Transition Metal-based Potential Therapy for Alzheimer's Disease

Speaker: Song Lijuan

Date: 2014-04-11

Alzheimer's Disease is the most common type of dementia: Degenerative brain syndromes which affect memory, thinking, behavior and emotion

Outline

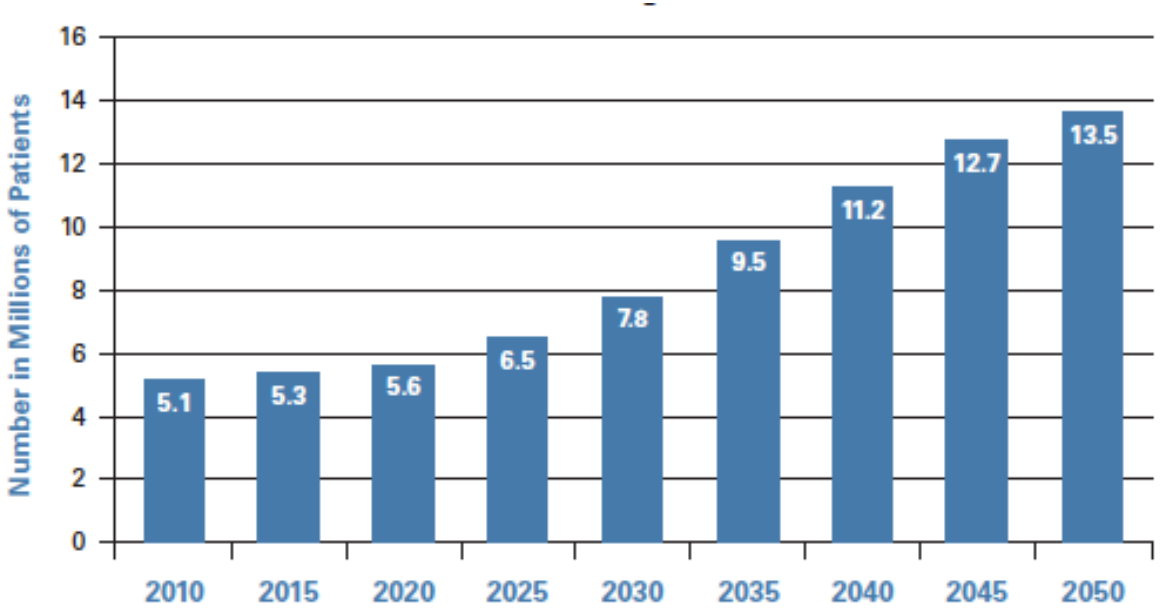
- Introduction
- Metal ions in amyloid aggregation
- Transition metal-based inhibitors

  Chelating ligands

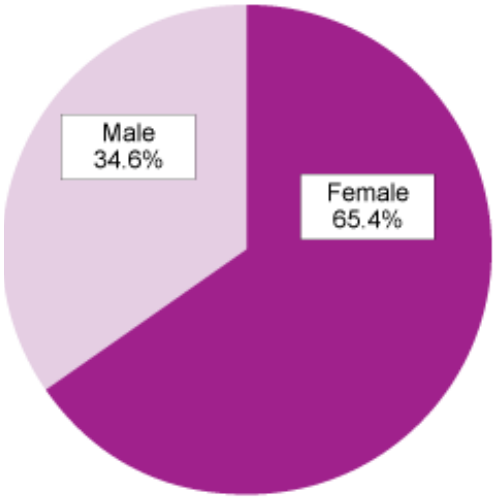
  Transition metal complexes
- Summary

Introduction

- Alzheimer's disease (AD) is a progressive neurodegenerative condition that results in synaptic failure and neuronal death. These symptoms initially manifest as mild forgetfulness but lead to complete loss of cognition.



65 Years and Older with AD in USA, 2012-2050



Adults Aged 65 and Older with AD By Sex, 2011

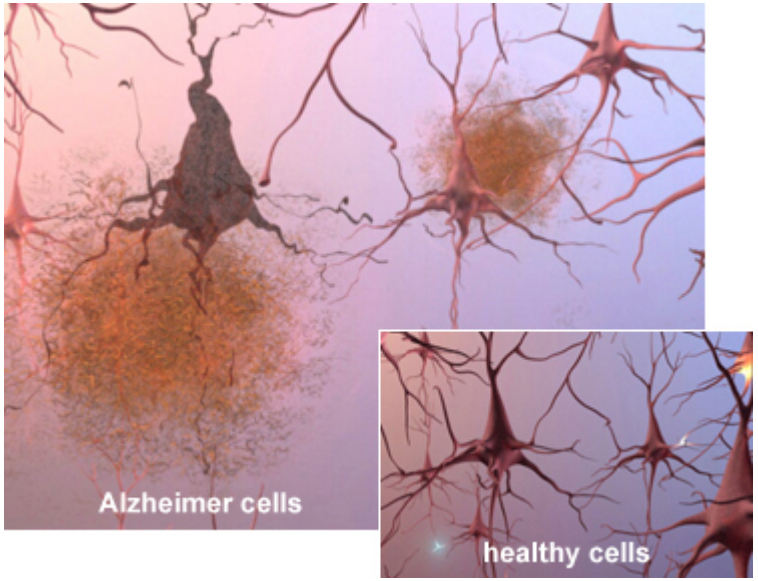
Am J Manag Care. **2011**,17, 339

Herbert et al. *Alzheimer Disease and Associated Disorders* . **2001**, 15, 169

Pathological Hallmarks

- Extracellular senile plaques (老年斑)
- Intracellular neurofibrillary tangles (神经纤维纠结)
- Altered levels of neurotransmitters

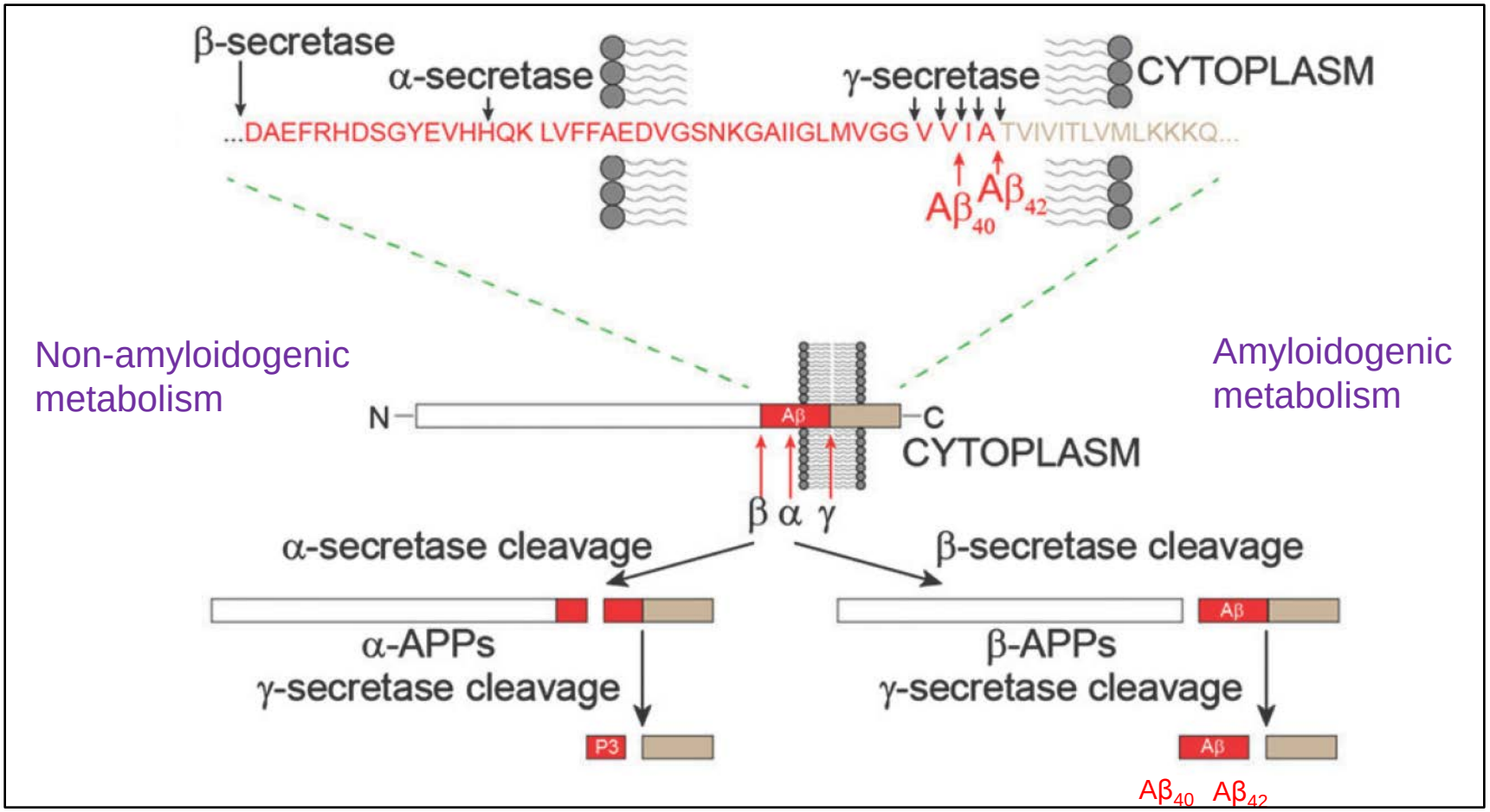
(reduced acetylcholine levels, loss of neurons, shrinkage of the brain)



