Chelation as a Tool of Therapy

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2022/09/01

Outline

1. **Introduction**

2. **Recent Attempts**
   i. Application to cancer
   ii. Application to Alzheimer’s disease

3. **Perspective & Summary**

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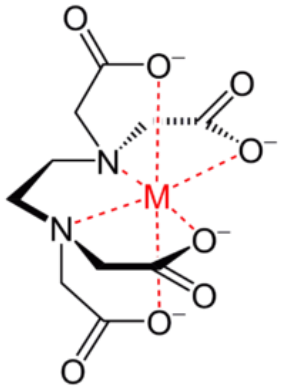
3. **Perspective & Summary**

What is Chelation ?

Chelation：

Formation of two or more coordination bonds
by a multidentate ligand to one central atom



In Organic Chemistry：

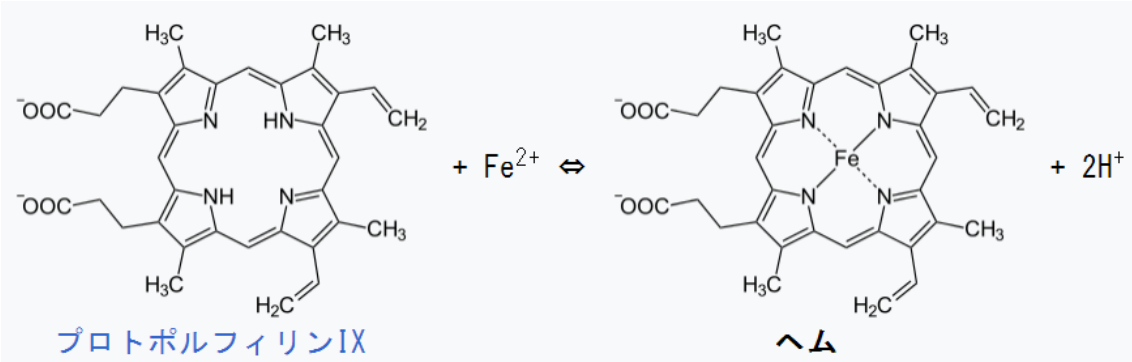
e.g., Crown Ether

- solubilize inorganic salts in nonpolar solvents
- create an unsolvated high reactive counter anion
- Transport anions as phase-transfer catalysts

https://www.chem-station.com/blog/2002/02/crown_ether.html

In Biochemistry：

- Heme complexes are found in various proteins.
  e.g., hemoglobin, P450, cytochrome



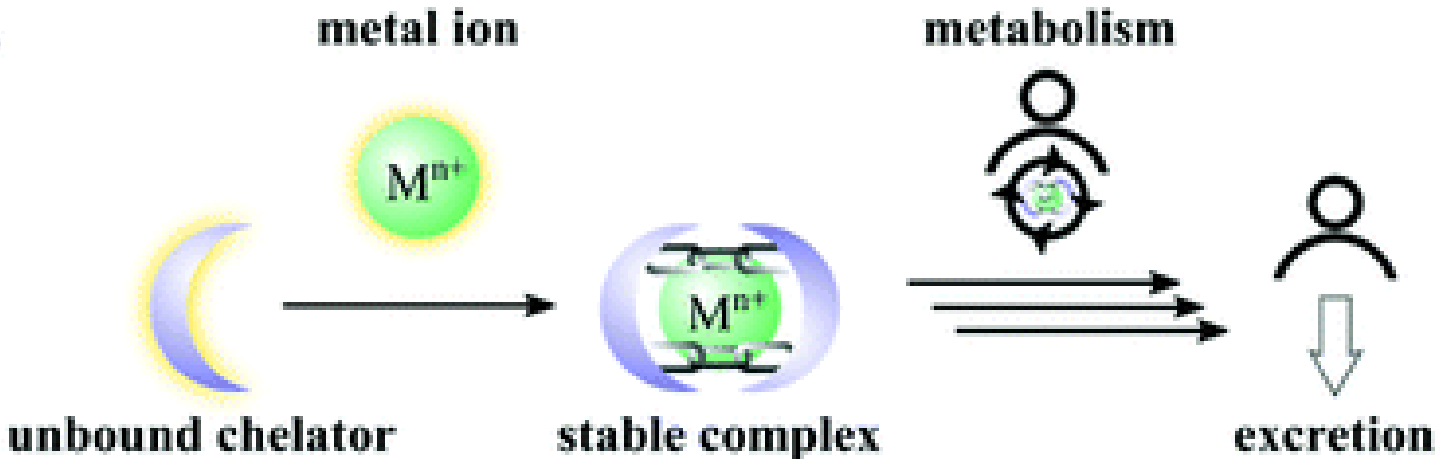
https://ja.wikipedia.org/wiki/%E3%83%98%E3%83%A0

Conventional Chelating Strategy

Conventional Application :

To trap metal cations to form stable complexes,
inactivating metal toxicity and helping excretion.

