	16.85 ± 0.96	0.40 ± 0.09	23.99 ± 4.85
2,3,4-OH-BBPT	79.14 ± 0.36	12.22 ± 0.09	80.06 ± 13.57

Palanimuthu, D.; Poon, R.; Sahni, S.; Anjum, R.; Hibbs, D.; Lin, H.Y.; Bernhardt, P.V.; Kalinowski, D.S.; Richardson, D.R., *Eur. J. Med. Chem.* **2017**, *139*, 612.

Multi-target drug BPT

Inhibition of AChE activity

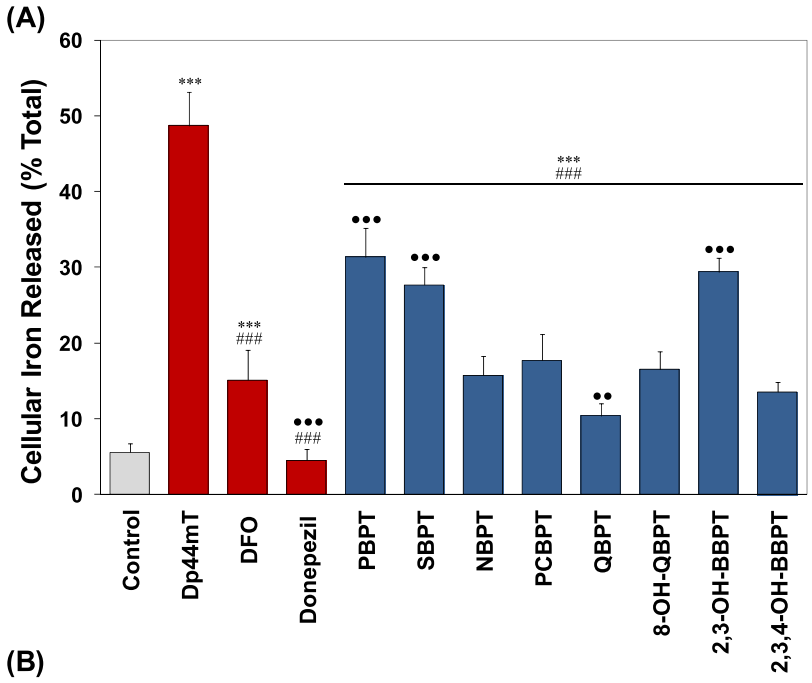


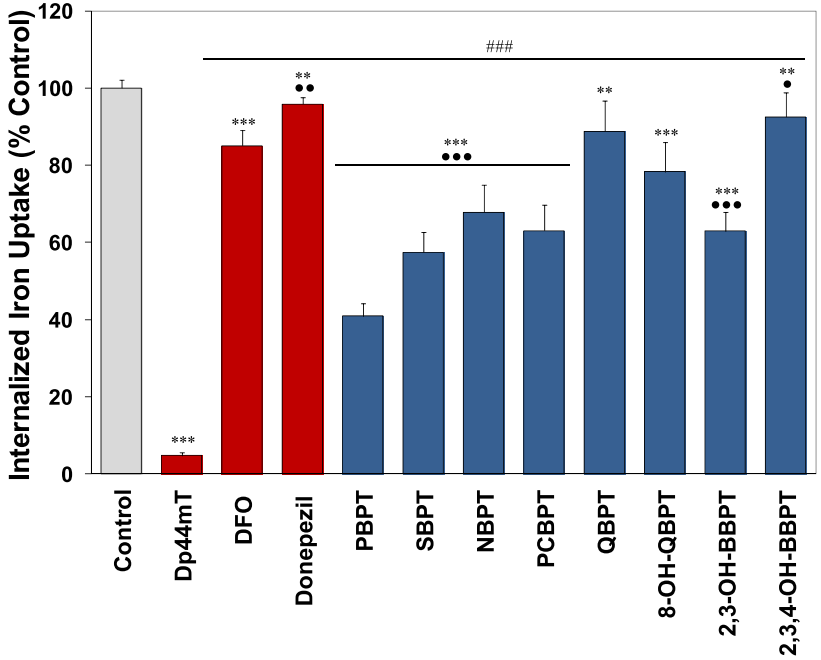
Palanimuthu, D.; Poon, R.; Sahni, S.; Anjum, R.; Hibbs, D.; Lin, H.Y.; Bernhardt, P.V.; Kalinowski, D.S.; Richardson, D.R., *Eur. J. Med. Chem.* **2017**, *139*, 612.

Multi-target drug BPT

Chelation of redox-active metals

- ^{59}Fe release from prelabeled cells
- Inhibiting ^{59}Fe uptake from ^{59}Fe-Transferrin





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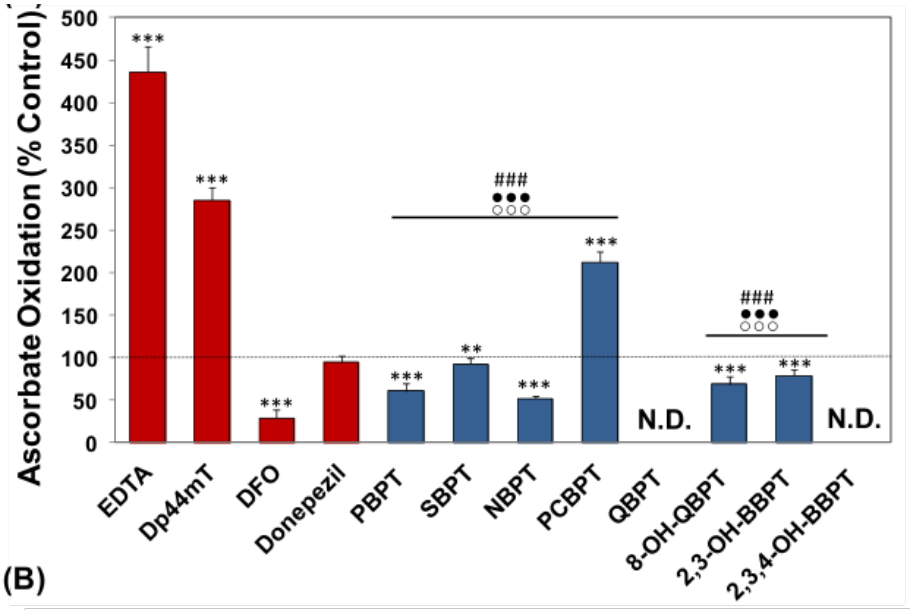
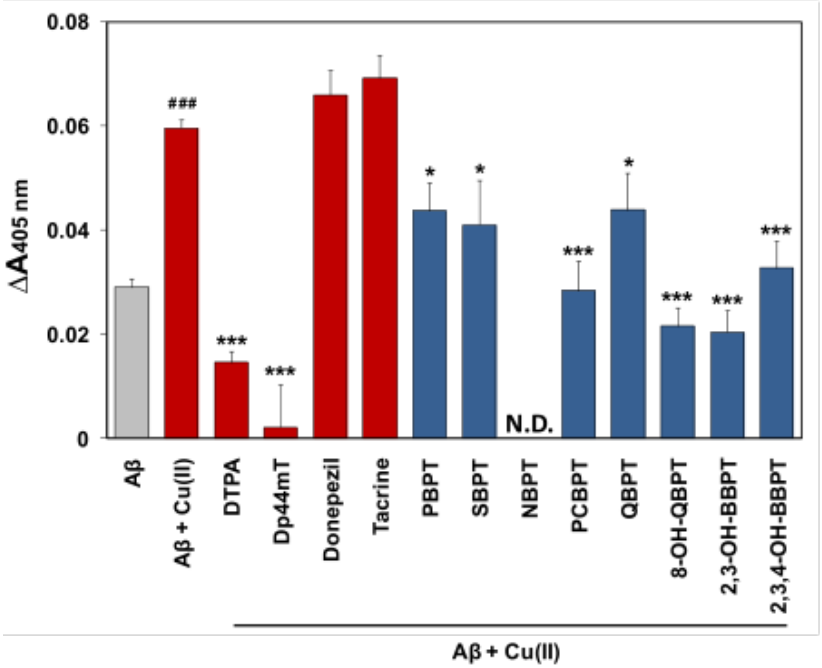
Multi-target drug BPT

Chelation of redox-active metals

- The effect on ascorbate oxidation



- Inhibiting copper-mediated Ab1-40 aggregation



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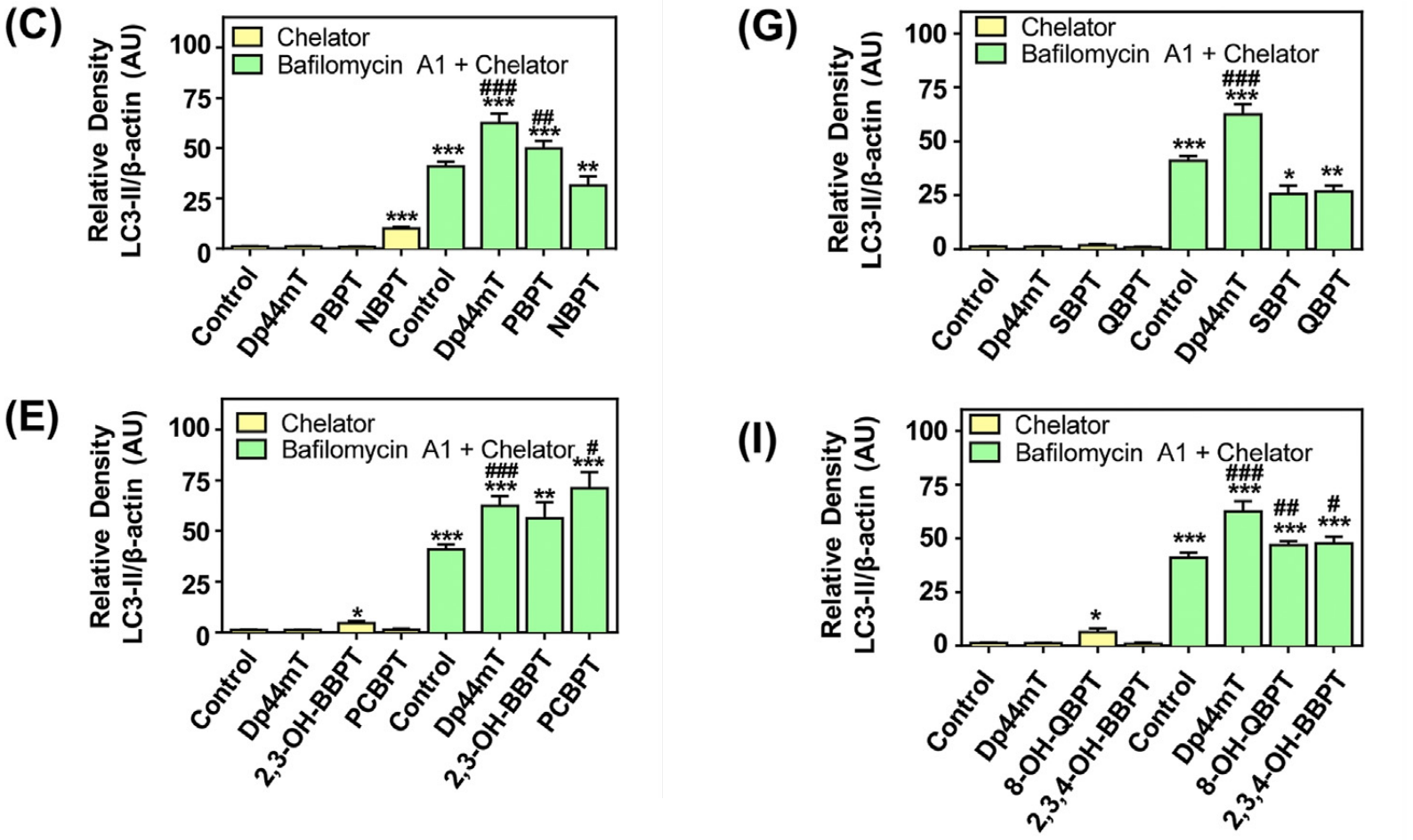
Multi-target drug BPT

Induction of autophagy



Palanimuthu, D.; Poon, R.; Sahni, S.; Anjum, R.; Hibbs, D.; Lin, H.Y.; Bernhardt, P.V.; Kalinowski, D.S.; Richardson, D.R., *Eur. J. Med. Chem.* **2017**, *139*, 612.