D. J. Hayne, S. Lim, P. S. Donnelly. *Chem. Soc. Rev.* **2014**, Advance Article

Amyloid-β plaques

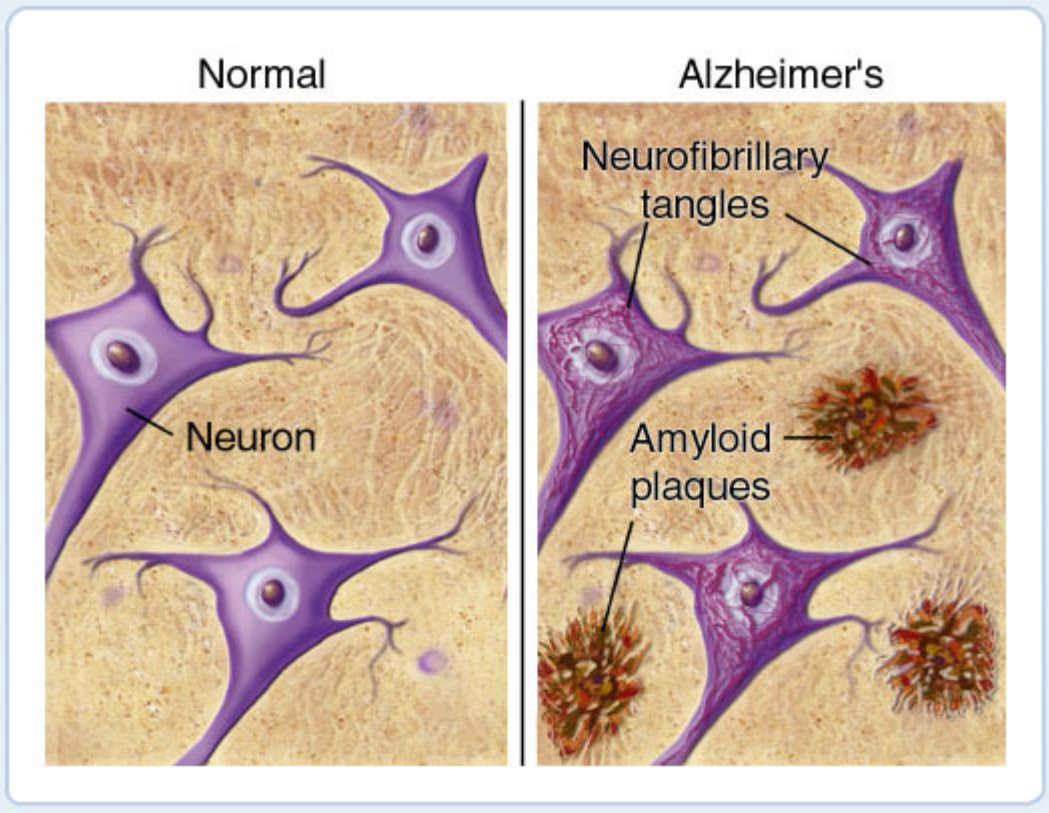
Amyloid plaques are composed of an insoluble aggregated peptide called amyloid-β(Aβ)，which contains 39–43 residues and derived from the Amyloid precursor protein (**APP**).



D. J. Hayne, S. Lim, P. S. Donnelly. *Chem. Soc. Rev.* **2014**, Advance Article

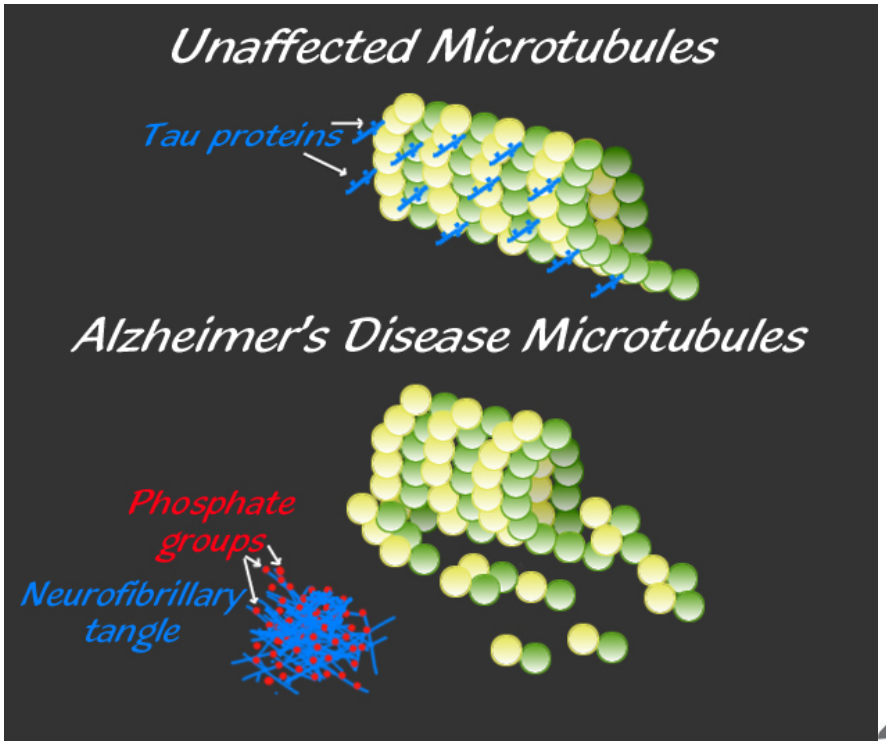
Amyloid-β plaques

- Abnormal accumulation of toxic Aβ oligomers forms extracellular deposits that build up between neurons block signals between cells.
- Ab plaques and/or their precursors trigger a cascade of events leading to synaptic dysfunction, microgliosis, and neuronal loss



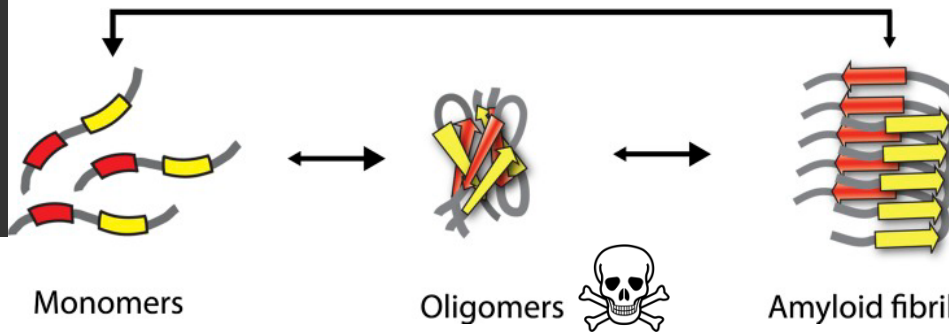
Aβ42 (Aβ1-42): DAEFRHDSGY[10]EVHHQKLVFF[20]AEDVGSNKGA[30]IIGLMVGGVV[40]IA

Intracellular Neurofibrillary Tangles



Neurofibrillary Tangles consist of a hyper phosphorylated form of a microtubule associated protein called tau

The hyper-phosphorylation of tau results in its detachment from microtubules that consequently lose structural integrity



Soluble oligomers: disruption of the synaptic function, effects on the integrity of the membrane bilayer, and production of ROS