→ Chelation has been used for **metal overload**



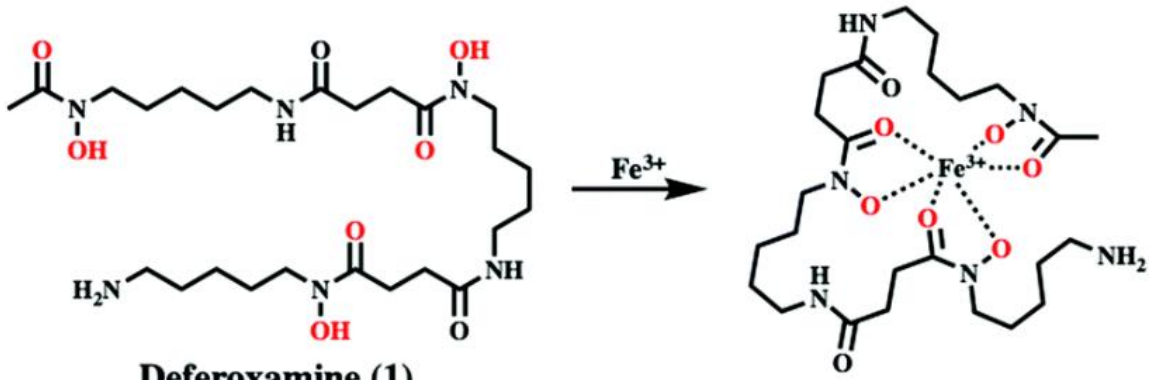
"Chelators" are for removal of metal ions

Axel S., *et al. Chem. Soc. Rev.*, **2020**, 49, 3726-3747

FDA approved Chelation

Deferoxamine (DFO) :

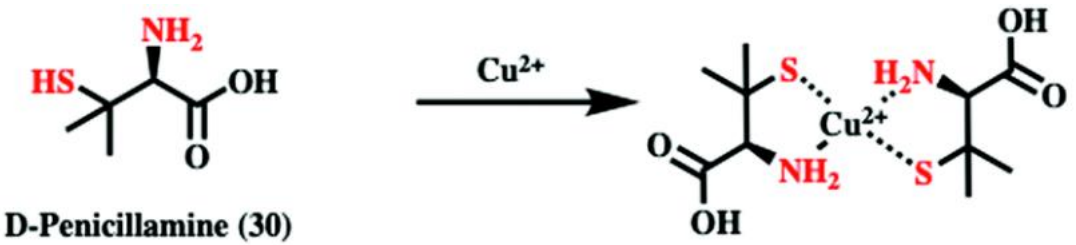
1st **Fe^{3+} chelator** approved by FDA
For iron overload



Deferoxamine (1)

D-penicillamine (DPA) :

1st **Cu^{2+} chelator** approved by FDA
For copper overload
e.g., **Wilson's disease**



D-Penicillamine (30)

Chelation strategies may be applied to cancer and Alzheimer's disease treatments !

Caution：Some of these attempts have targeted Fe and Zn, but I will focus on **Cu** Today.

Outline

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The role of copper in Cancer cell

Elevated Cu concentrations have been reported in the tumors or serum with many type of cancers : breast, lung, gastrointestinal, oral, thyroid, gall bladder, gynecologic, prostate

→ ***Cuproplasia*** = **Cu dependent cell growth and proliferation**

- Directly activation of proangiogenic factors: VEGF, FGF2, TNF, IL-1
  → **Angiogenesis**
- Arosterically activation of MEK1/2 stimulating RAF-MEK-ERK signaling
  → **Proliferation**
- Arosterically activation of ULK1/2
  → **Autophagy**
- Cofactor of cytocrom c oxidase
  → **ATP synthesis**