Multi-target drug BPT

BBB permeability

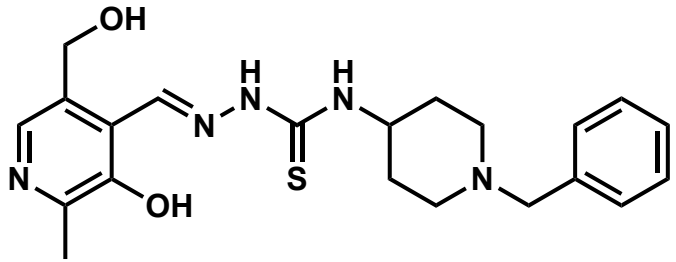
- Evaluation of physicochemical parameters to cross the blood brain barrier (BBB)
  1. Lipinski's Rule of Five (Oral bioavailability)
     - Hydrogen bond donors (OH and NH) $\leqq$ 5
     - Hydrogen bond acceptors (N and O) $\leqq$ 10
     - Molecular weight $\leqq$ 500
     - LogP $\leqq$ 5
  2. Successful CNS agents
     - Topological polar surface area < 90 $Å^2$
     - 2 < cLogP <5
     - LogBB > -1 (LogBB = -0.0148 × TPSA + 0.152 × cLogP +0.139)

Compound	M.W[a]	LogP[a]	HBA (N+O)	HBD (NH+OH)	Rot. bonds[b]	TPSA[a]	cLogP[a]	LogBB[c]
Tacrine	198.27	2.91	2	2	0	38.38	3.27	0.07
Donepezil	379.50	4.01	4	0	6	38.77	4.60	0.26
PBPT	413.54	2.30	7	4	8	92.48	2.69	−0.82
SBPT	368.50	3.51	5	3	7	59.89	3.79	−0.17
NBPT	418.56	4.51	5	3	7	59.89	4.97	0.01
PCBPT	353.49	2.98	5	2	7	52.02	2.43	−0.26
QBPT	403.55	4.41	5	2	7	52.02	3.81	−0.05
8-OH-QBPT	419.55	4.02	6	3	7	72.25	3.91	−0.34
2,3-OH-BBPT	384.50	3.12	6	4	7	80.12	3.42	−0.53
2,3,4-OH-BBPT	400.50	2.73	7	5	7	100.35	2.82	−0.92
Required Parameters[d]	≤500	≤5	≤10	≤5	≤10	<90	2−5	>-1

Palanimuthu, D.; Poon, R.; Sahni, S.; Anjum, R.; Hibbs, D.; Lin, H.Y.; Bernhardt, P.V.; Kalinowski, D.S.; Richardson, D.R., *Eur. J. Med. Chem.* **2017**, *139*, 612.
D.E. Clark, *J. Pharm. Sci.*, **1999**, *88*, 815.

Multi-target drug BPT

Summary of Multi-Target Drug Therapy



pyridoxal 4-(1-benzylpiperidin-4-yl)thiosemicarbazone (PBPT)

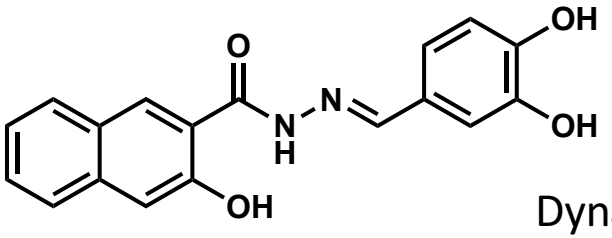
- PBPT is best of the 8 compounds.
- Low anti-proliferative activity.
- Moderate AChE inhibitory activity.
- Favorable iron chelation properties.
- The inhibition of Fe(III)-mediated ascorbate oxidation.
- The inhibition of Cu(II)-mediated aggregation of Ab1-40.
- Increase autophagic initiation.
- The physicochemical properties of PBPT are favorable for CNS permeation.

Lead compound with promising multi-functional activity to treat the complex pathology associated with AD.

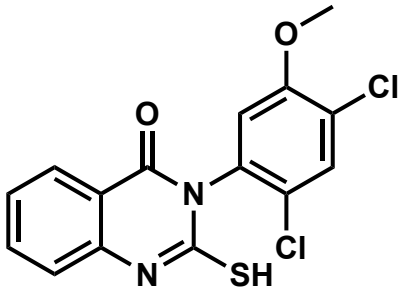
Mitochondrial dysfunction target drug DDQ

Design strategy of Mitochondrial dysfunction target drug

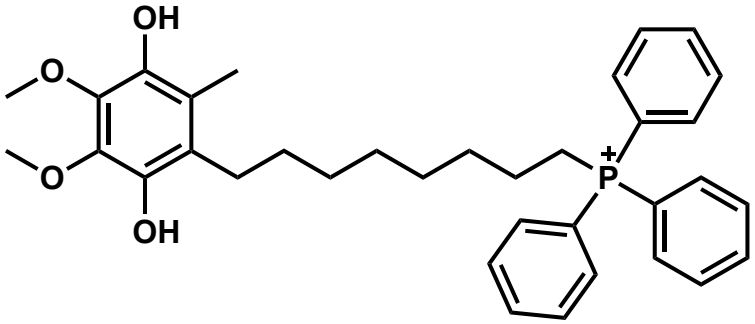
- Existing Drp1 inhibiting drugs



Dynasore



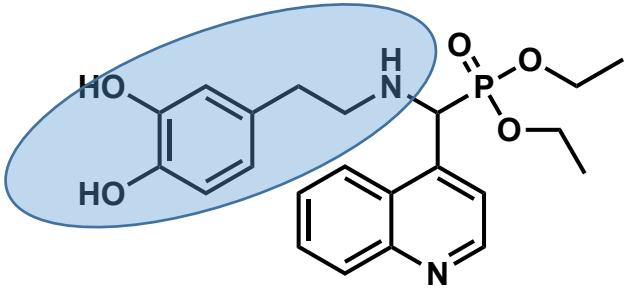
Mdivi1



MitoQ

- New Drp1 inhibiting drugs

Dopamine based structure



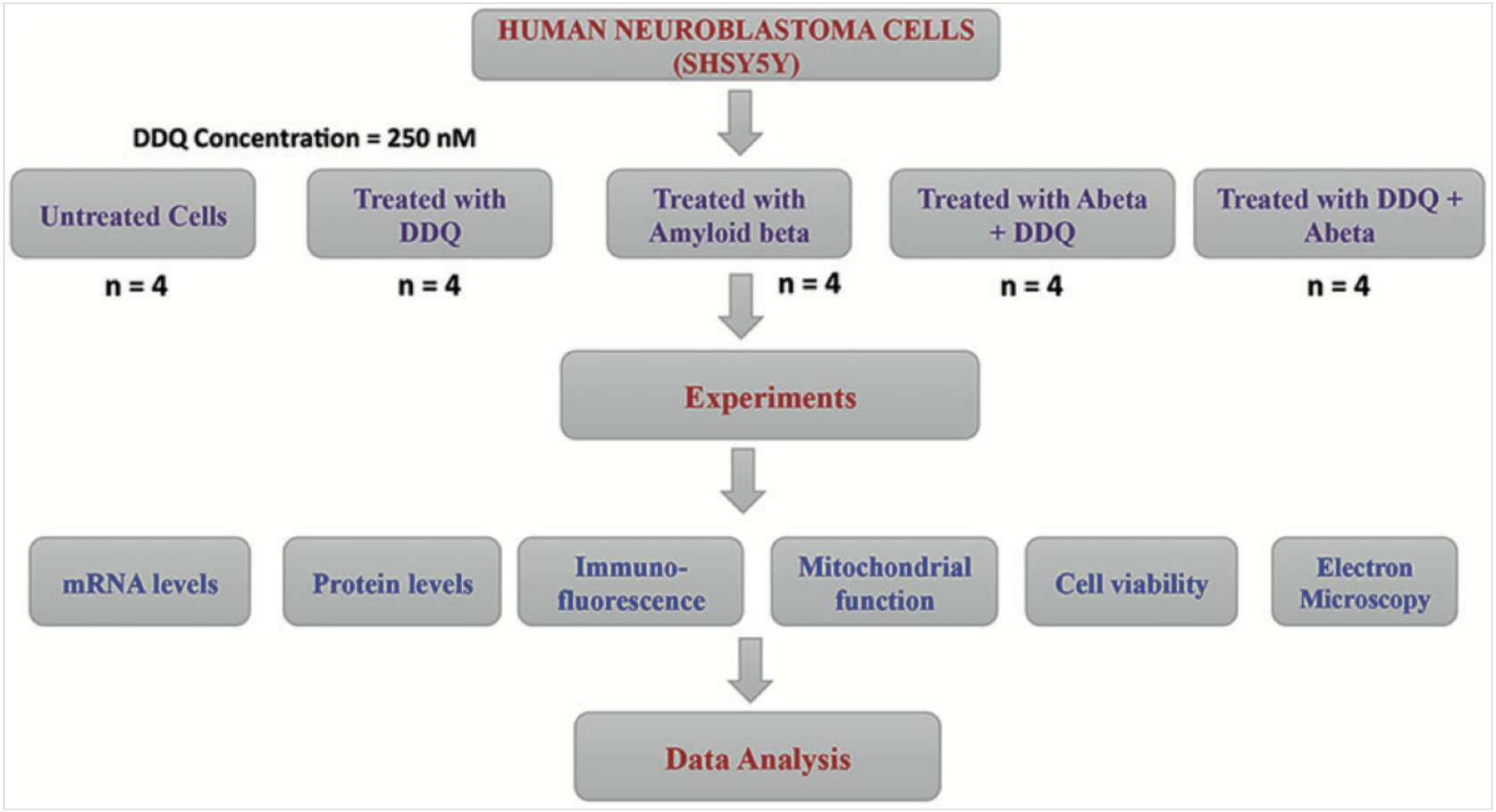
Diethyl (3,4-dihydroxyphenethylamino) (quinolin-4-yl)methylphosphonate (DDQ)

Ligand	Docking Score (Kcal/mol)
DDQ	-10.8462
MitoQ	-9.8205
Dynasore	-9.0080
Midvi1	-7.0117

Kuruva, C.S.; Manczak, M.; Yin, X.; Ogunmokun, G.; Reddy, A.P.; Reddy, P.H., *Hum. Mol. Genet.* **2017**, *26*, 3375.

Mitochondrial dysfunction target drug DDQ

Experimental design



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Mitochondrial dysfunction target drug DDQ

mRNA levels

Genes	mRNA fold changes compare with untreated cells				mRNA fold changes compare with Aβ-treated cells	
	DDQ	Aβ	Aβ+DDQ	DDQ+Aβ	Aβ+DDQ	DDQ+Aβ
Mitochondrial Structural genes						
Drp1	−2.2*	2.2**	1.9*	−2.1*	−1.7*	−4.6***
Fis1	−4.4***	1.7*	−1.2	−1.3	−2.0*	−2.5*
Mfn1	1.7*	−2.3**	1.4	1.2	3.3**	2.9**
Mfn2	2.3**	−2.6**	1.3	1.1	3.4**	2.9**
Synaptic genes						
Synaptophysin	1.4*	−3.7***	−2.4*	−1.6*	1.6*	2.4*
PSD95	1.4*	−2.5**	−1.4*	−1.2	1.8*	2.1*
Synapsin1	1.0	−1.9*	1.1	1.3	2.1*	2.5*
Synapsin2	1.7*	−1.4*	1.1	1.8*	2.4*	2.9**
Synaptobrevin1	1.0	−2.4**	−1.1	−1.4	2.0*	1.7*
Synaptobrevin2	1.3	−2.3*	1.0	1.0	2.1*	2.3*
Synaptopodin	1.0	−2.3**	−1.1	−1.1	2.0*	2.1*
GAP43	1.2	−1.9**	1.1	1.1	1.7*	1.7*
Mitochondrial Biogenesis genes						
PGC1a	1.5*	−4.4**	−1.8*	−1.1	2.5*	3.9**
Nrf1	1.9*	−4.1**	−1.7*	1.1	2.6**	4.9***
Nrf2	2.7*	−2.8*	−1.3	−1.1	2.1*	2.6*
TFAM	1.7*	−4.6***	−2.0*	−1.5*	2.3*	3.2**