J. Marx and cowaorkers, Science, 2007, 316, 1416.

D. J. Hayne, S. Lim, P. S. Donnelly. *Chem. Soc. Rev.* **2014**, Advance Article

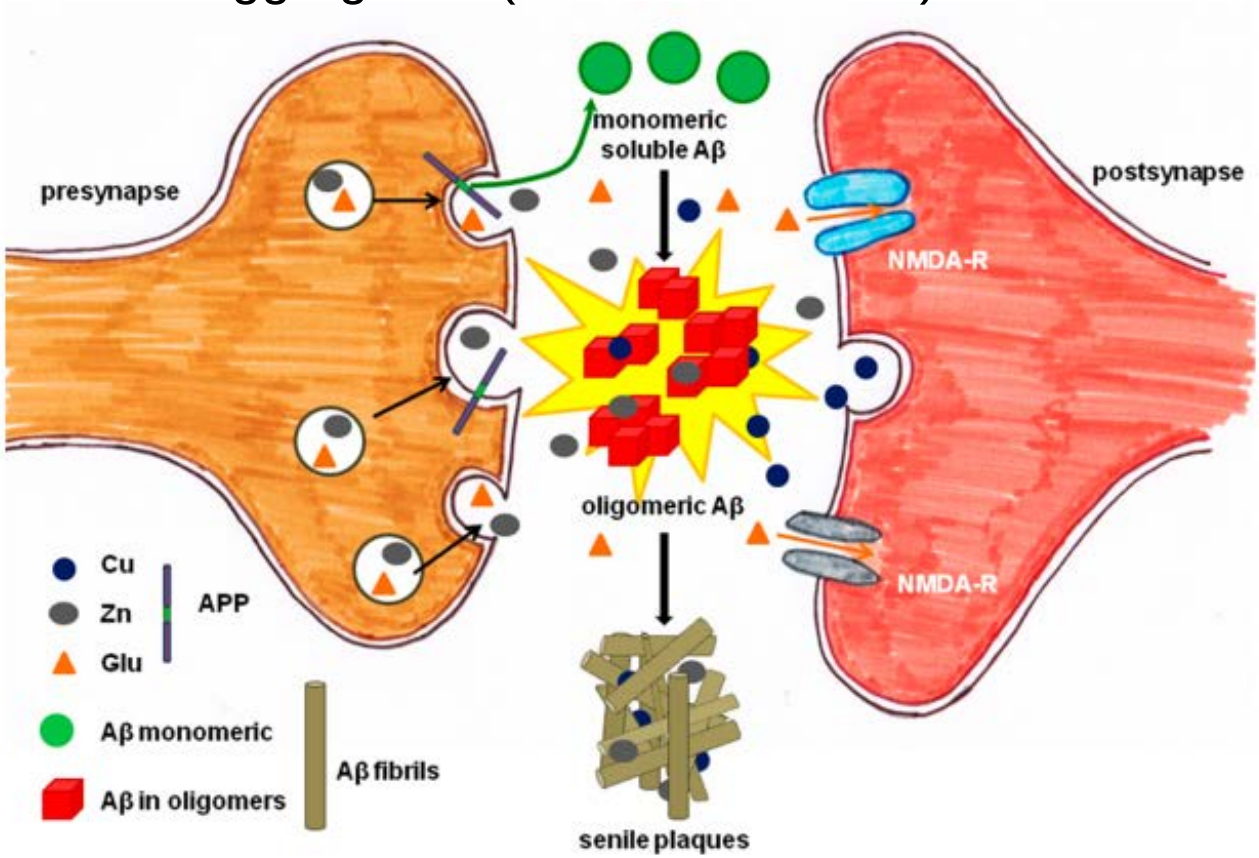
Metal Ions in Amyloid Aggregation

Metal Ions: $Cu^{I/II}$, Zn^{II}, $Fe^{II/III}$

The binding of metal ions changes both the structure and the charge of Aβ. The decrease in the overall charge at physiological pH increases the overall driving force for aggregation (easier nucleation)

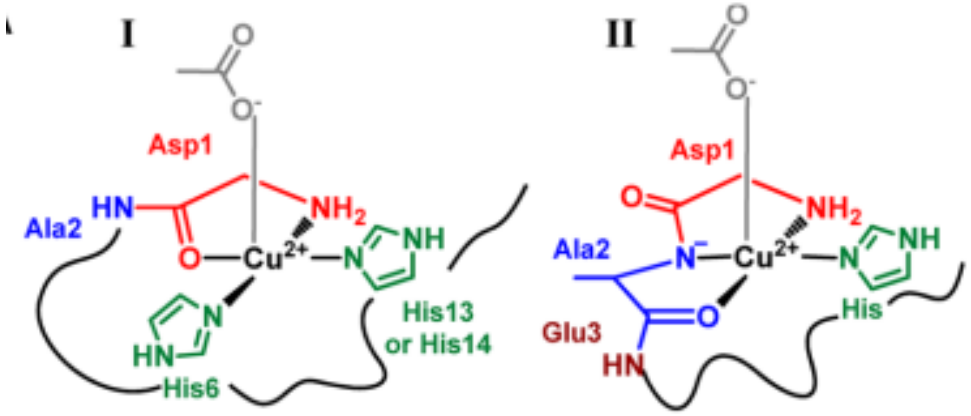
Cu^{II}, Zn^{II} involved in the Aβ aggregation process

Abnormally high concentration of Cu^{II}, Zn^{II}



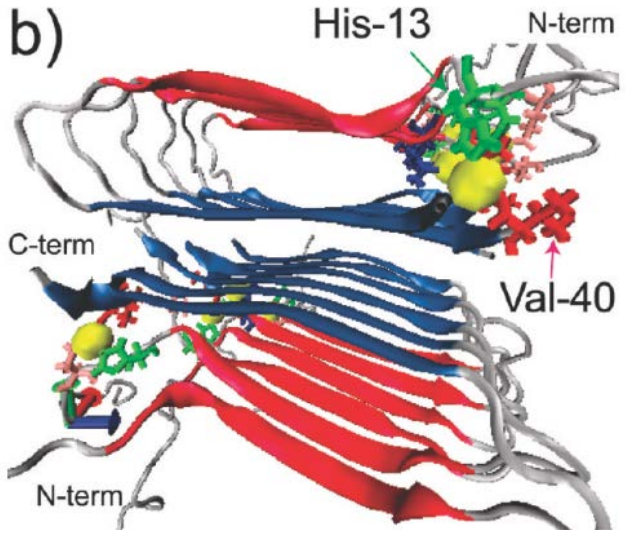
P. Faller, C. Hureau, O. Berthoumieu. *Inorganic Chemistry.* **2013** *52*,12193

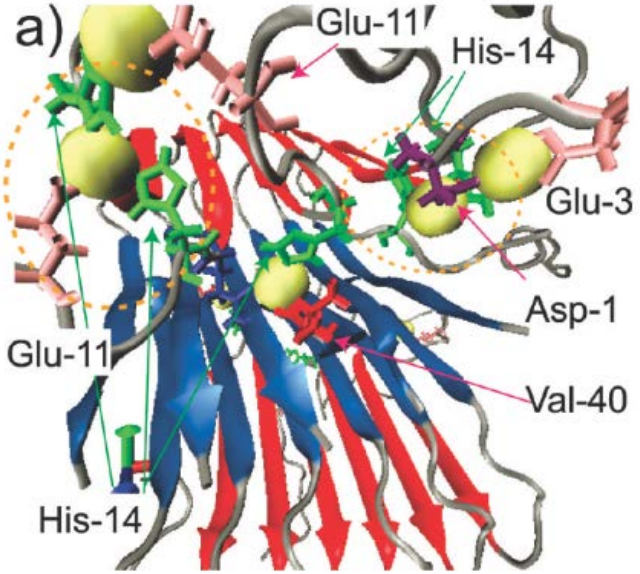
Binding Modes



pH 6.5
(component 1)

pH ≥ 8
(component 2)





Primary Cu^{2+} binding sites in Aβ(1- 40) fibrils:

His6, His13 and His14

Asp1, Asp1− Ala2, Ala2− Glu3

Y. Ishii and coworkers. J. Am. Chem. Soc., **2011**, *133*, 3390
D. Kim, N. H. Kim, S. H. Kim. *Angew. Chem., Int. Ed.* **2013**, 52, 1139

Metal Ions in production of ROS

The interaction of redox-active copper ions with Aβ is linked to production of reactive oxygen species (**ROS**), which has been associated with oxidative stress and neuronal damages.

Reaction 1

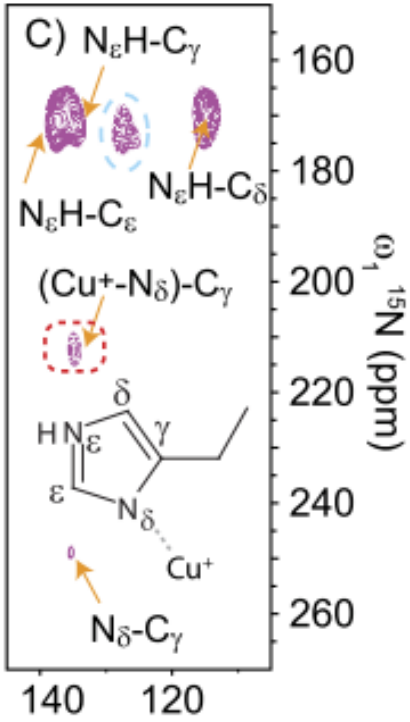
Cu^{2+} -Aβ + Asc ⟶ Cu^{+} -Aβ + Oxd.Asc + H^{+}

Reaction 2

Cu^{+} -Aβ + H^{+} + $1/_2O_2$ ⟶ Cu^{2+} -Aβ + $1/_2\mathbf{H_2O_2}$

Reducing agent: ascorbate

Enzyme-like reaction: Aβ fibrils become a strong catalyst that attracts copper ions and introduce cyclic redox reactions involving Cu^{2+}/Cu^{+} ions