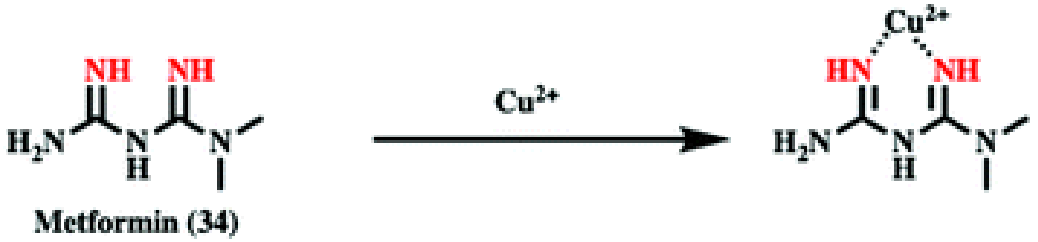
→ Cu chelator can inhibit cuproplasia

Ge, E.J., *et al. Nat Rev Cancer.* **2022.** 22, 102–113.

Cu chelators for cancer treatment

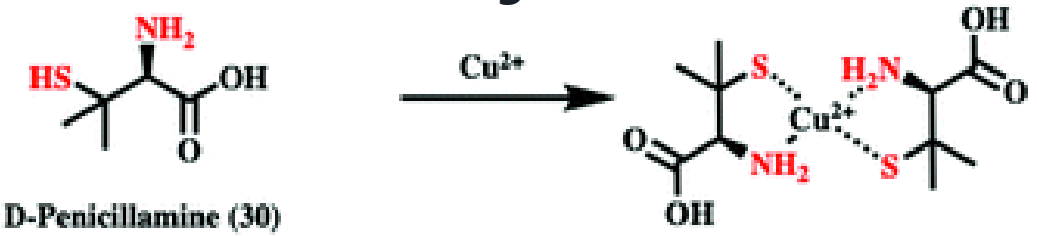
Drug reporposing/repositioning

- From type II diabetes drug

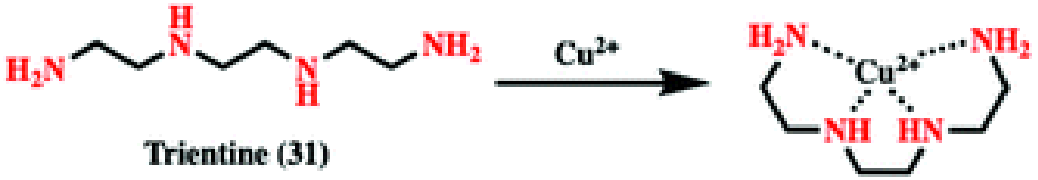


Metformin (34)

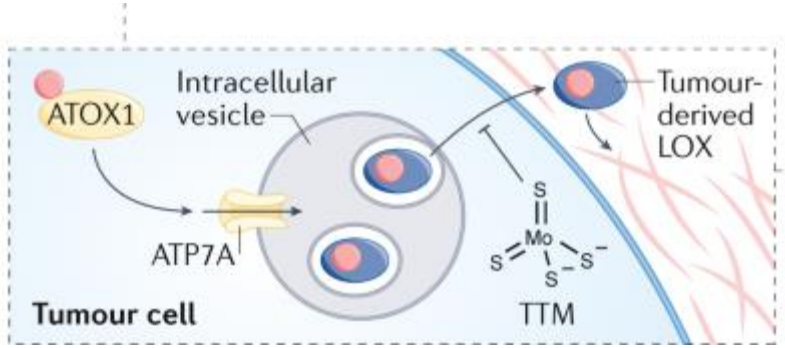
- From Wilson's disease drug

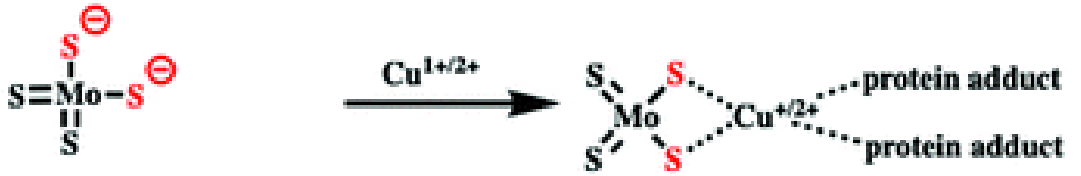


D-Penicillamine (30)



Trientine (31)





Tetrathiomolybdate (32)