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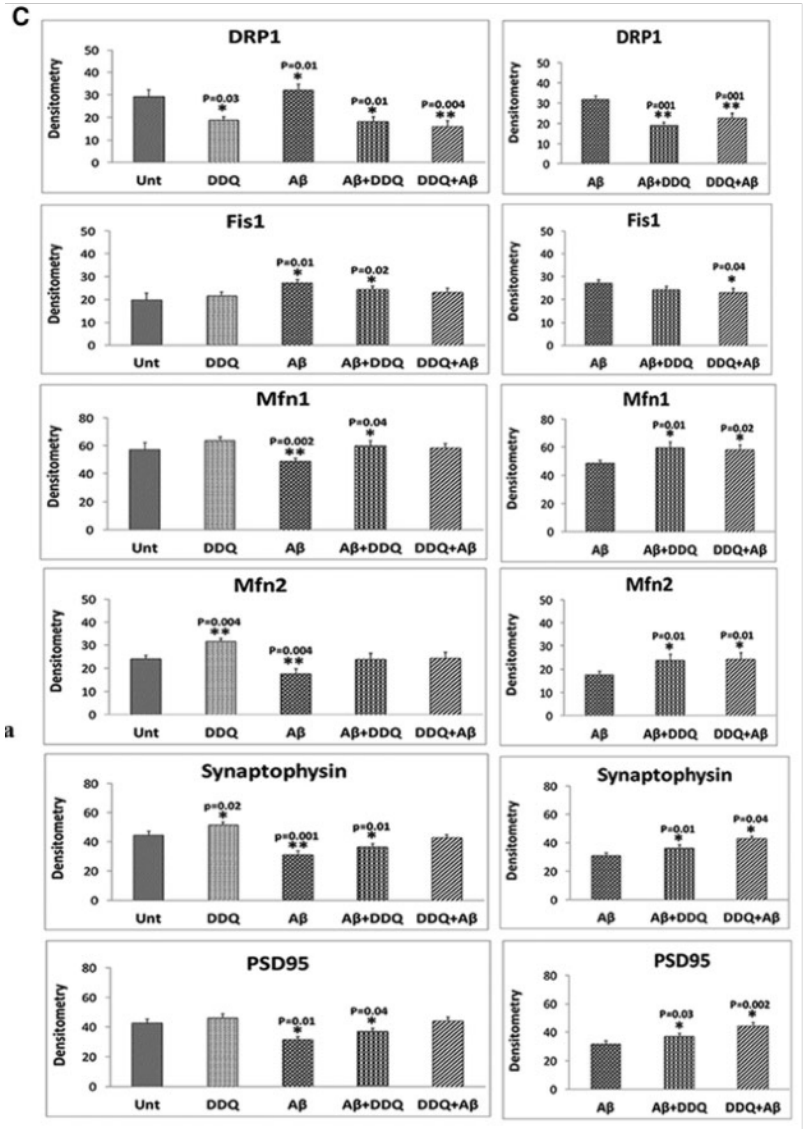
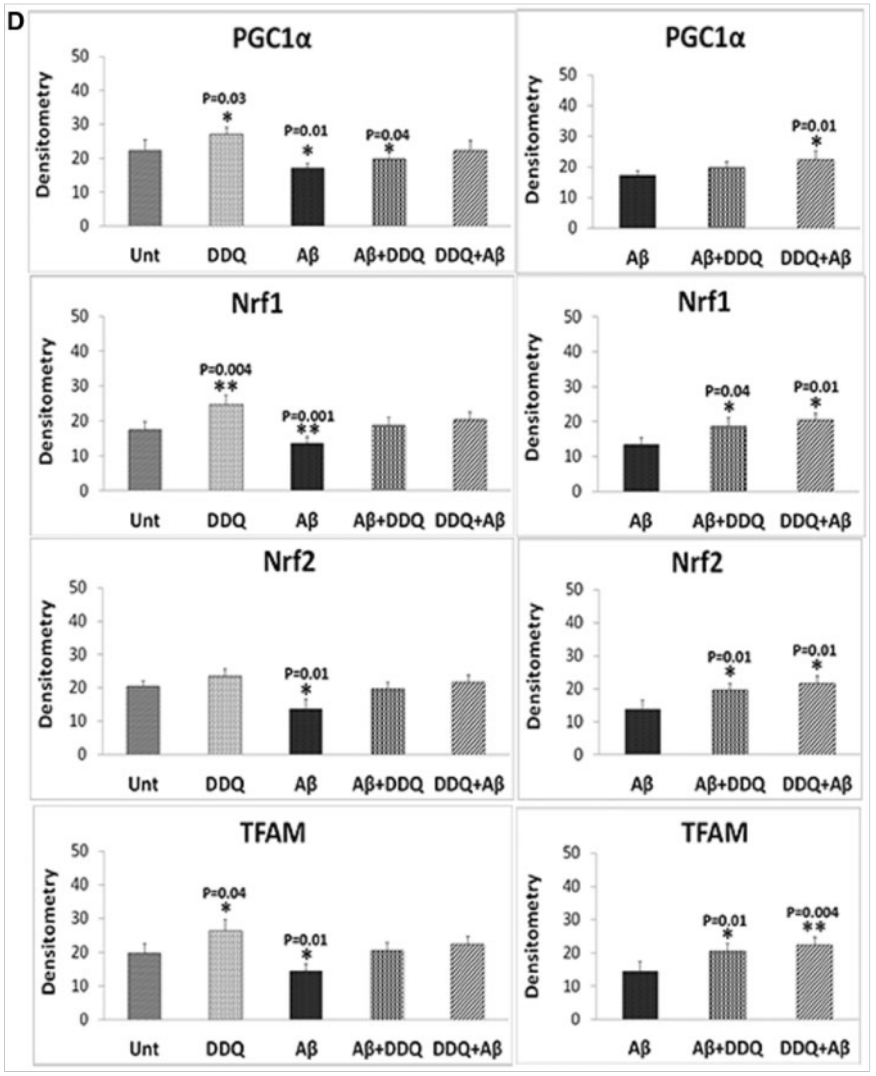
Mitochondrial dysfunction target drug DDQ

Protein levels





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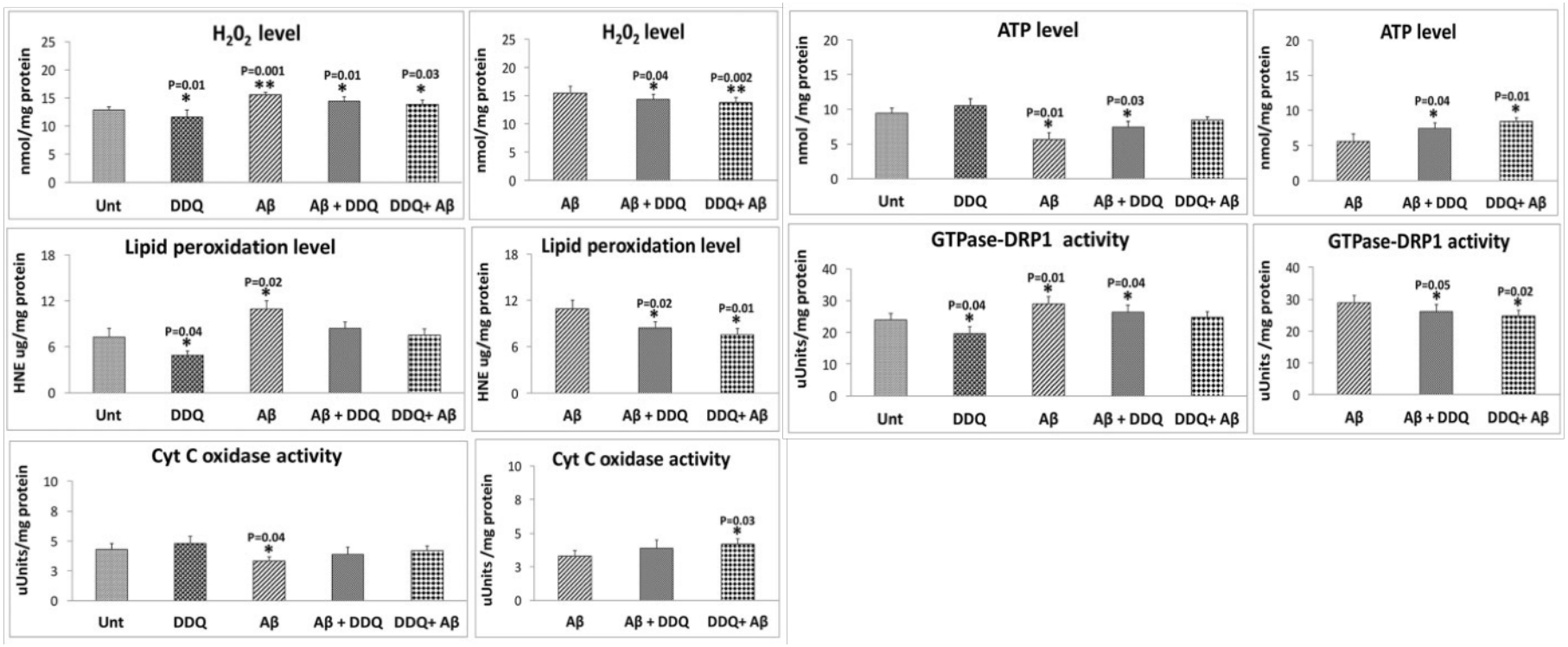
Mitochondrial dysfunction target drug DDQ

Mitochondrial functional assays



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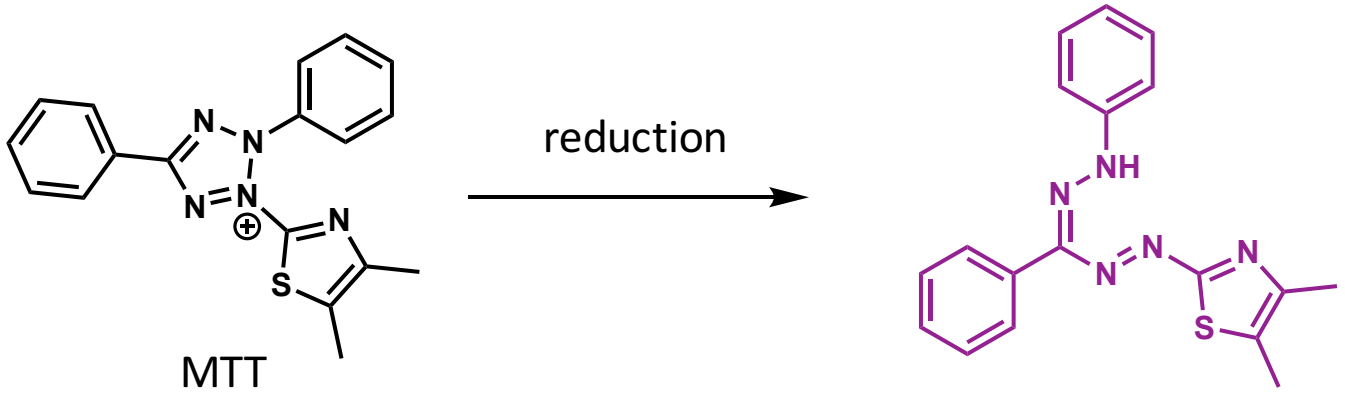
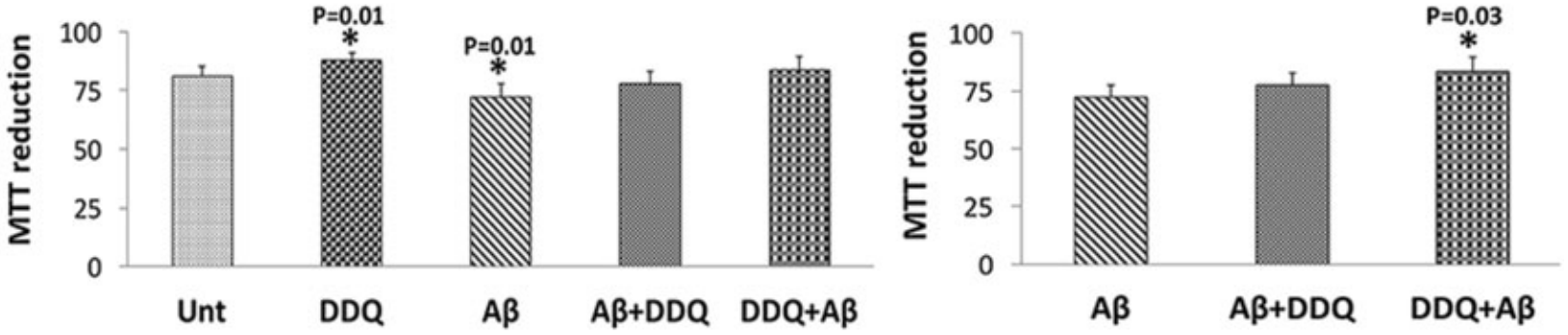
Mitochondrial dysfunction target drug DDQ