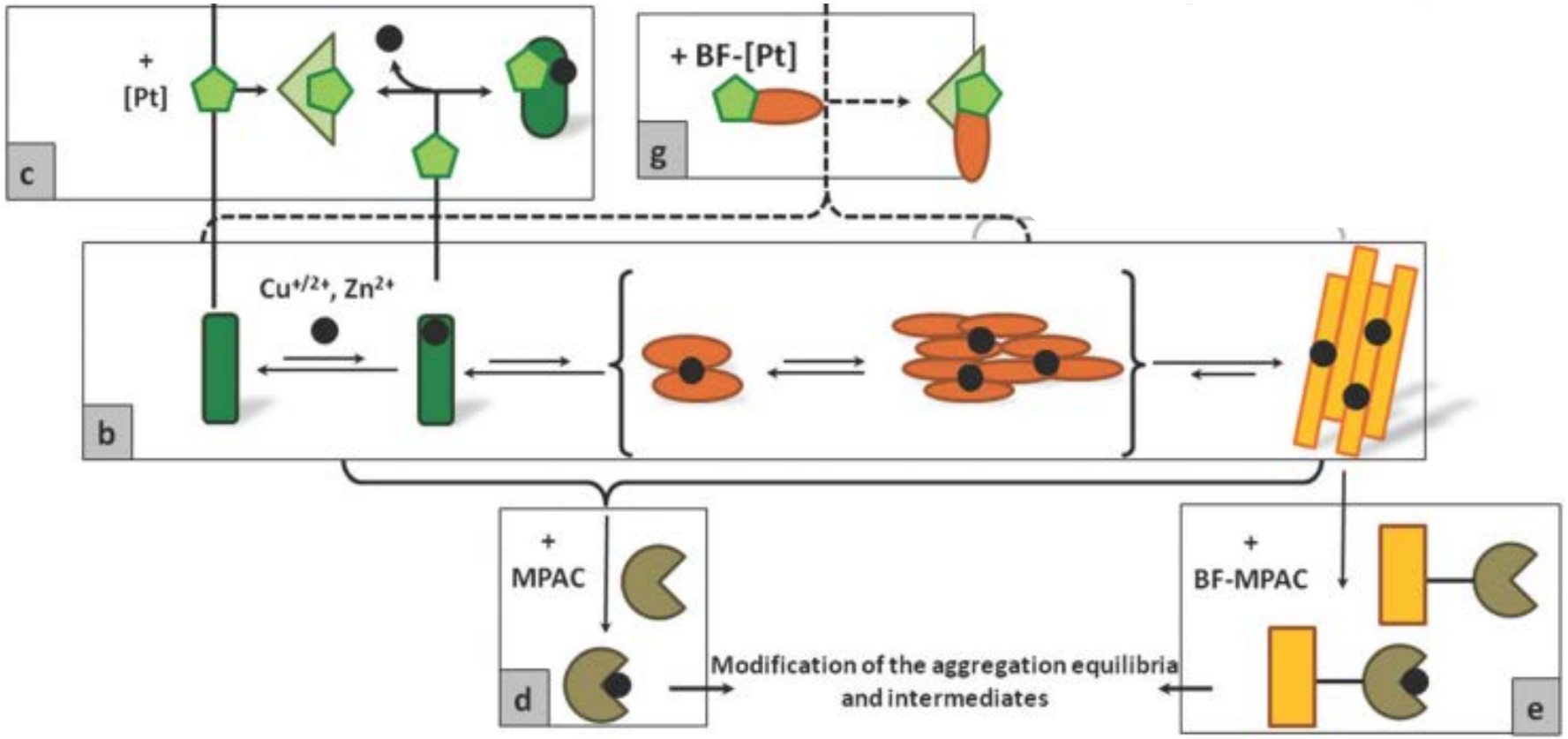


Reactive state : Cu^{+}- Aβ

S. Parthasarathy, B. Yoo, D. McElheny, W. Tay, Y. Ishii. *J. Biol. Chem*. **2014**, 289, 9998

Strategies of design metal ion inhibitors

Transition metal complexes (targeting side trains of Aβ)

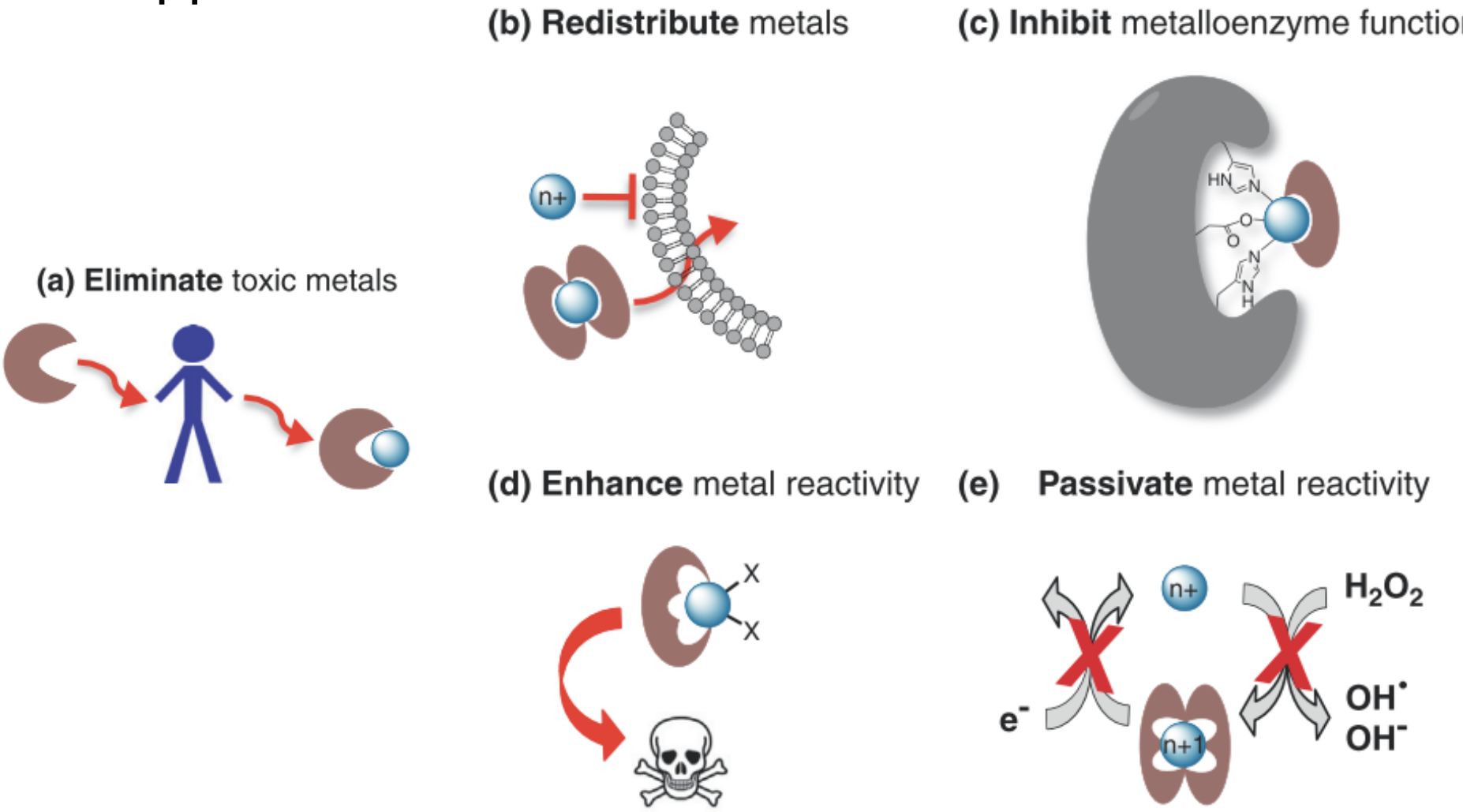


Chelating ligands (targeting metal ions)