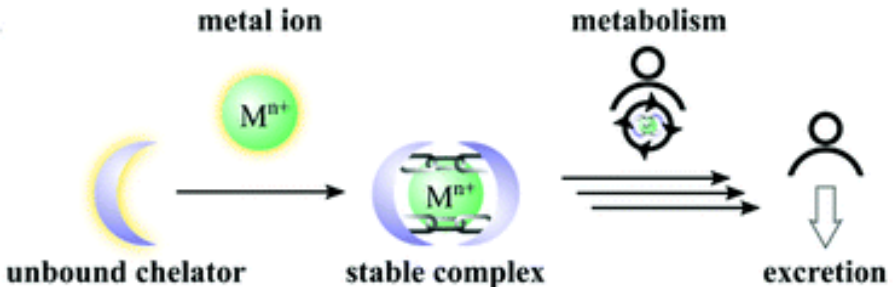
Tetrathiomolybate is expected to also inhibit **cancer metastasis** by inhibiting **ATOX-ATP7A-LOX pathways**

Axel S., *et al. Chem. Soc. Rev.*, **2020**, 49, 3726-3747
Ge, E.J., *et al. Nat Rev Cancer.* **2022.** 22, 102–113.

Another Metal-targeting therapy

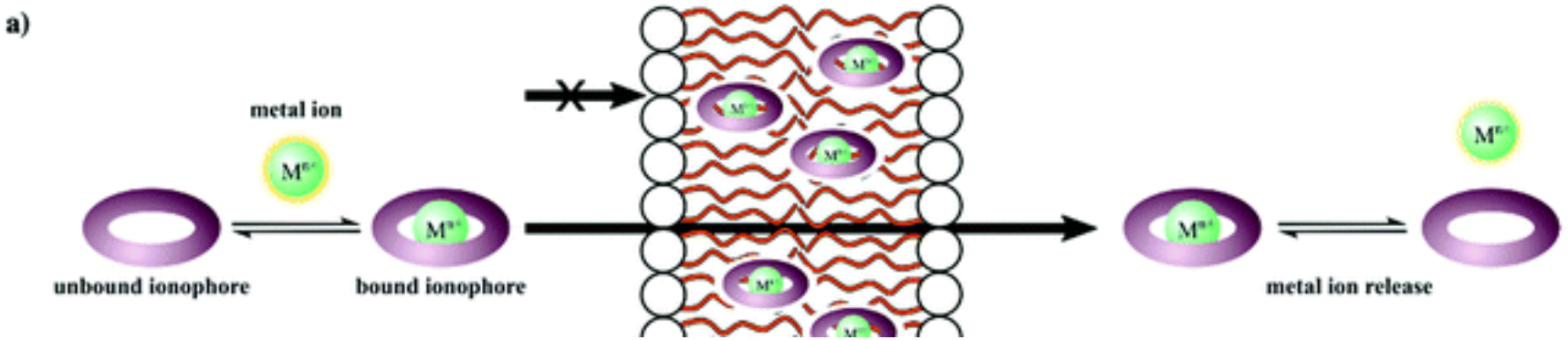
Chelator (for removal) :

To disrupt the deleterious interaction of metal ions with biomolecules and then inactivate them or help their excretion



Ionophores (for redistribution) :

To transfer (across a membrane) the removed metal ions to the biological compartment, where they become beneficial



Increased Cu^+ in cytosol cause *Cuproptosis*

Axel S., *et al. Chem. Soc. Rev.*, **2020**, 49, 3726-3747

Ionophores: Example

Glyoxal-bis(4-methylthiosemicarbazone) (GTSM) :