Cell viability analysis





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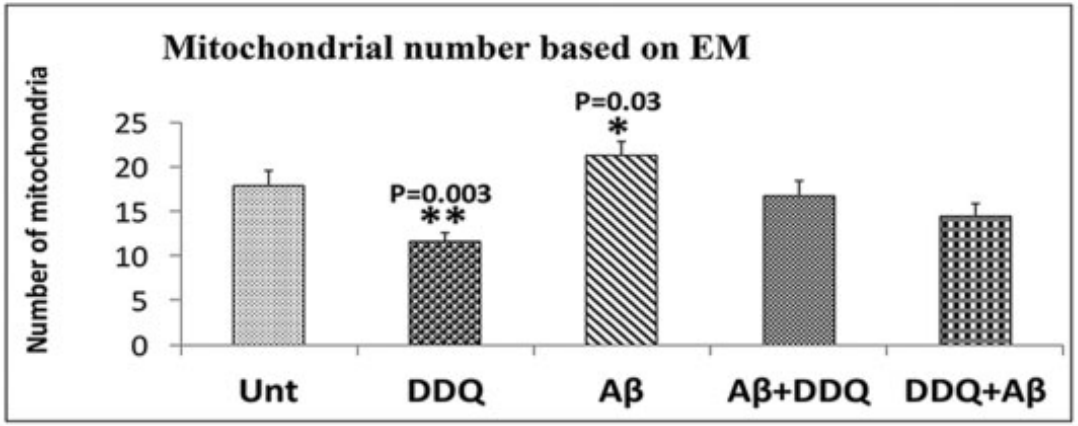
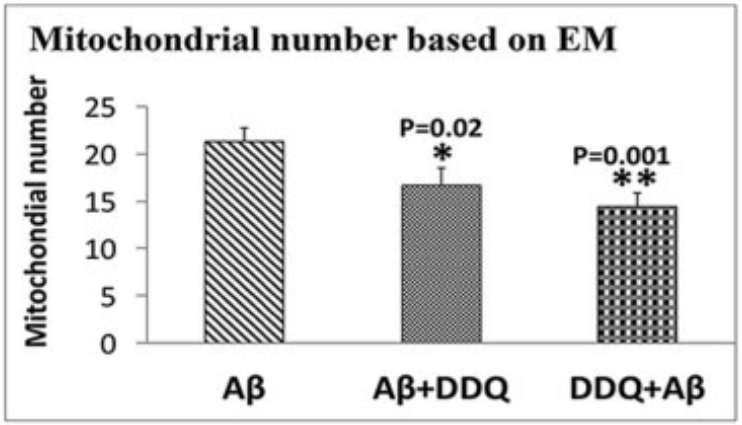
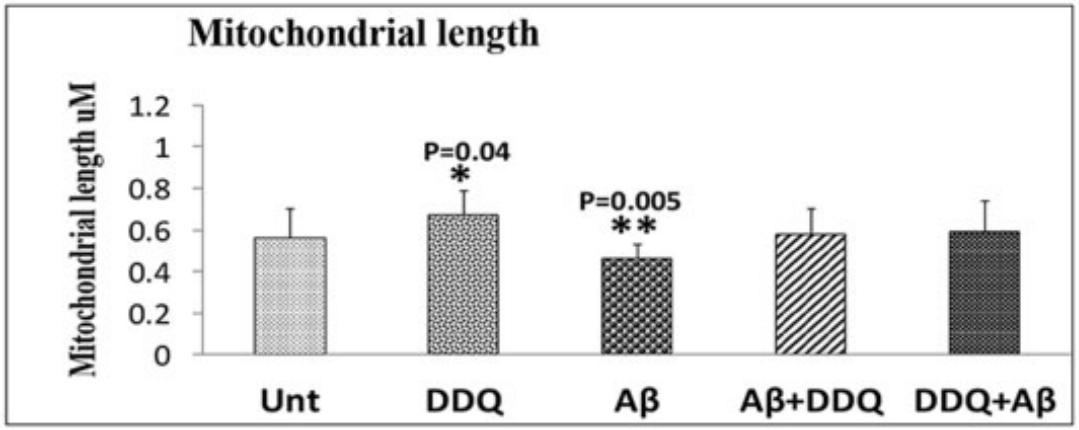
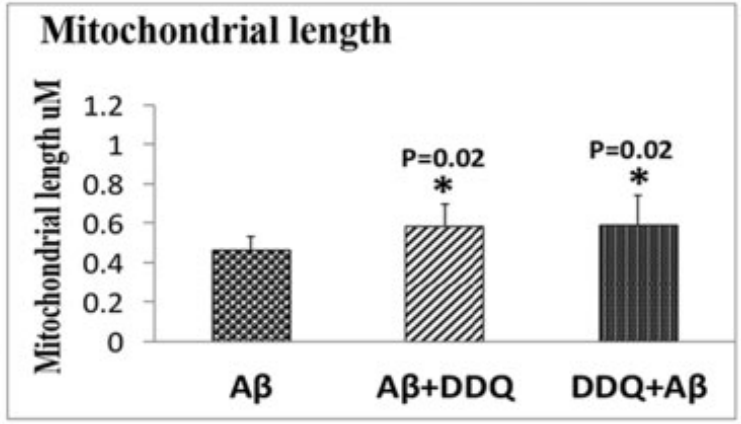
Mitochondrial dysfunction target drug DDQ

Transmission electron microscopy









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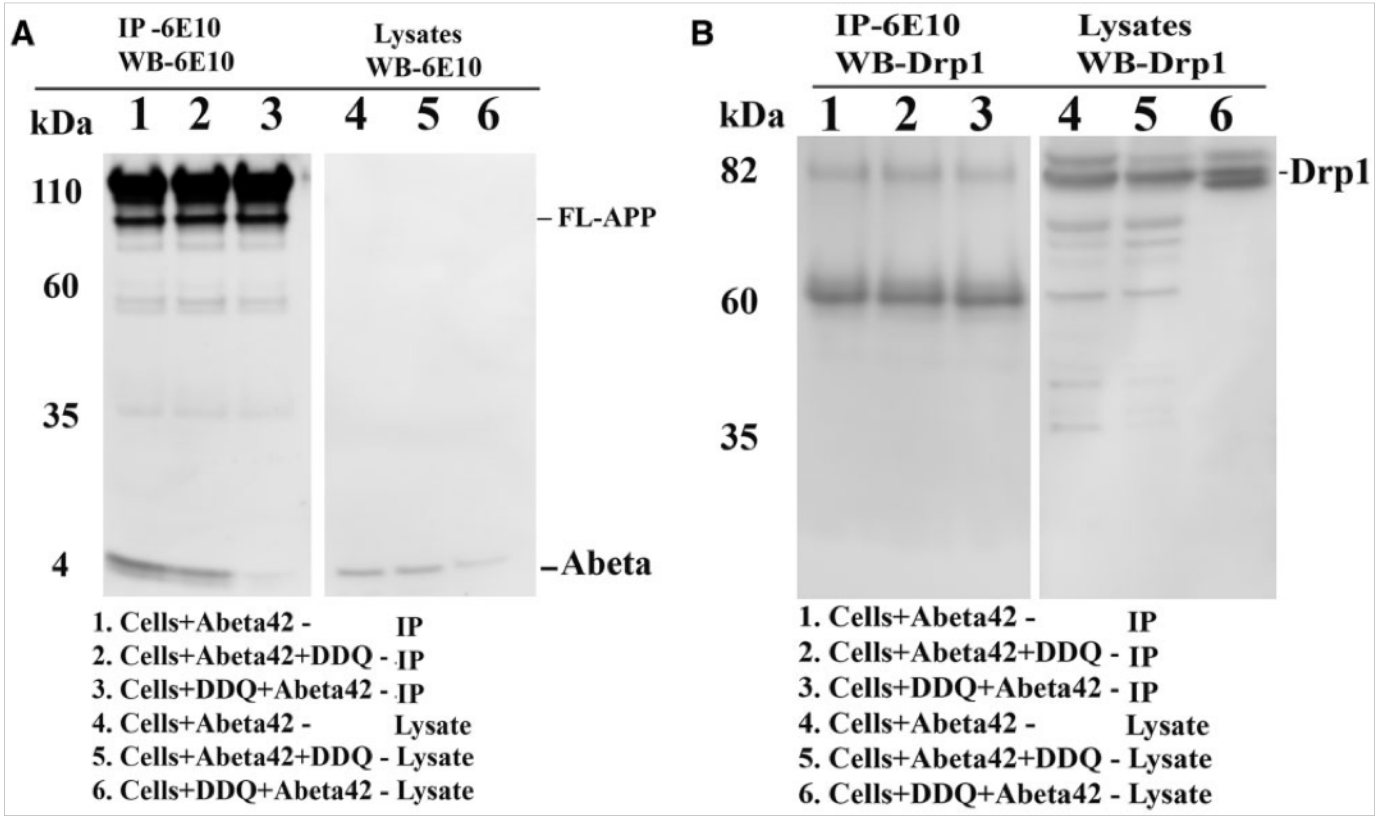
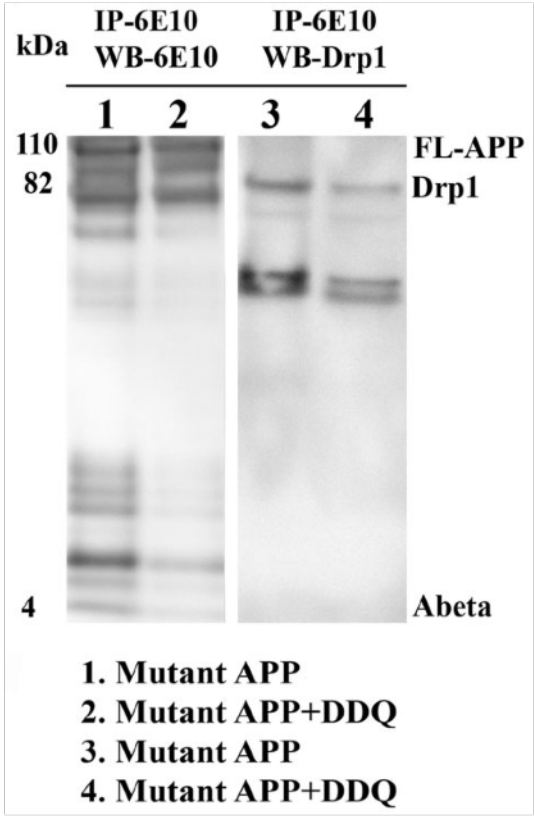
Mitochondrial dysfunction target drug DDQ

Interaction between Aβ and Drp1





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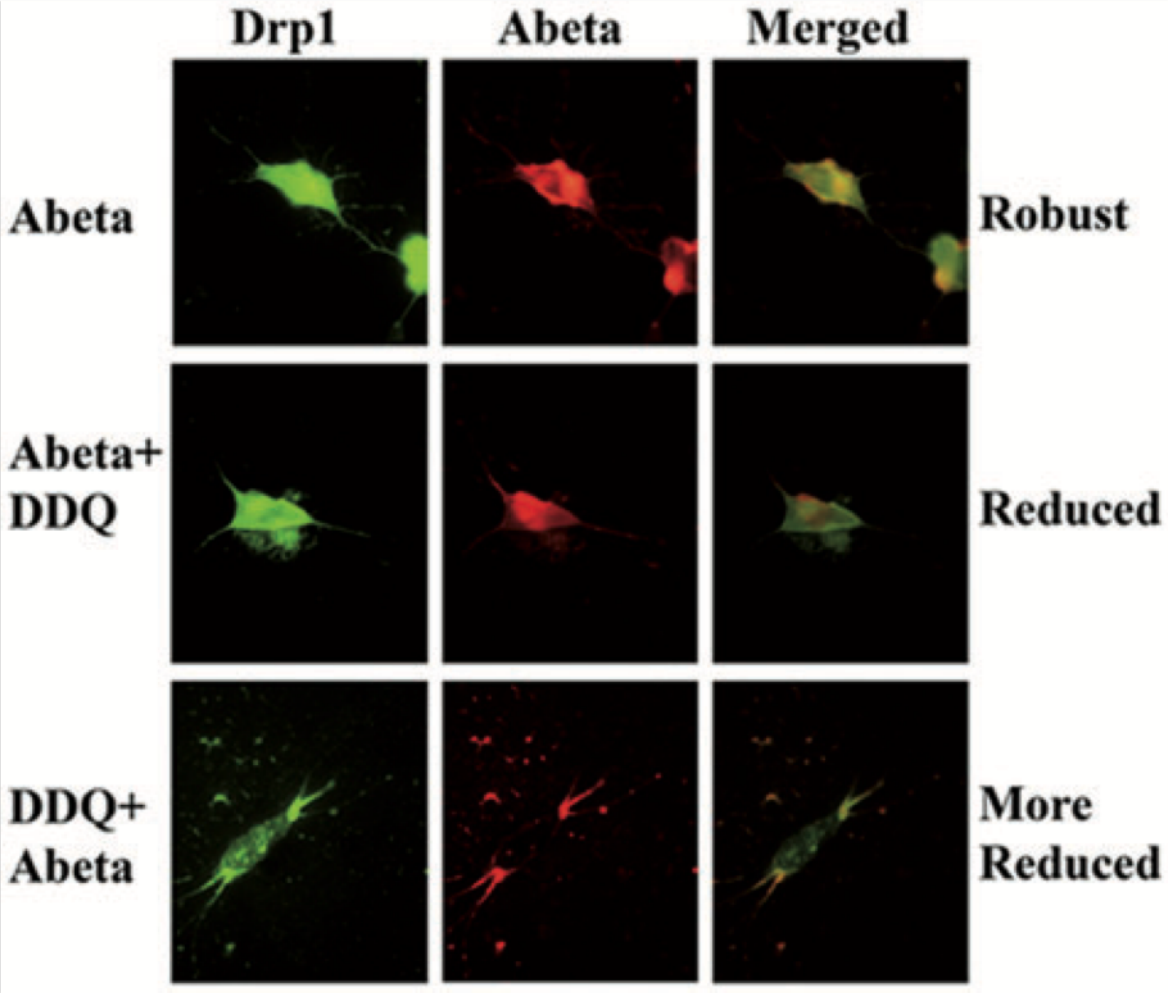
Mitochondrial dysfunction target drug DDQ

The localization of Drp1 and Aβ



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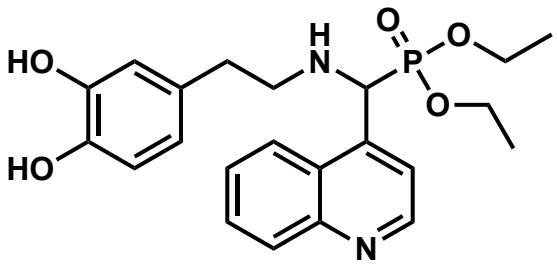
Mitochondrial dysfunction target drug DDQ