C, Hureau. P. Faller. *Dalton Trans.* **2014**, 43, 4233

Chelating Ligands

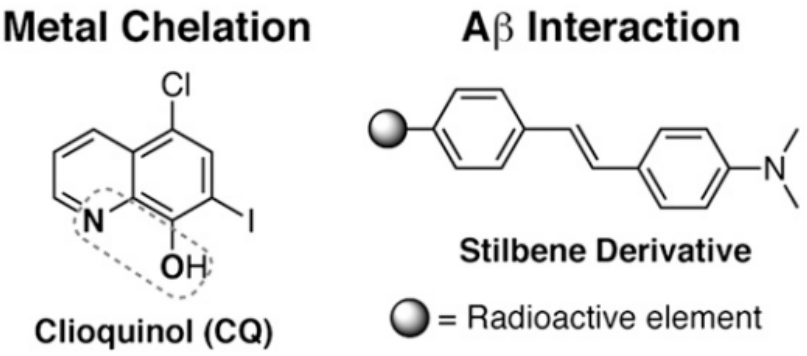
- Approaches



A. S. Pithadia, M. H. Lim, *Curr. Opin. Chem. Biol.*, **2012**, 16, 67

Chelating Ligands

Bifunctional ligands



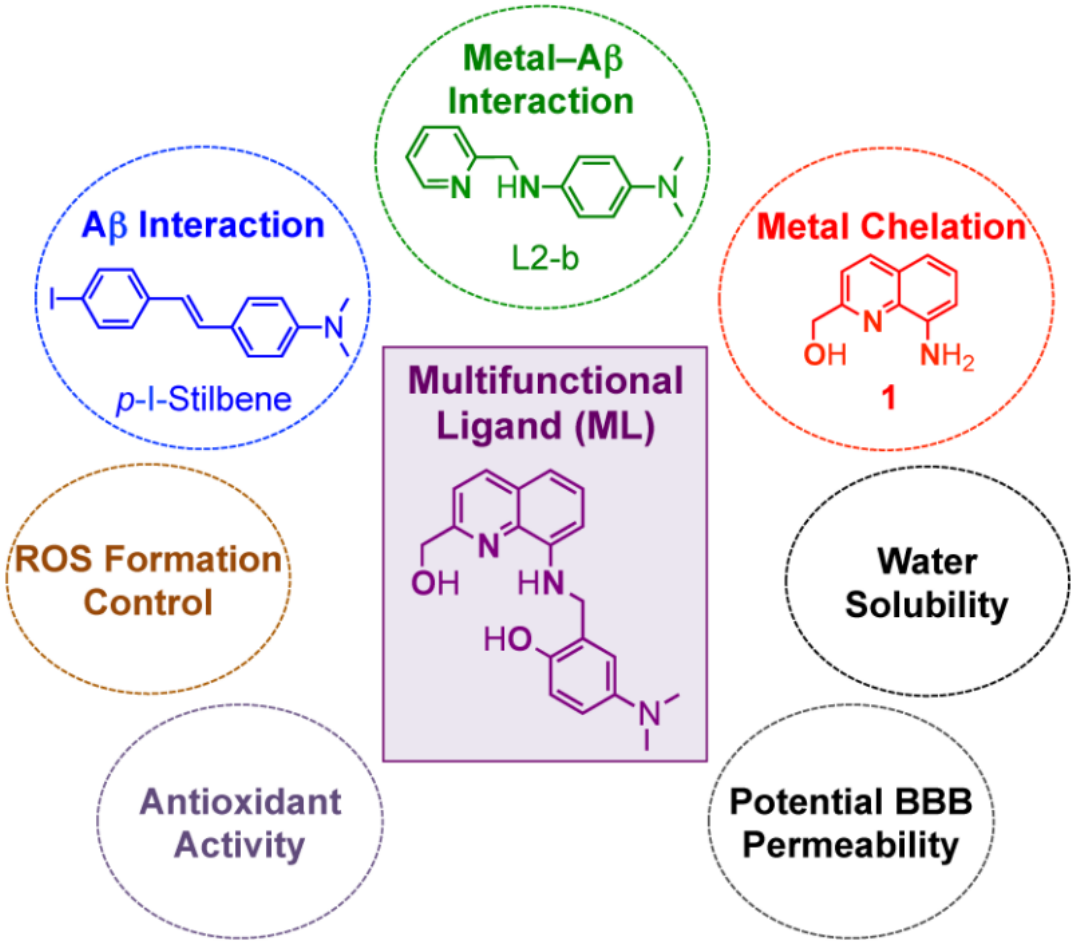
CQ have moved into clinical trials and showed improved cognition but limited by its synthetic difficulties and toxicity

Aromatic ring

J.k Choi, J. J. Braymer, R. P. R. Nanga, A. Ramamoorthy, M. H. Lim. *Proc. Natl. Acad. Sci*. **2010**.107, 21990

Chelating Ligands

- Rational structure-based design of a multifuncitonal ligand

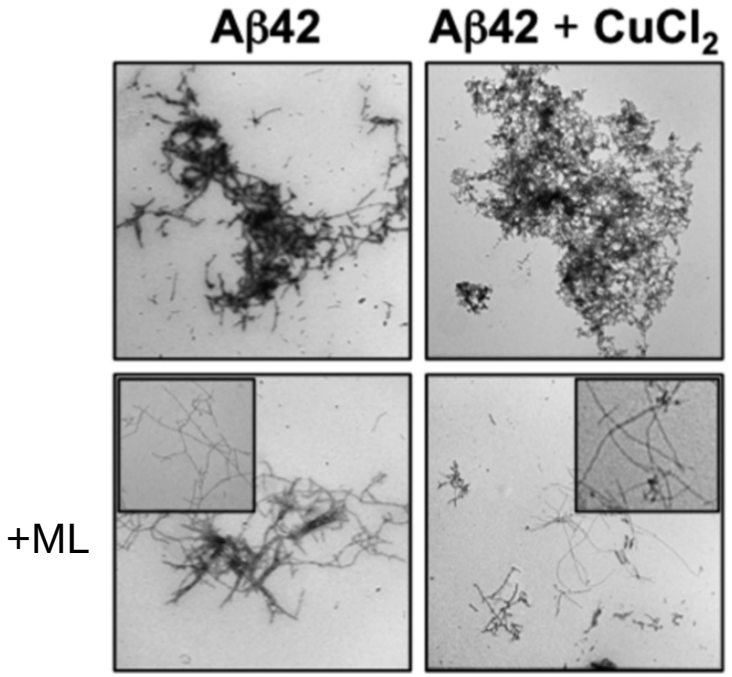


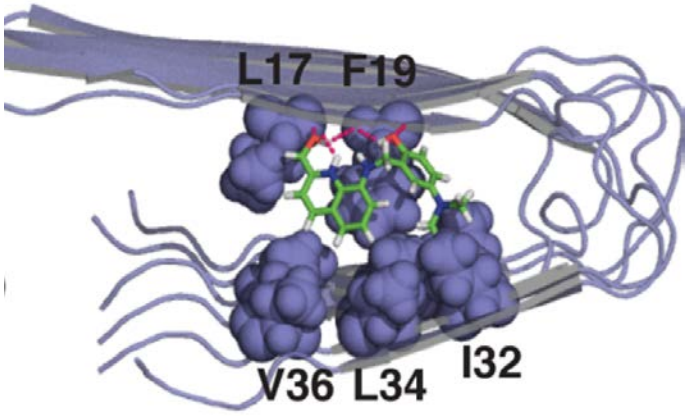
- ✓ Tetradentate ligand for Cu(II)
- ✓ substituents (e.g., quinoline and phenolic groups)
- ✓ polar functionalities(e.g., hydroxyl and amino groups)
- ✓ logBB

A. Ramamoorthy, M. T. Bowers. M. H. Lim and coworkers. *J. Am. Chem. Soc*. **2014**, 136, 299

Chelating Ligands

- Interactions with soluble forms of Aβ
- Control of Aβ aggregation
- Regulation metal induced toxicity
- Control of ROS formation, antioxidant capacity and BBB permeability





ML interact with unpaired β sheet at the end of the A β fiber:

hydrogen bonding

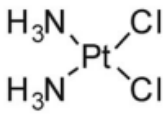
π−π stacking

Van der Waals interactions

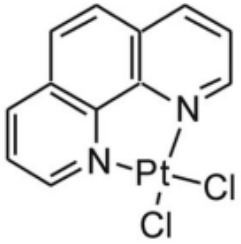
A. Ramamoorthy, M. T. Bowers. M. H. Lim and coworkers, *J. Am. Chem. Soc*. **2014**, 136, 299

Transition Metal Complexes

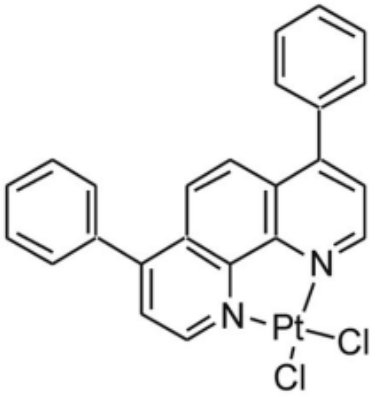
- Platinum-based inhibitors



cisplatin
(1)



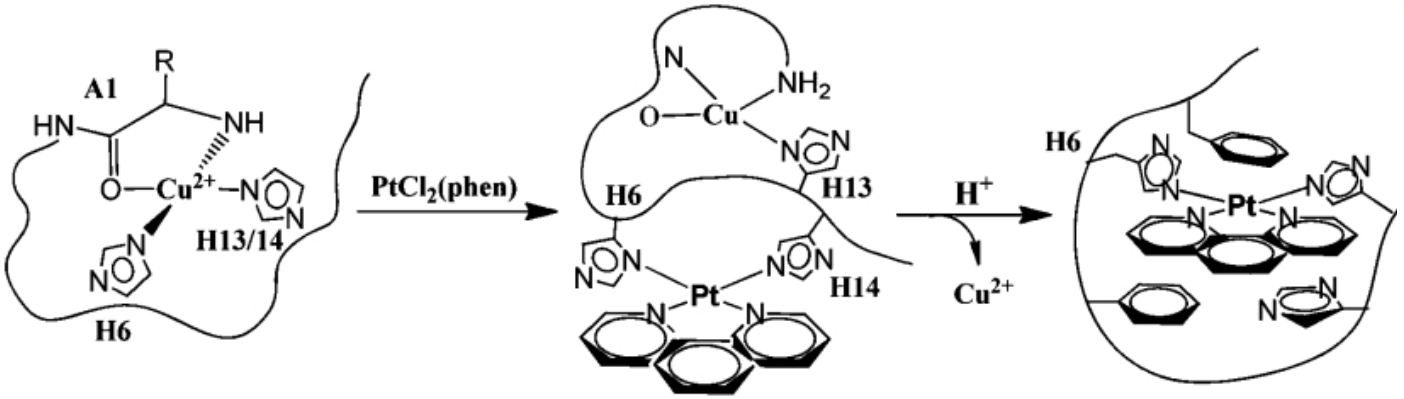
Pt(1,10-phenathroline)Cl_2
(2)