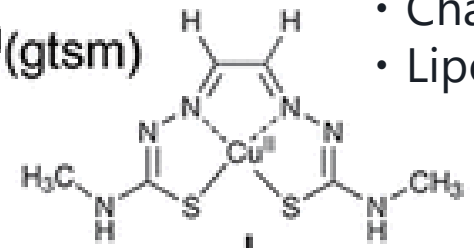
GTSM (39): $R_1 = H$

ATSM (40): $R_1 = Me$

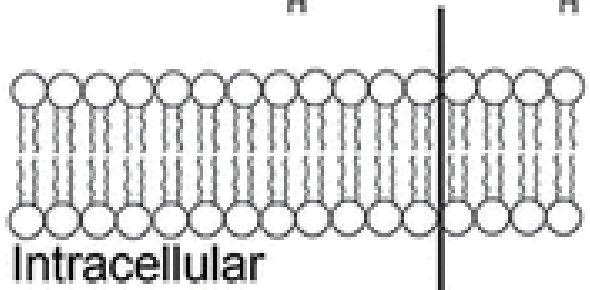
$+ Cu^{2+}$

$- 2 H^+$

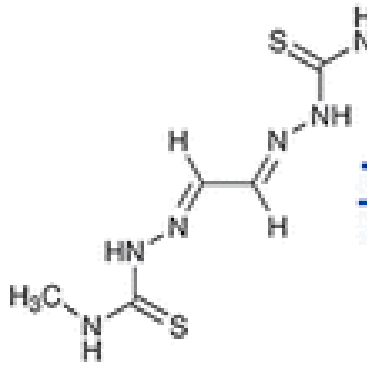
$Cu^{II}(gtsm)$



- Charge neutral
- Lipophilic

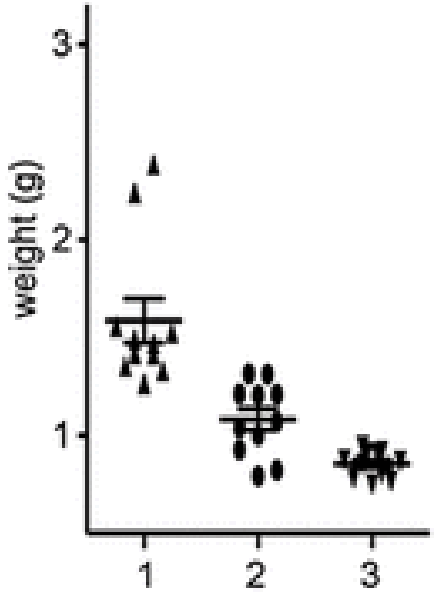


Reduction



+ Bioavailable Cu^I

Prostate Cancer Burden



1. Vehicle alone
2. $Cu^{II}(gtsm)$ [2.5mg/kg/day]
3. wtC57BL/6 (untreated)

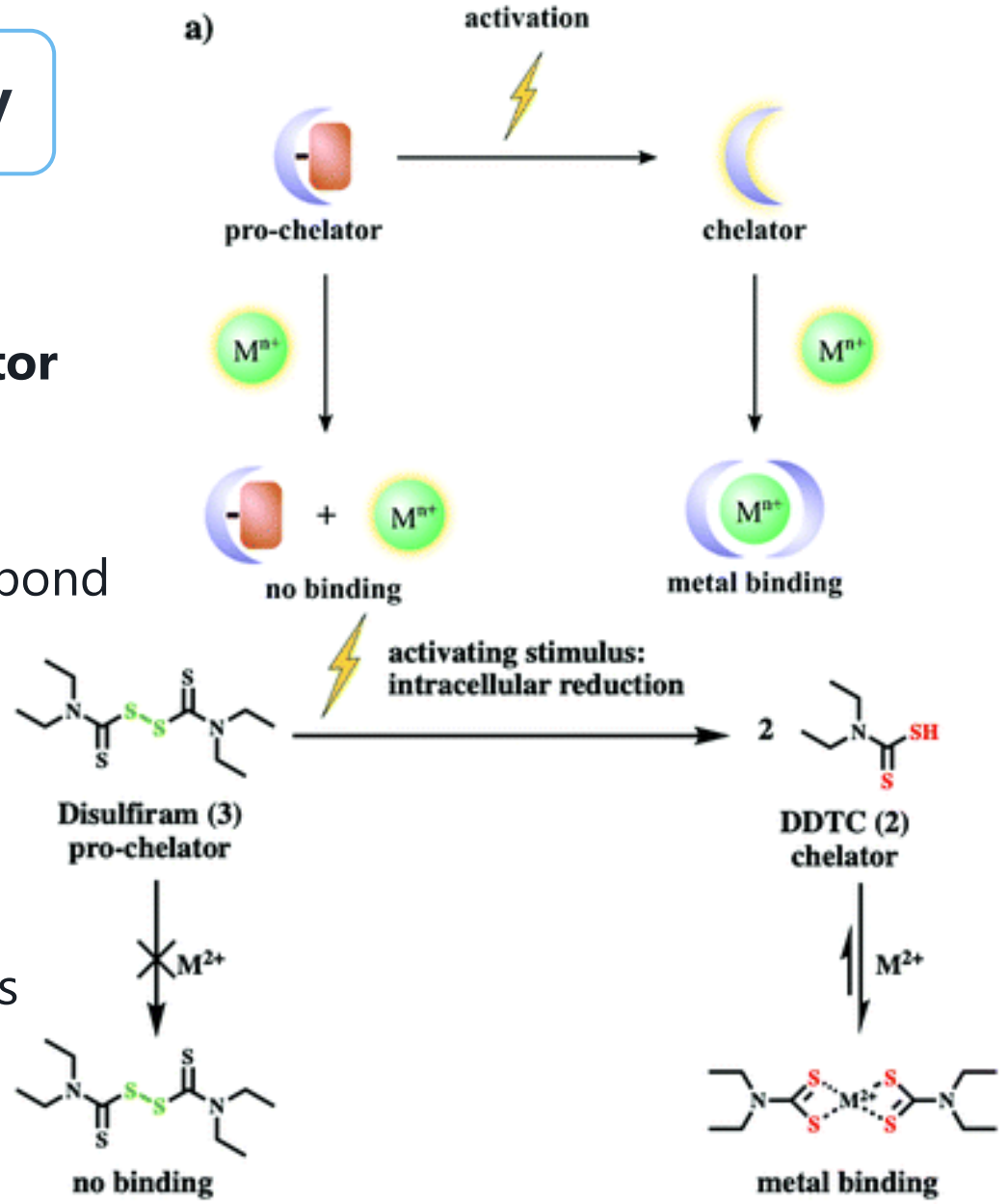
Axel S., *et al. Chem. Soc. Rev.*, **2020**, 49, 3726-3747
Michael A., *et al. ACS Chemical Biology* **2013** *8* (7), 1621-1631