Summary of DDQ



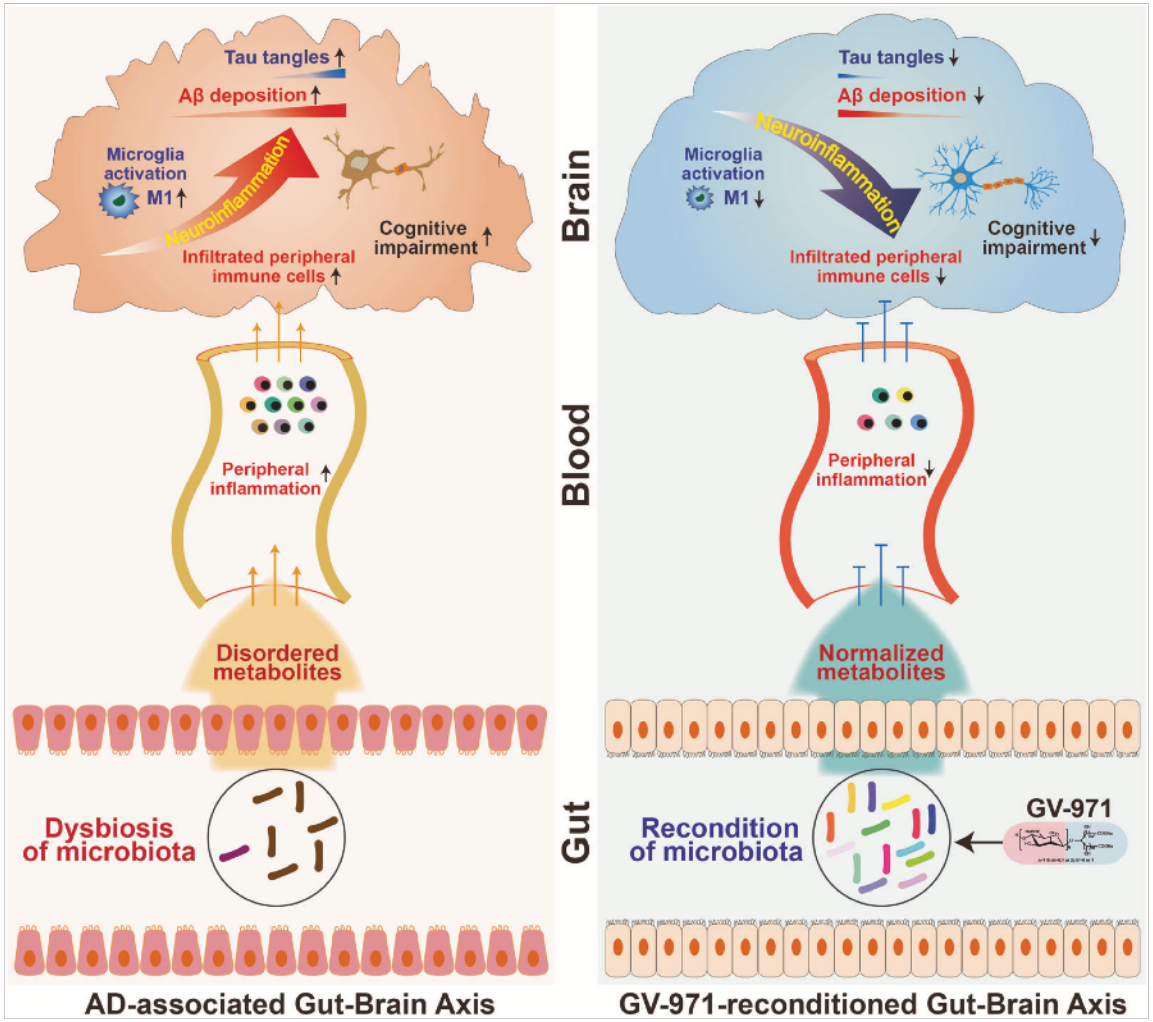
Diethyl (3,4-dihydroxyphenethylamino)
(quinolin-4-yl)methylphosphonate (DDQ)

- Bound at Ab and Drp1 interacting sites to Inhibit Ab and Drp1 complex formation
- showed better docking score.
- Enhanced fusion activity, reduced fission machinery, and increased mitochondrial biogenesis and synaptic activities.
- Reduces the levels of Ab and Drp1 and interaction between Ab and Drp1.
- Maintains mitochondrial function and cell viability.
- DDQ can reduce the negative effects of Aβ
- Prevention is better than treatment.

Promising molecule to treat AD neurons.

Approved novel AD treatment

AD & gut microbiota

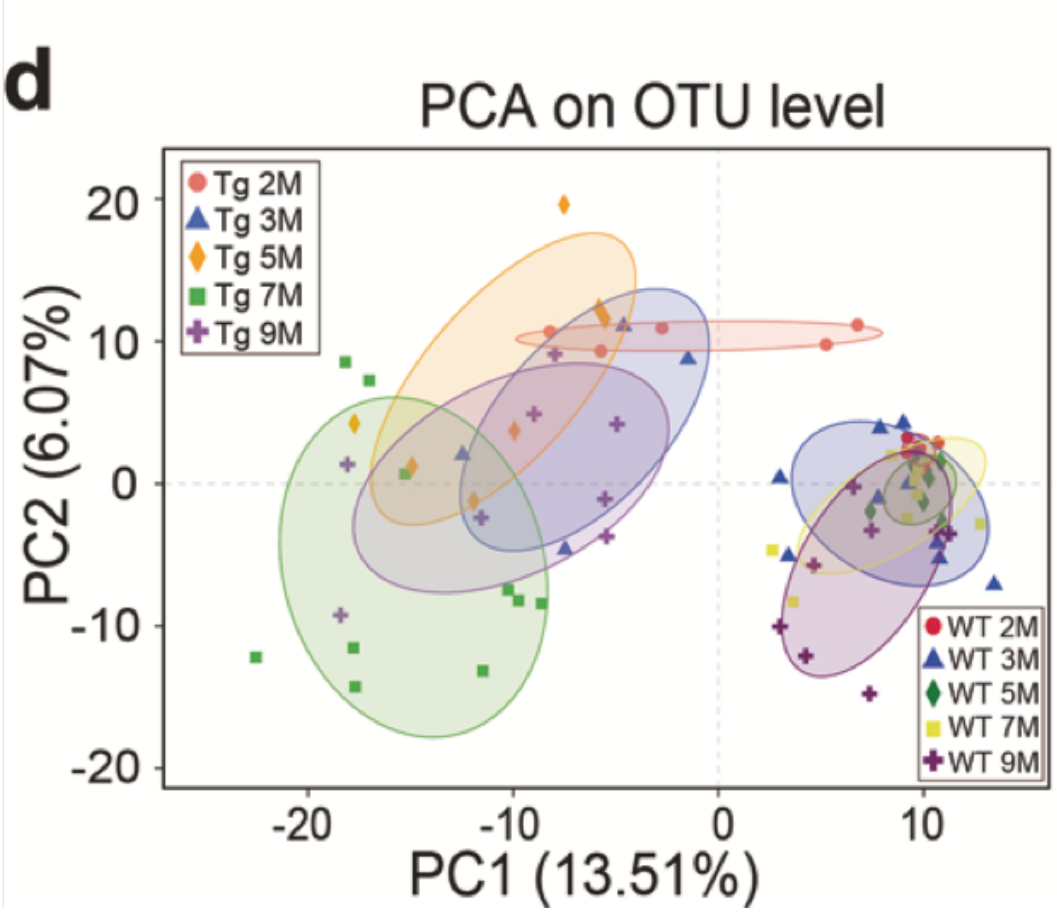


Wang, X., Sun, G., Feng, T. *et al. Cell Res.*, **2019**, *29*, 787.

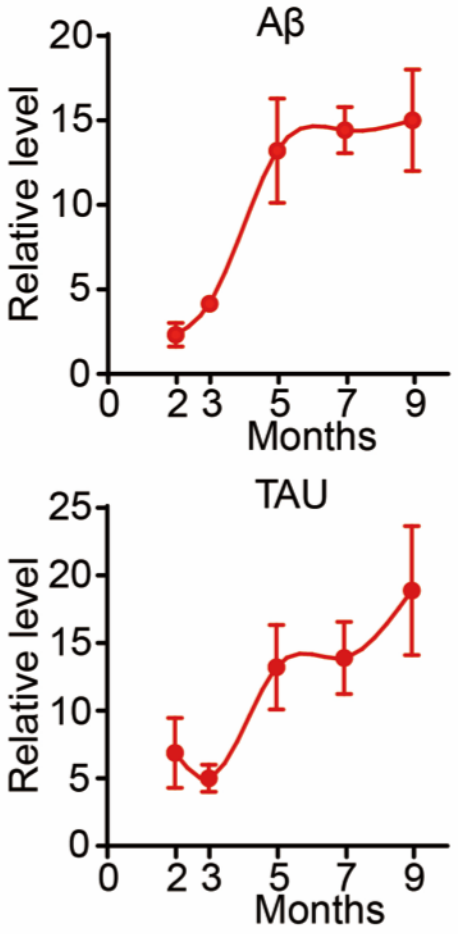
Approved novel AD treatment

AD progression is associated with the alteration of gut microbiota

- **The gut microbiome composition of WT and Tg mice**



- **Aβ & Tau level of Tg mice**



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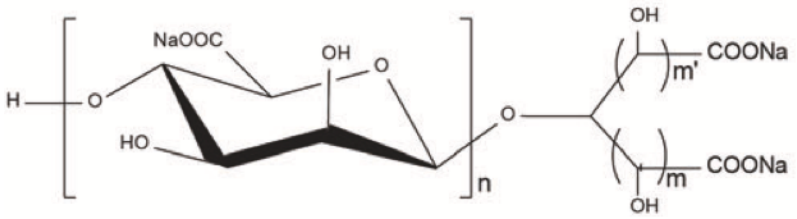
Approved novel AD treatment

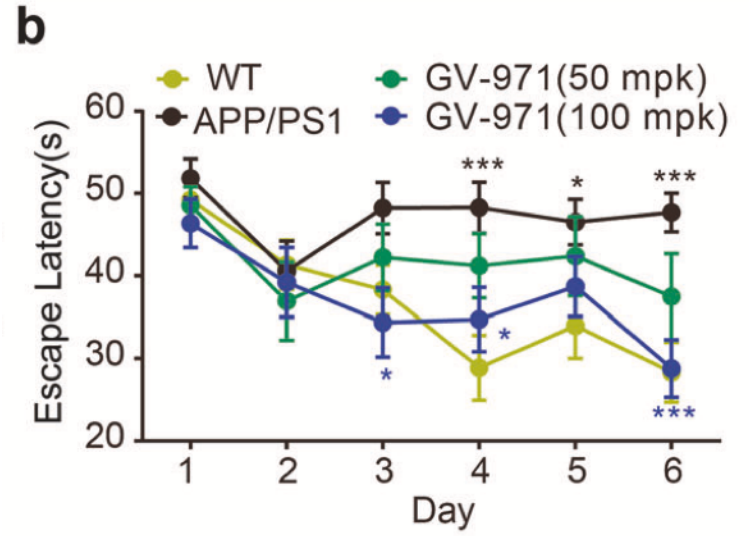
GV-971 exhibits ameliorative effects on cognitive impairment

Structure of GV-971

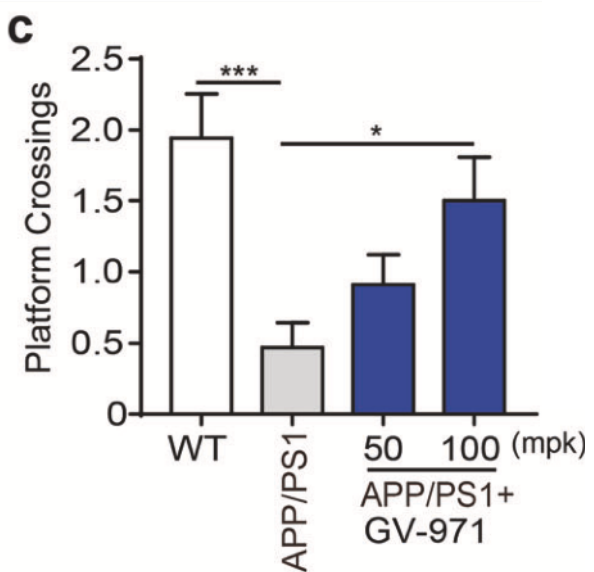


n=1-9; m=0,1 or 2; m'=0 or 1

The escape latency time results of the Morris Water Maze



The number of platform-site crossovers in MWM test

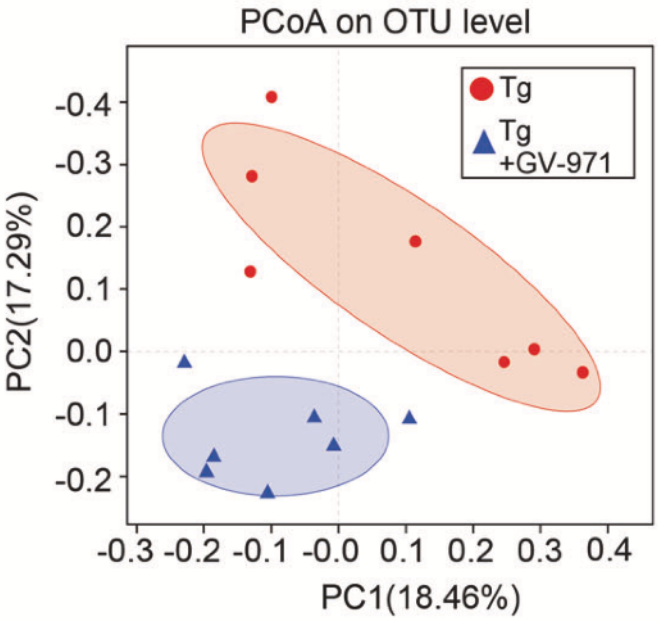


Wang, X., Sun, G., Feng, T. *et al. Cell Res.*, **2019**, *29*, 787.