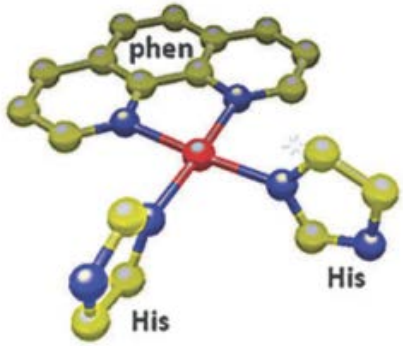


Pt(4,7-diphenyl-[1,10]phenanthroline)Cl_2
(3)

ligand-Aβ interact through π–π stacking

Proposed reaction mechanism of $PtCl_2$(phen) targeting [Cu^{II}–Aβ]

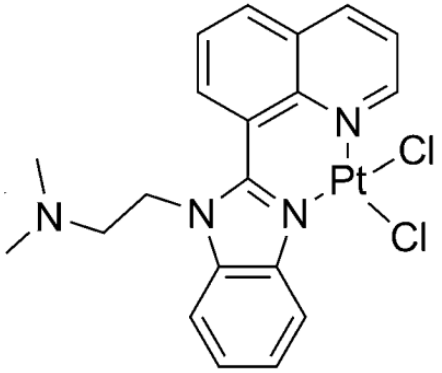




K. J. Barnham, *Proc. Natl. Acad. Sci.* **2008**, 105
Y. Liu and coworkers, *Metallomics*, **2013**, 5, 879

Transition Metal Complexes

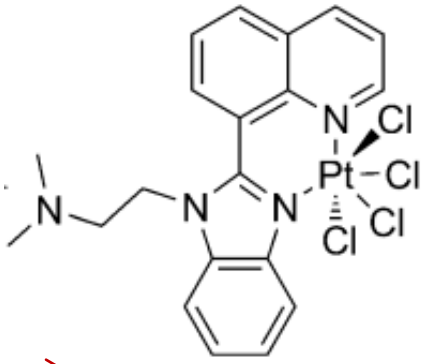
Platinum complex as an anti-amyloid agent



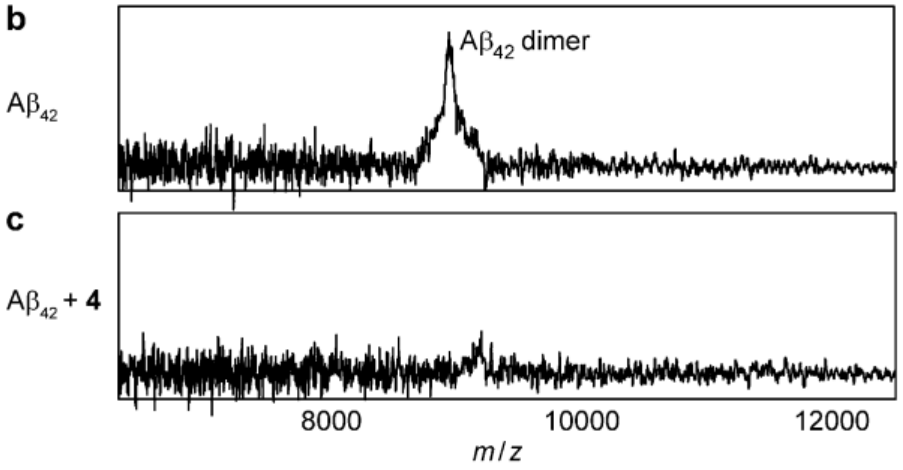
4

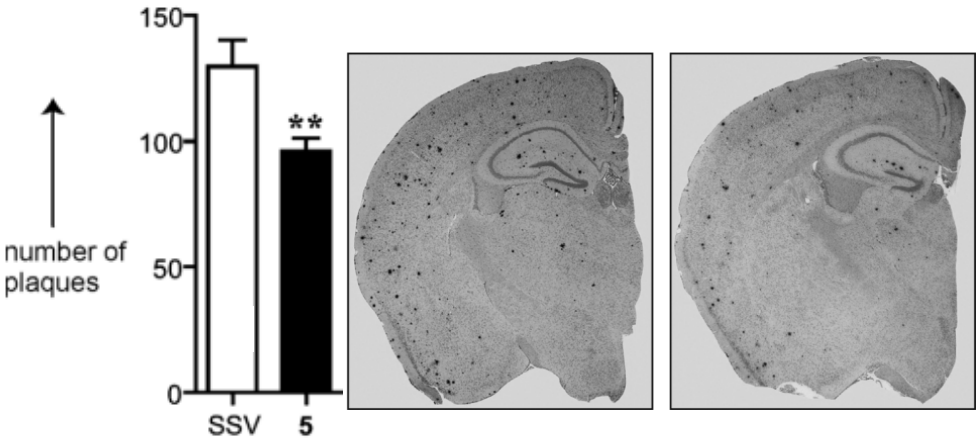
- Labile positions (replaced by the imidazole ring of His)
- Non-toxic
- BBB penetration

Improving bioavailability



5



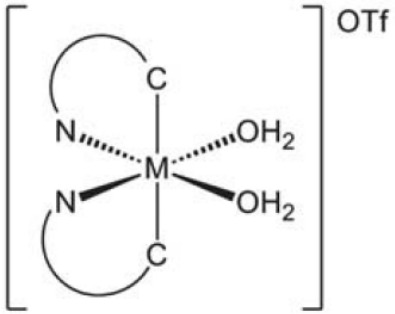


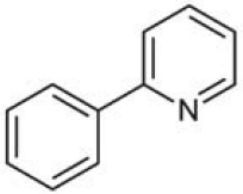
Reduced Aβ levels in APP/PS1 mice after treatment with **5**