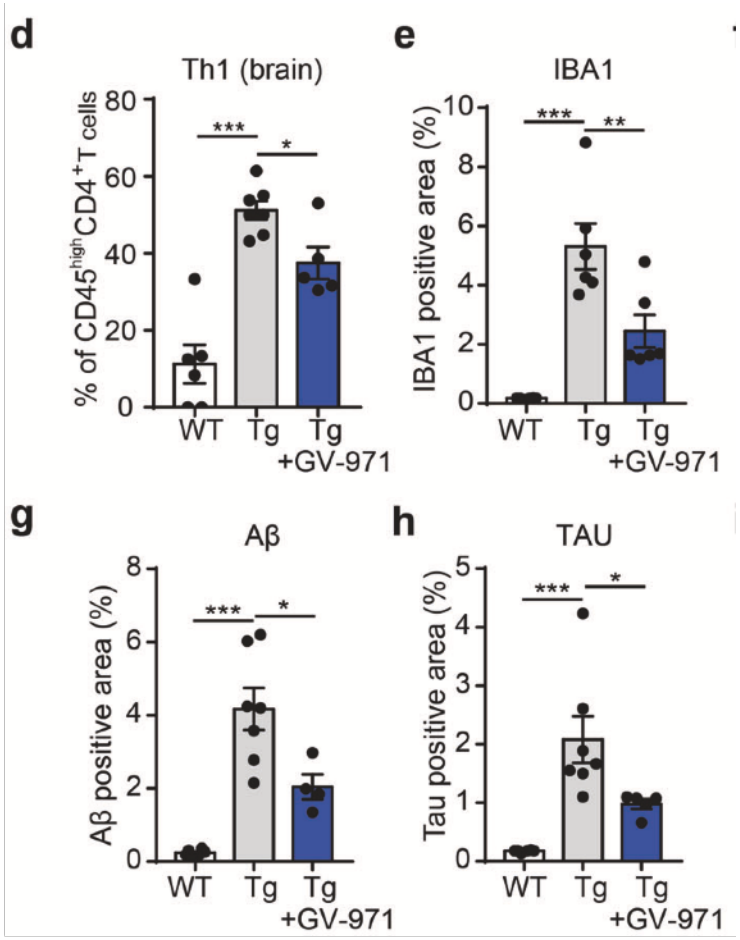
Approved novel AD treatment

GV-971 alleviates neuroinflammation by shaping the gut microbiota

gut microbiota



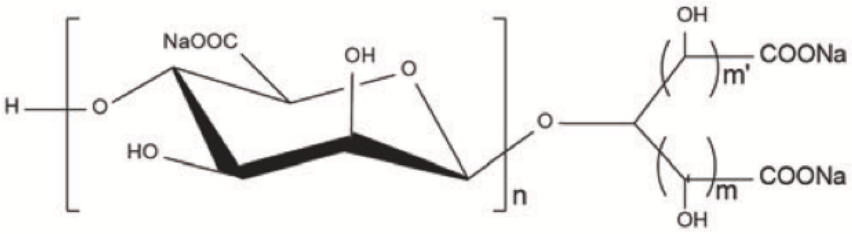
brain



Wang, X., Sun, G., Feng, T. *et al. Cell Res.*, **2019**, *29*, 787.

Approved novel AD treatment

oligomannate



n=1-9; m=0,1 or 2; m'=0 or 1

(Shanghai Green Valley Pharmaceuticals)

2003 Memantine was approved

16 years

2019 Oligomannate was approved in China

2020 The Phase 3 clinical trial in U.S.A & Europe

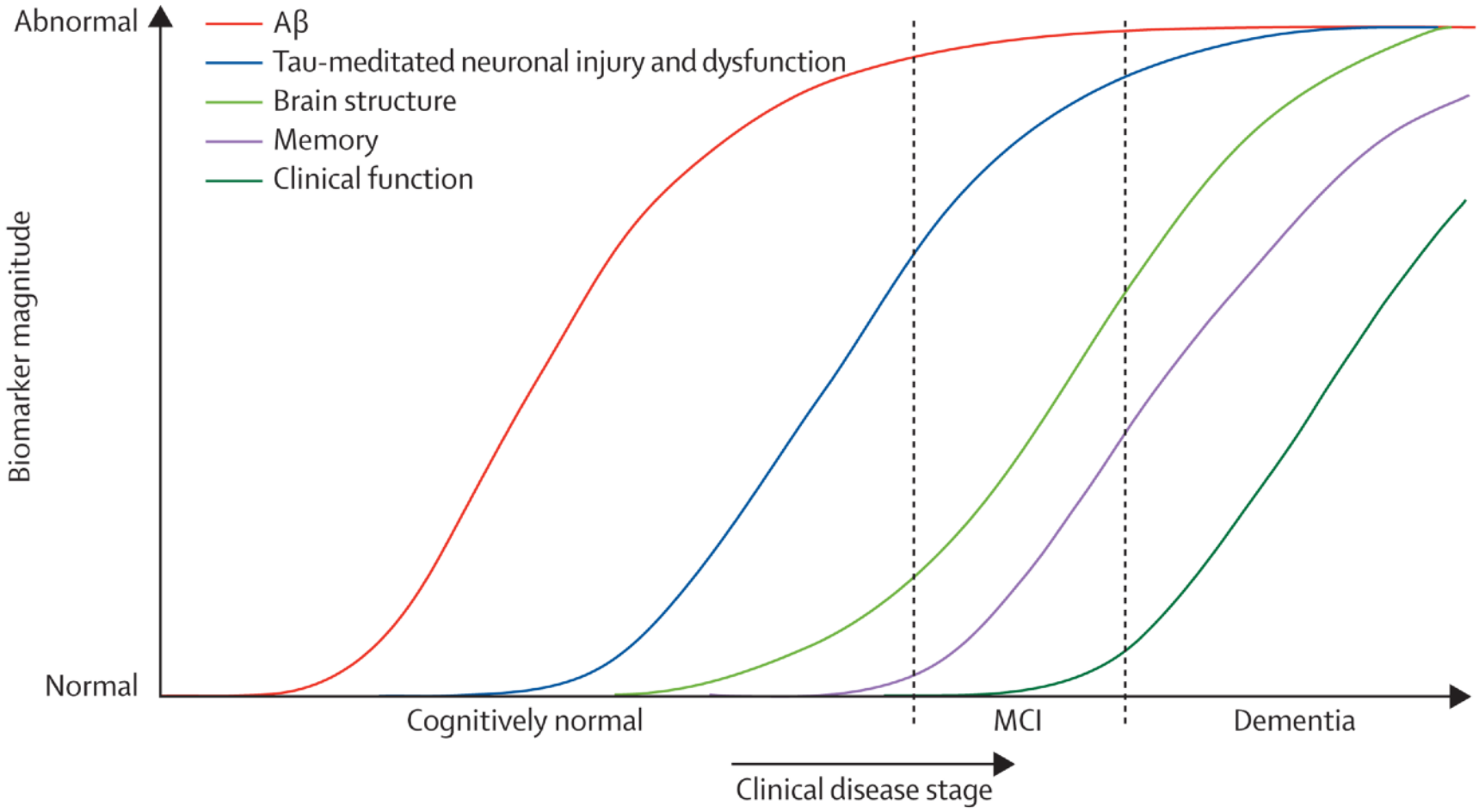
Contents

Summary

- In addition to Aβ and tau, multiple factors are involved in Alzheimer's disease.
- Drug discovery research on various causative factors of Alzheimer's disease is being conducted.

Appendix

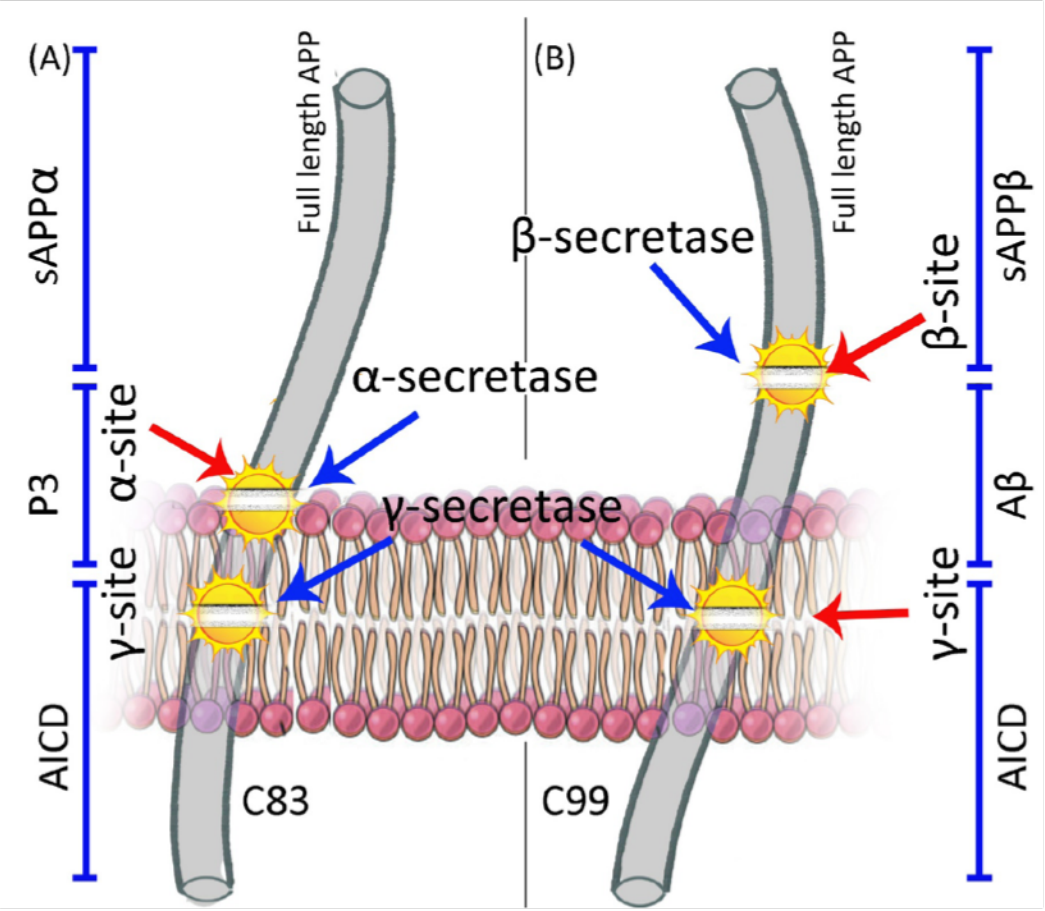
Dynamic biomarkers of the Alzheimer's pathological cascade



John Q Trojanowski, *et al.*, *Lancet Neurol.* , **2010**, *9*, 119.

Appendix

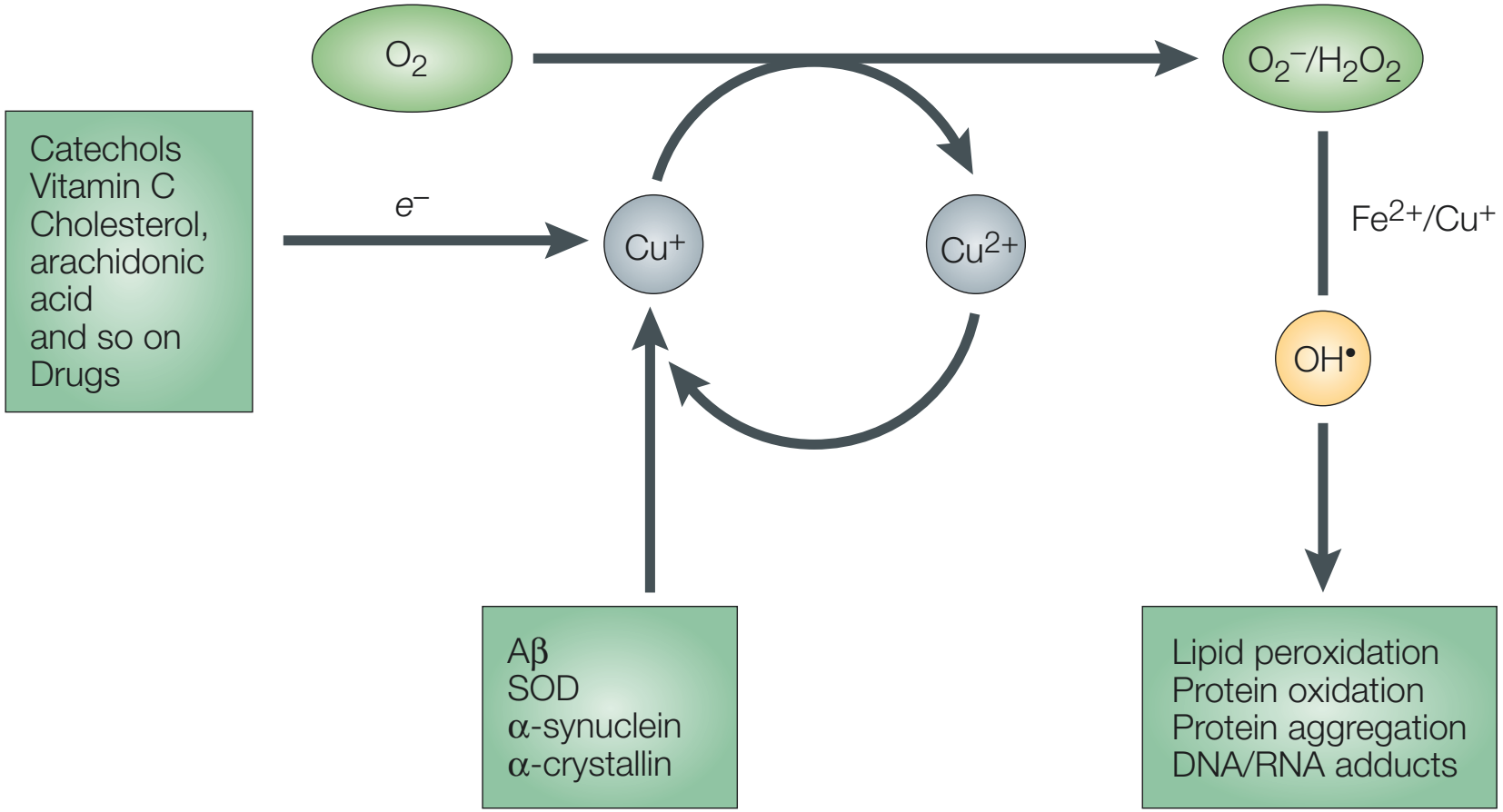
Proteolytic cleavage of APP



Dileep K. Vijayan, and Remya C, *Current Drug Targets*, **2019**, *20*, 148.
PJ Ward, *et al.*, *Science*, **1990**, *248*, 1122.
BA Yankner, *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, **1999**, *96*, 6959.
BA Yankner, *et al.*, *Nat. Natl. Cell Biol.*, **2000**, *2*, 463.
W Song, *et al.*, *FASEB J.*, **2006**, *20*, 285.

Appendix

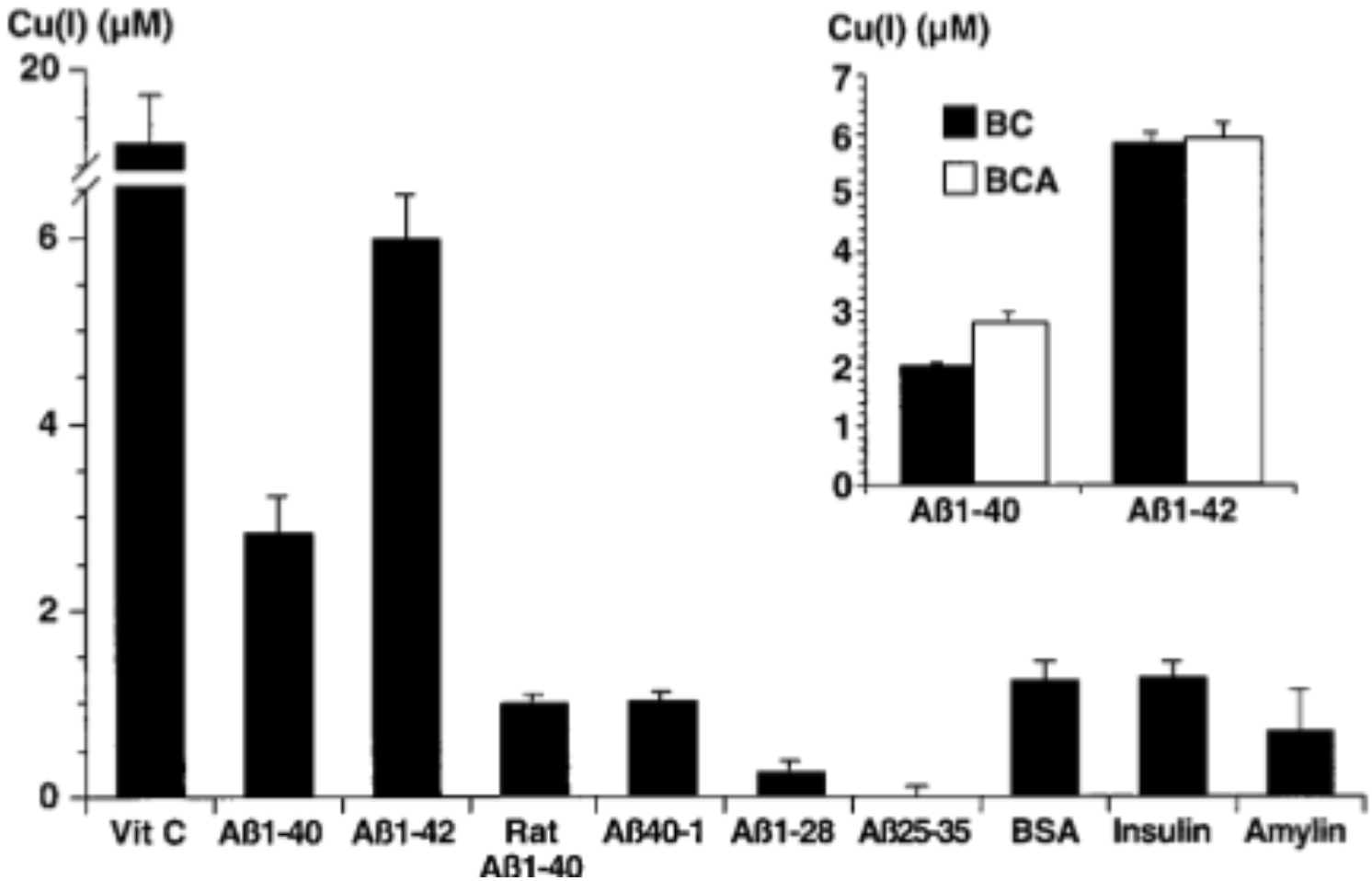
Cu & Aβ generate H_2O_2



Barnham, K.J.; Masters, C.L.; Bush, A.I., *Nat. Rev. Drug Dis.*, **2004**, *3*, 205.

Appendix

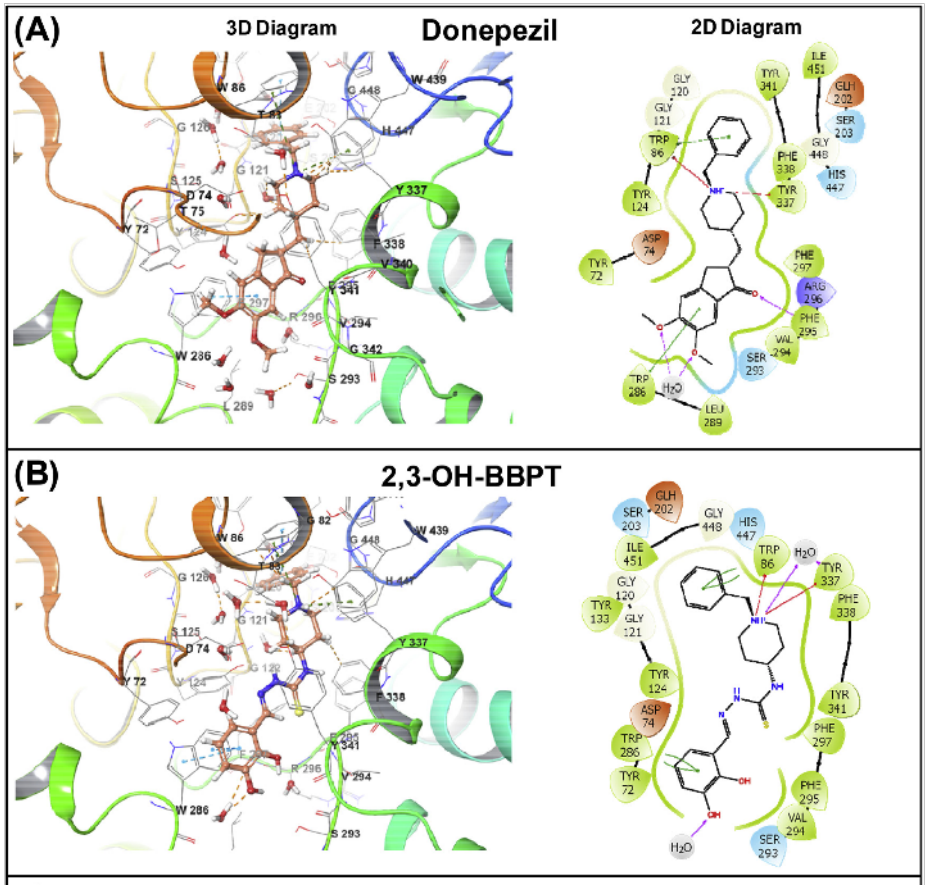
Aβ Reduces Cu(Ⅱ)

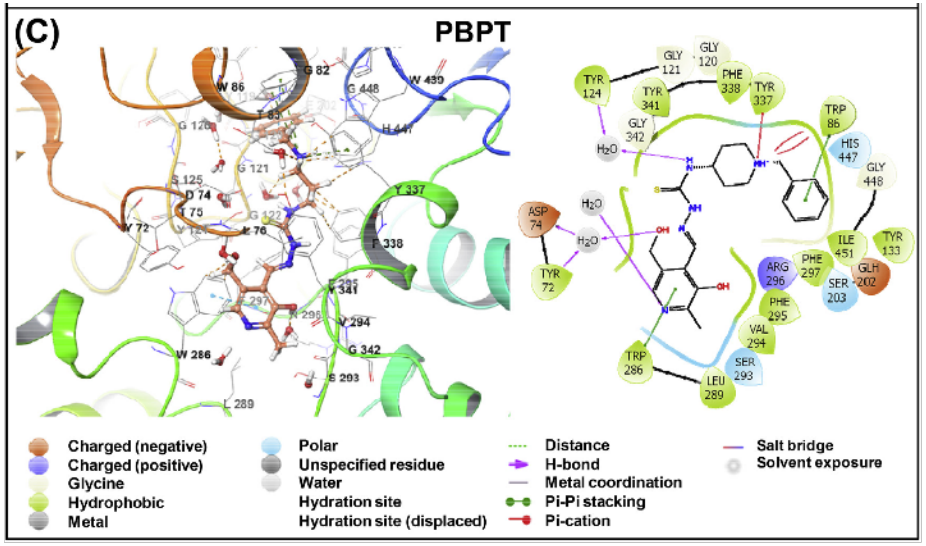


Bush A. I. *et al.*, *J. Biol. Chem.*, **1999**, *274*, 37111.

Appendix

3D and 2D docking diagrams showing the binding mode

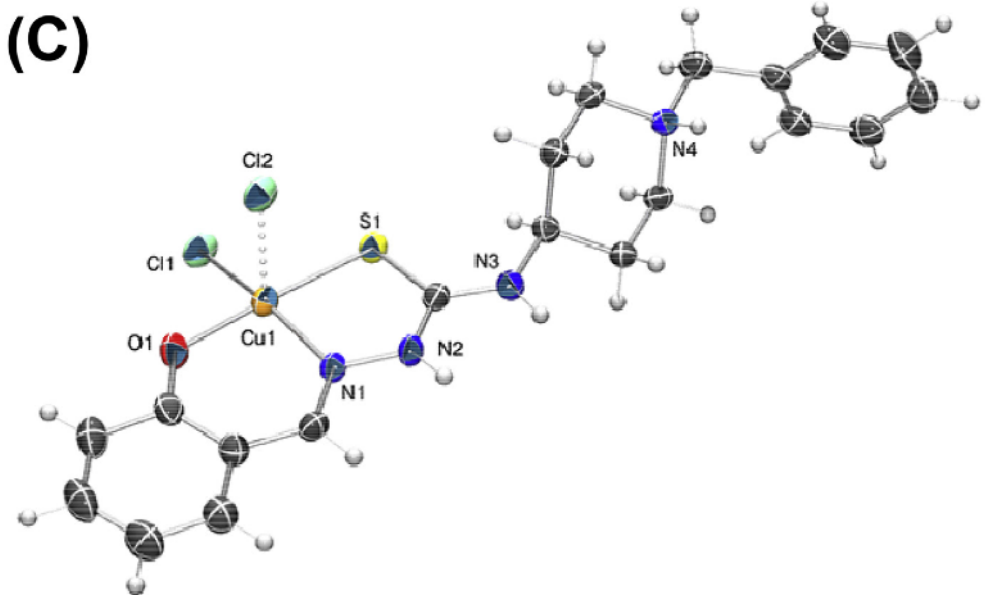


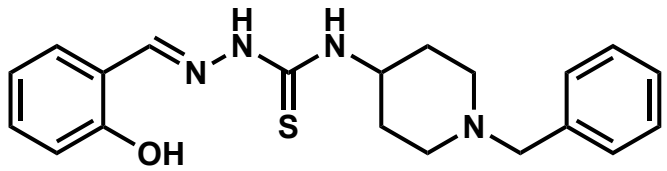


Palanimuthu, D.; Poon, R.; Sahni, S.; Anjum, R.; Hibbs, D.; Lin, H.Y.; Bernhardt, P.V.; Kalinowski, D.S.; Richardson, D.R., *Eur. J. Med. Chem.* **2017**, *139*, 612.