K. J. Barnham and coworkers. *Angew. Chem. Int. Ed*. **2013**, 52, 3374

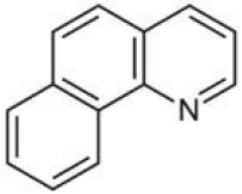
Transition Metal Complexes

- Group 9 metal-based inhibitor

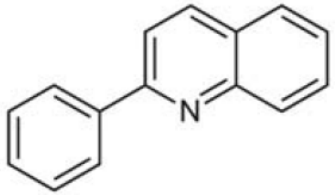




ppy



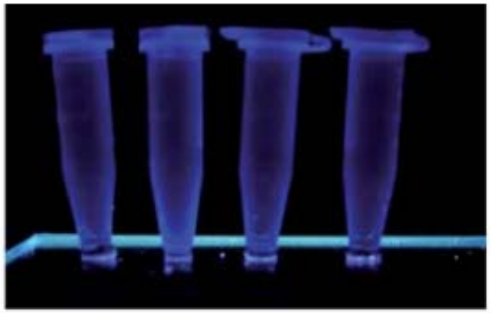
bzq

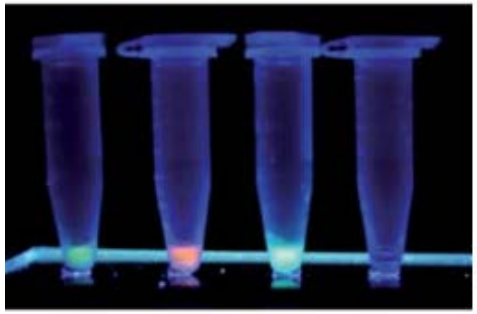


phq

1a: M = Ir, C^N = ppy
1b: M = Rh, C^N = ppy

2: M = Ir, C^N = bzq
3: M = Ir, C^N = phq

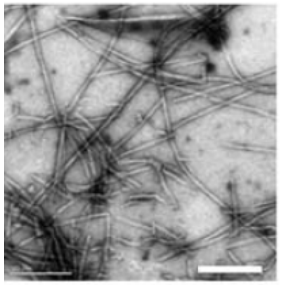


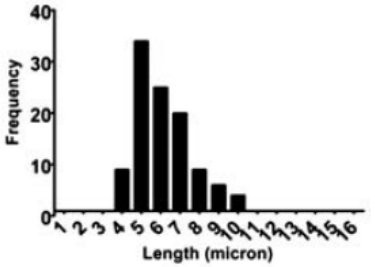


+$A\beta_{1\text{-}40}$

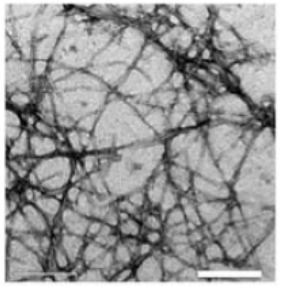
TEM | Frequency Histogram

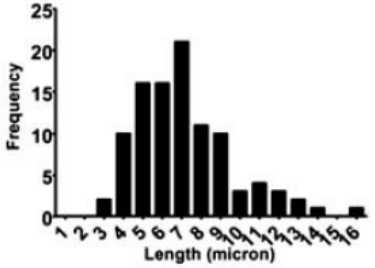
0 μM



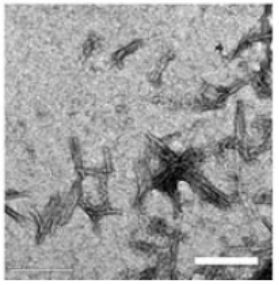


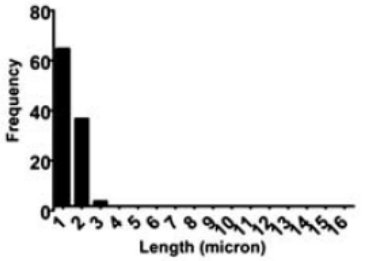
1 μM





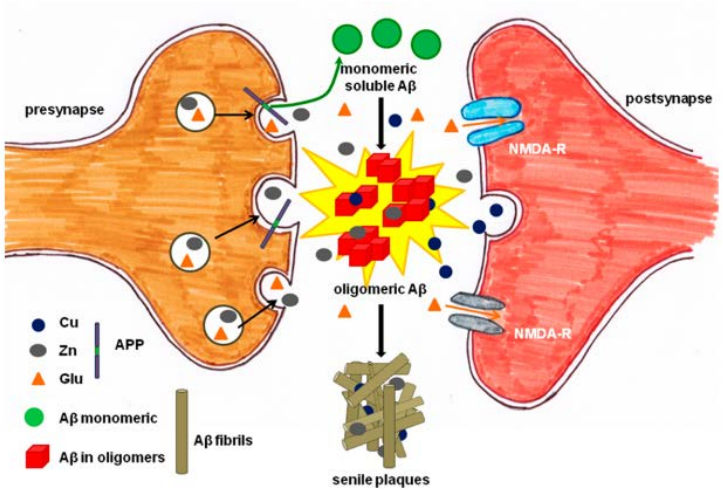
5 μM





H-W. Li, D-L. Ma and coworkers. *Chem. Sci*. **2011**, 2, 917

Summary

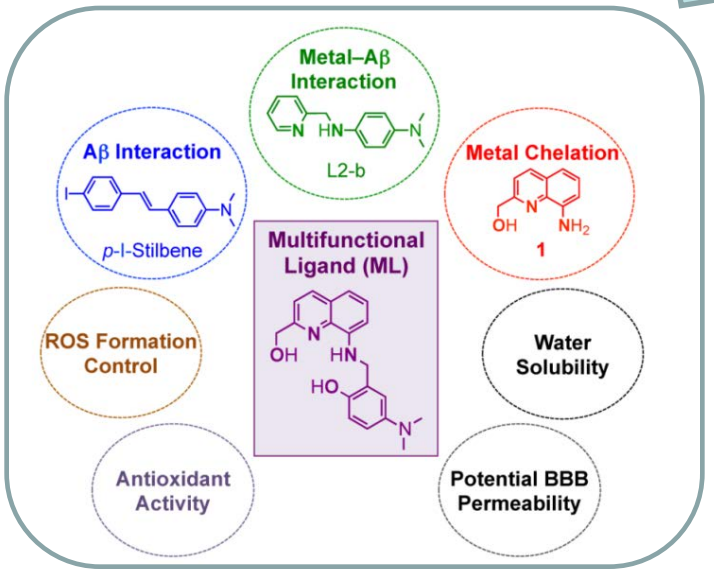


Metal ions binding to Aβ to promote aggregation and show neurotoxic

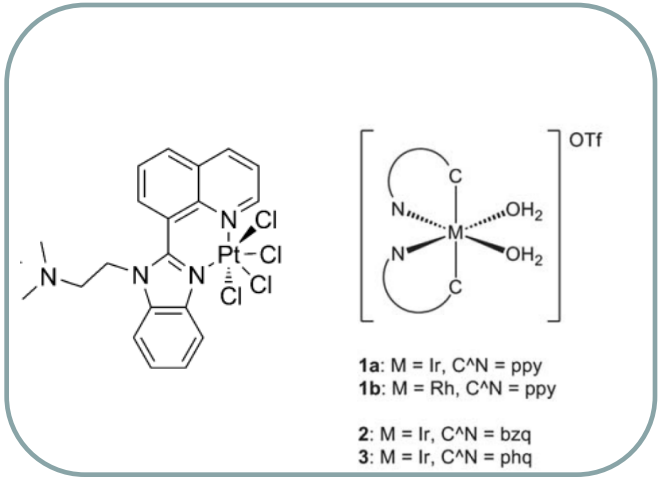
Chelating ligands

Inhibitors

Transition metal complexes



Peptide structural modification (methylation of His)

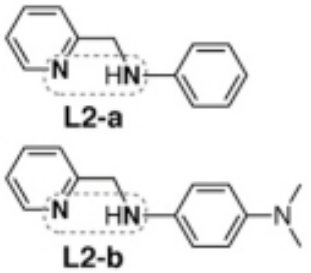


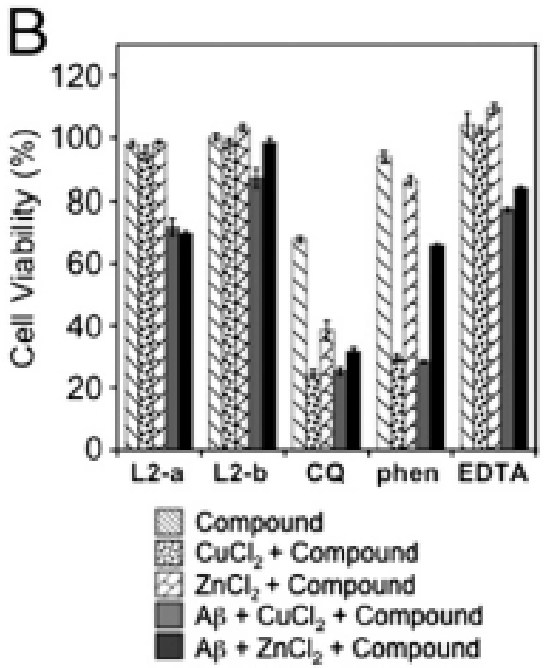
Thank you for you attention!

p14

Inhibition Experiment

Aβ (Fresh) + **M^{2+}** (**Cu^{2+}** or **Zn^{2+}**) → 2 min → **L2-a** or **L2-b** → 24 h → **Aβ Species**





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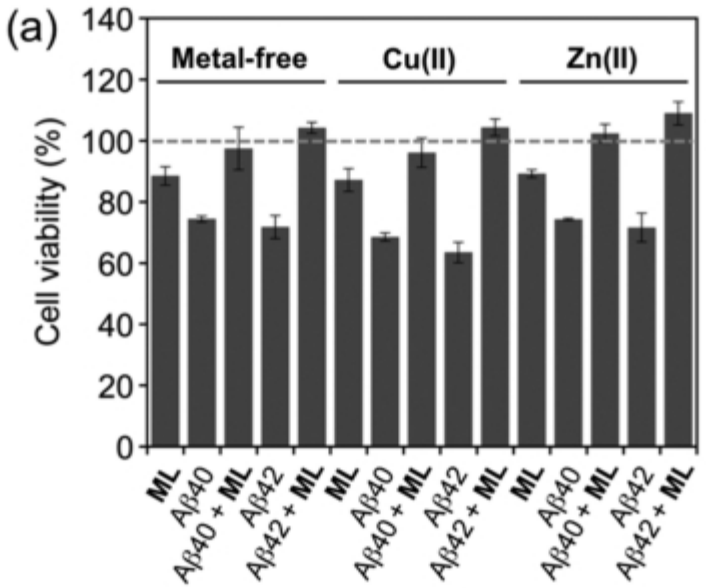
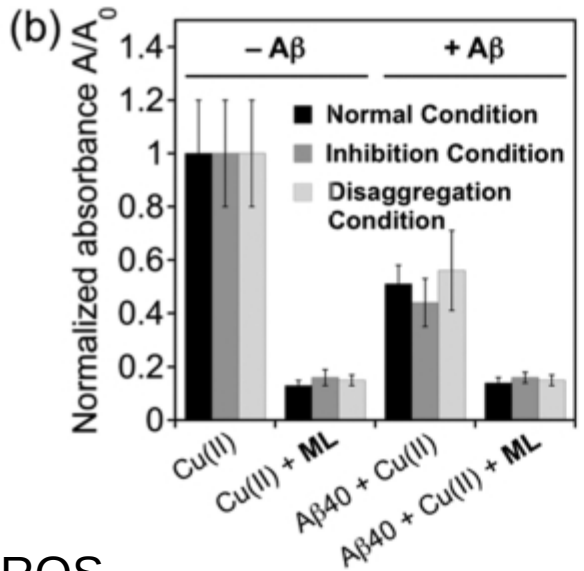
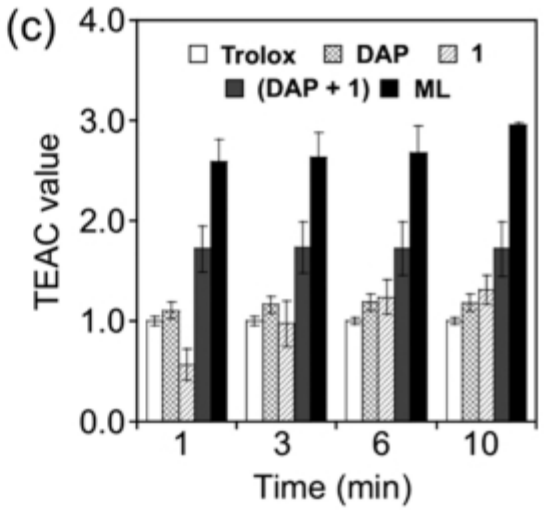


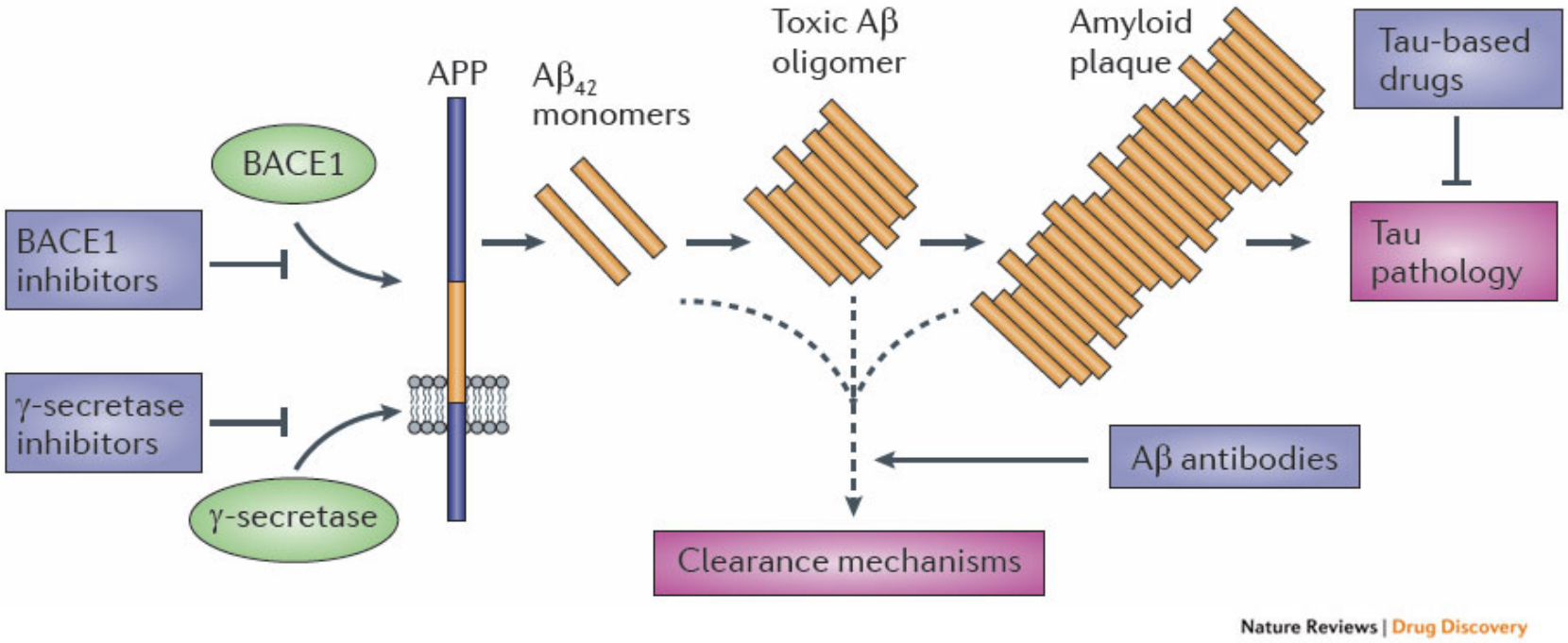
toxicity

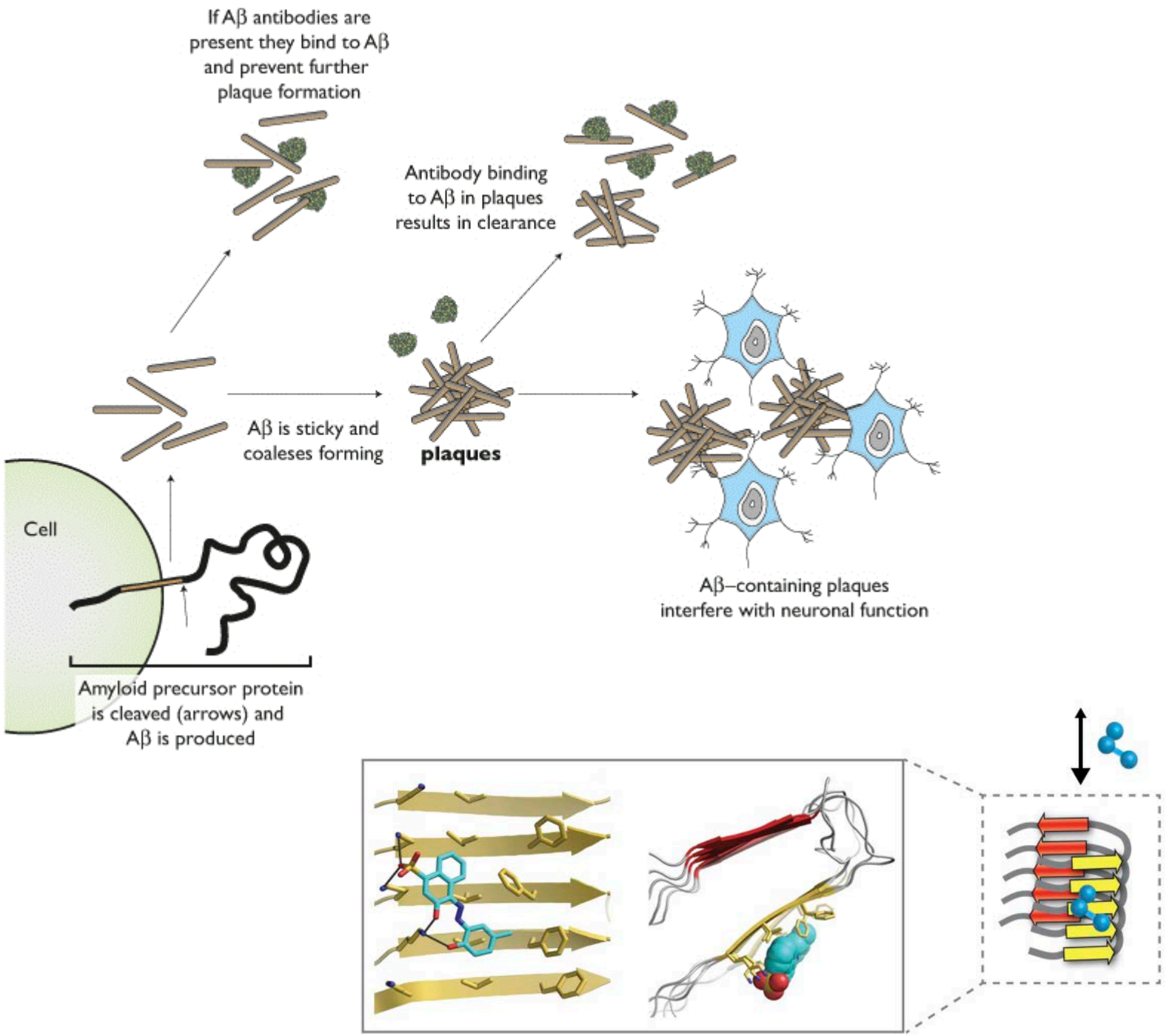




ROS

antioxidant


APP
$A\beta_{42}$ monomers
Toxic Aβ oligomer
Amyloid plaque
Tau-based drugs
BACE1
BACE1 inhibitors
γ-secretase inhibitors
γ-secretase
Tau pathology
Aβ antibodies
Clearance mechanisms
Nature Reviews | Drug Discovery


If Aβ antibodies are present they bind to Aβ and prevent further plaque formation
Antibody binding to Aβ in plaques results in clearance
Aβ is sticky and coaleses forming
plaques
Aβ–containing plaques interfere with neuronal function
Cell
Amyloid precursor protein is cleaved (arrows) and Aβ is produced