Appendix

X-ray crystal structures of [Cu(SBPT)Cl2]



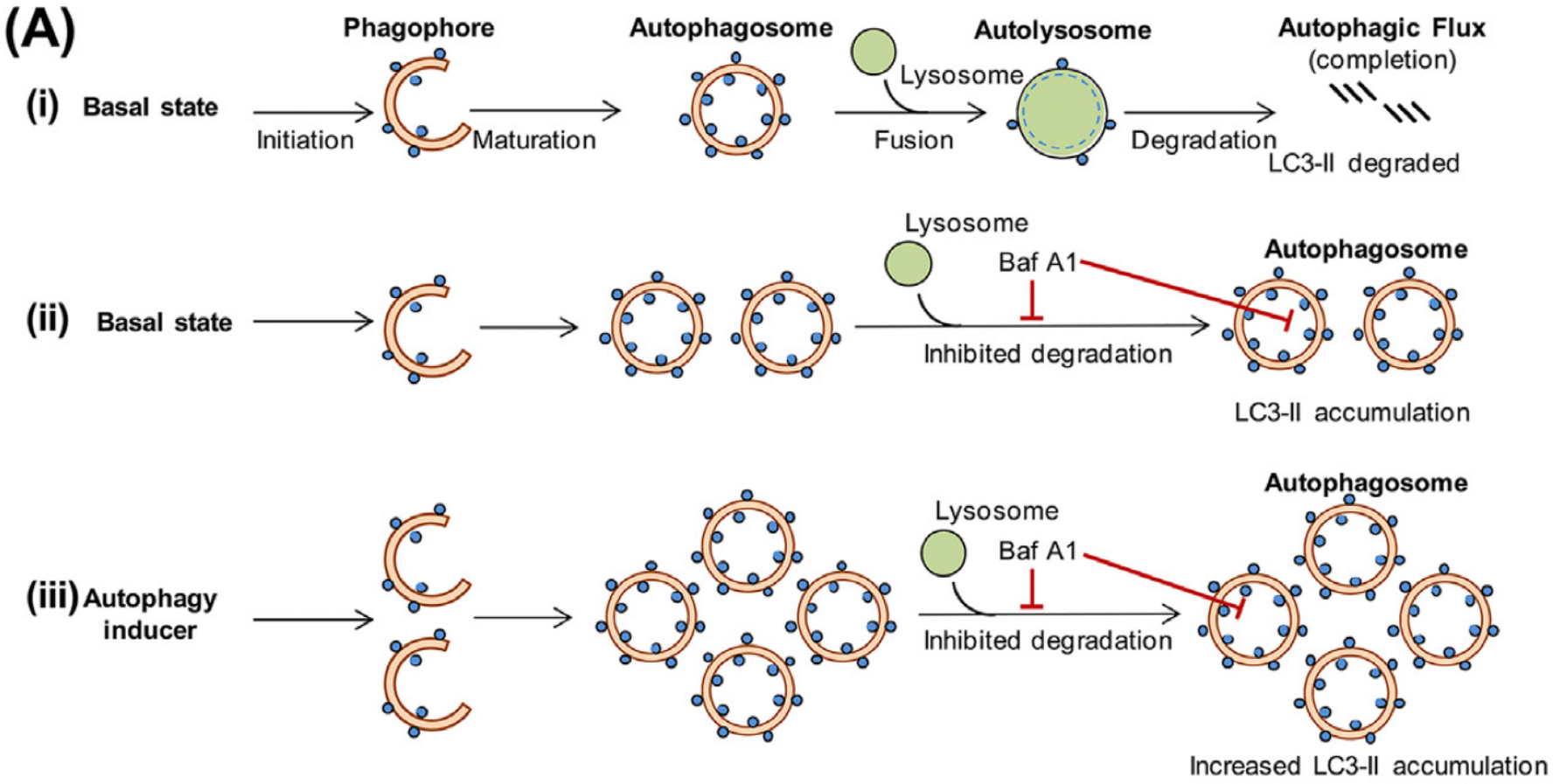


SBPT

Palanimuthu, D.; Poon, R.; Sahni, S.; Anjum, R.; Hibbs, D.; Lin, H.Y.; Bernhardt, P.V.; Kalinowski, D.S.; Richardson, D.R., *Eur. J. Med. Chem.* **2017**, *139*, 612.

Appendix

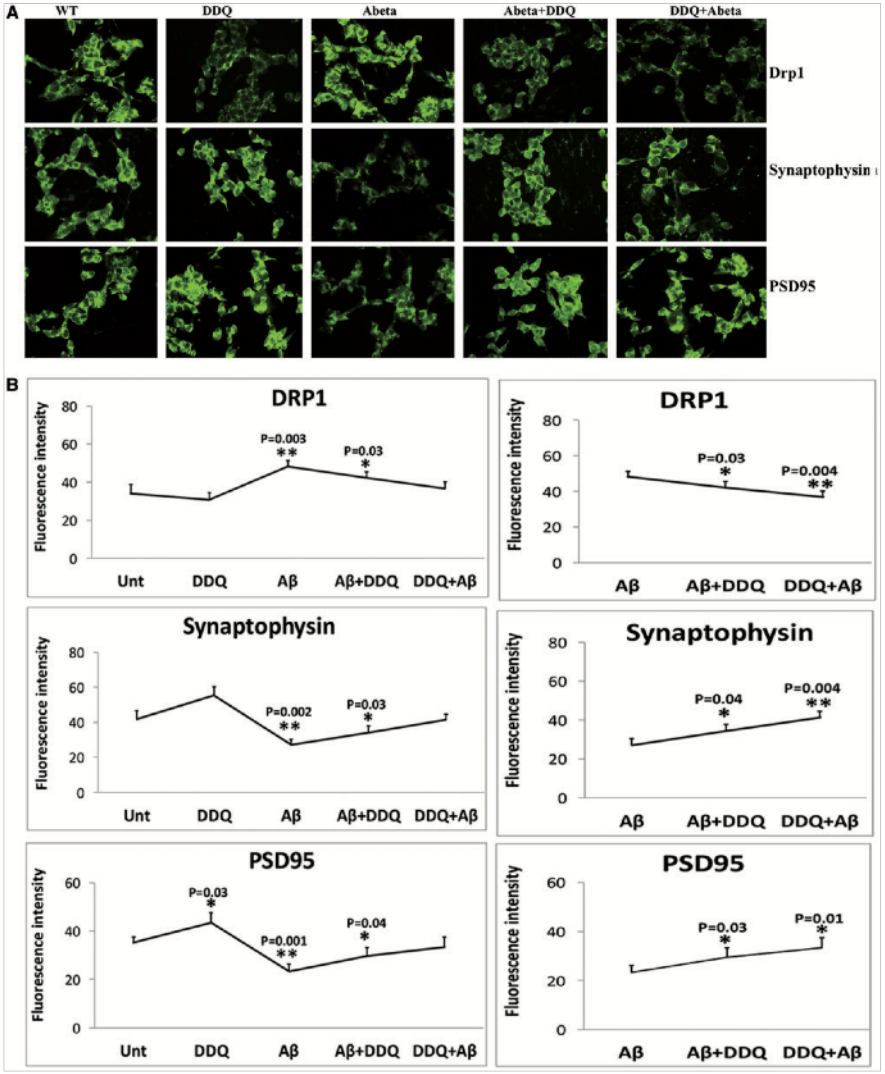
Bafilomycin's effect



Palanimuthu, D.; Poon, R.; Sahni, S.; Anjum, R.; Hibbs, D.; Lin, H.Y.; Bernhardt, P.V.; Kalinowski, D.S.; Richardson, D.R., *Eur. J. Med. Chem.* **2017**, *139*, 612.

Appendix

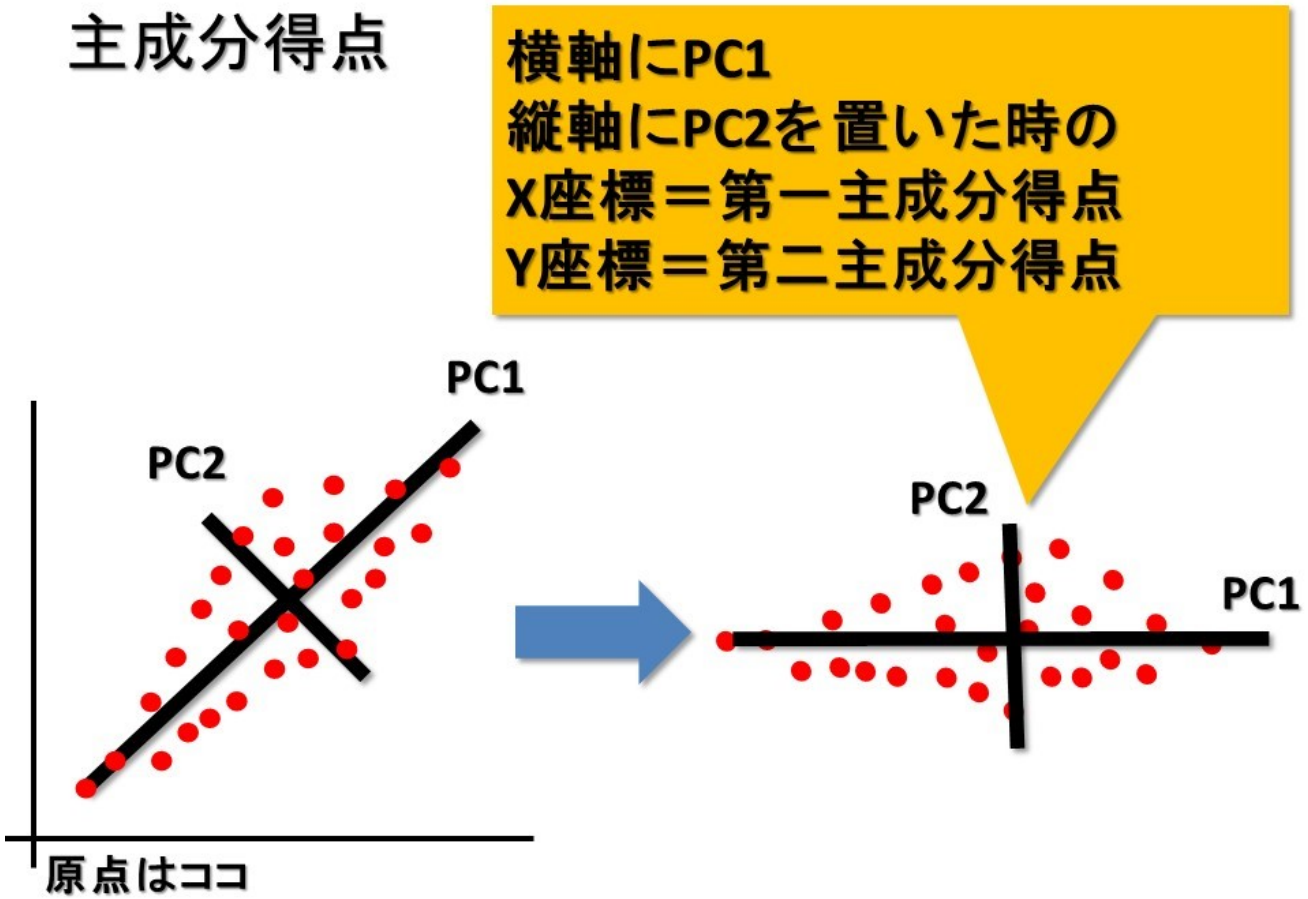
Immunofluorescence analysis (DDQ)



Kuruva, C.S.; Manczak, M.; Yin, X.; Ogunmokun, G.; Reddy, A.P.; Reddy, P.H., *Hum. Mol. Genet.* **2017**, *26*, 3375.

Appendix

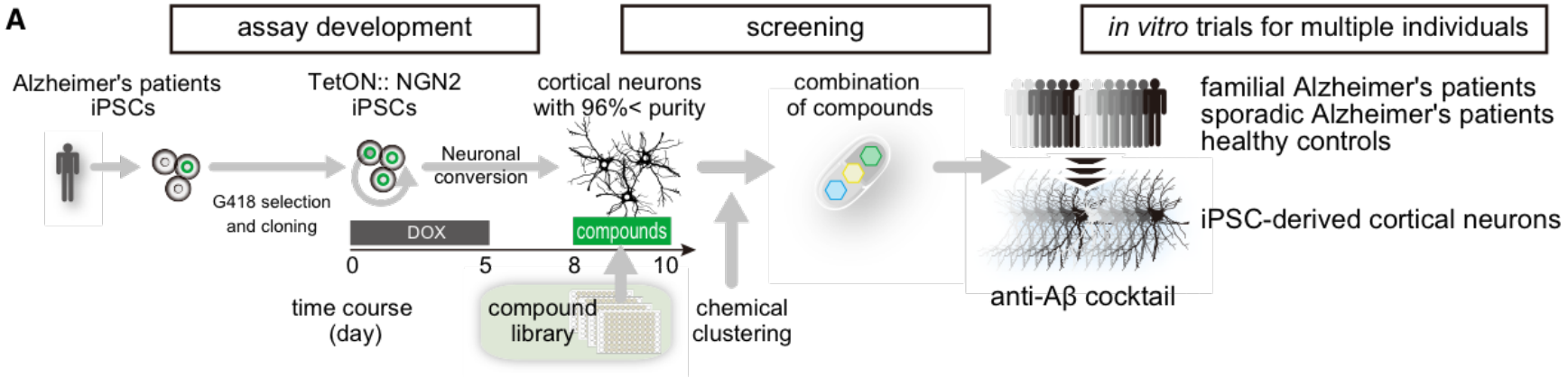
Principal component analysis



https://logics-of-blue.com/principal-components-analysis/

Appendix

iPSC-Based Compound Screening



Anti-Aβ Cocktail of BCroT (bromocriptine, cromolyn, topiramate)

Inoue H. *et al.*, *Cell Rep*. **2017**, *21*, 2304.