Prochelators

Prochelator: Like prodrug, to improve **selectivity**

Disulfiram (DSF)

- FDA-approved **aldehyde dehydrogenase (ALDH) inhibitor** for the treatment of alcoholism, and it has been used for over 60 years.
- Activated by intracellular thiol cleavage of the disulphide bond
  →**Diethyldithiocarbamate (DDTC or DTC): Ionophore**
- (Zn^{2+} and) **Cu^{2+} complexes of DTC** :
  act as ionophore
  Inhibition of turnover by targeting NPL4
  promote the generation of ROS via redox cycling
  → push cancer cells towards various apoptosis pathways

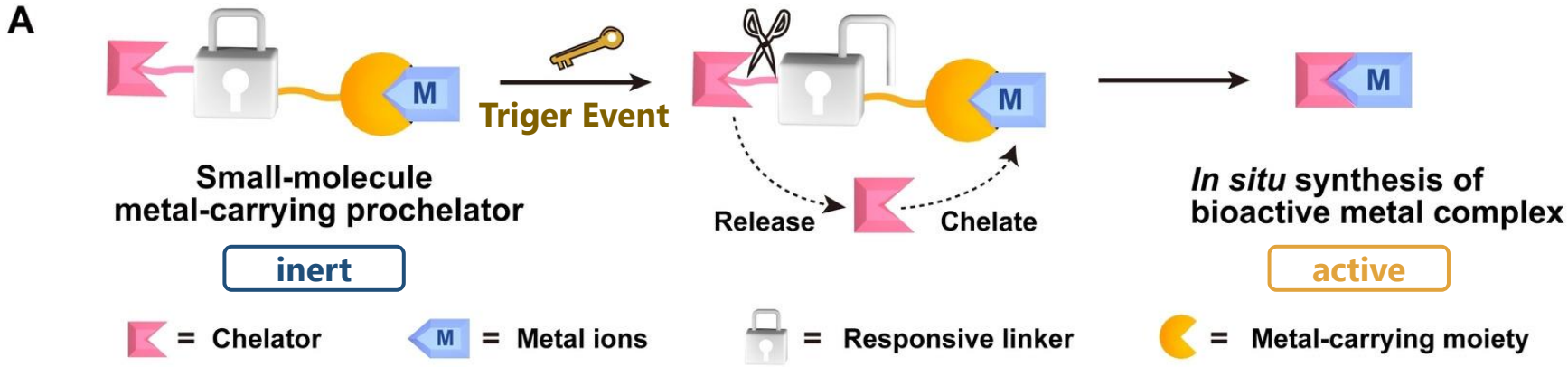


Skrott, Z., *et al. Nature.* **2017.** 552, 194–199.
Axel S., *et al. Chem. Soc. Rev.*, **2020**, 49, 3726-3747

Metal-Carrying Prochelator

metal-carrying prochelator (= prodrug of metal complex)

- co-carry a metal ion and chelator within a single small-molecule compound
- synthesize active metal complexes *in situ* by intramolecular chelation reactions in specific environments



Advantages

① Co-delivery of metal ion and chelator within 1 compound

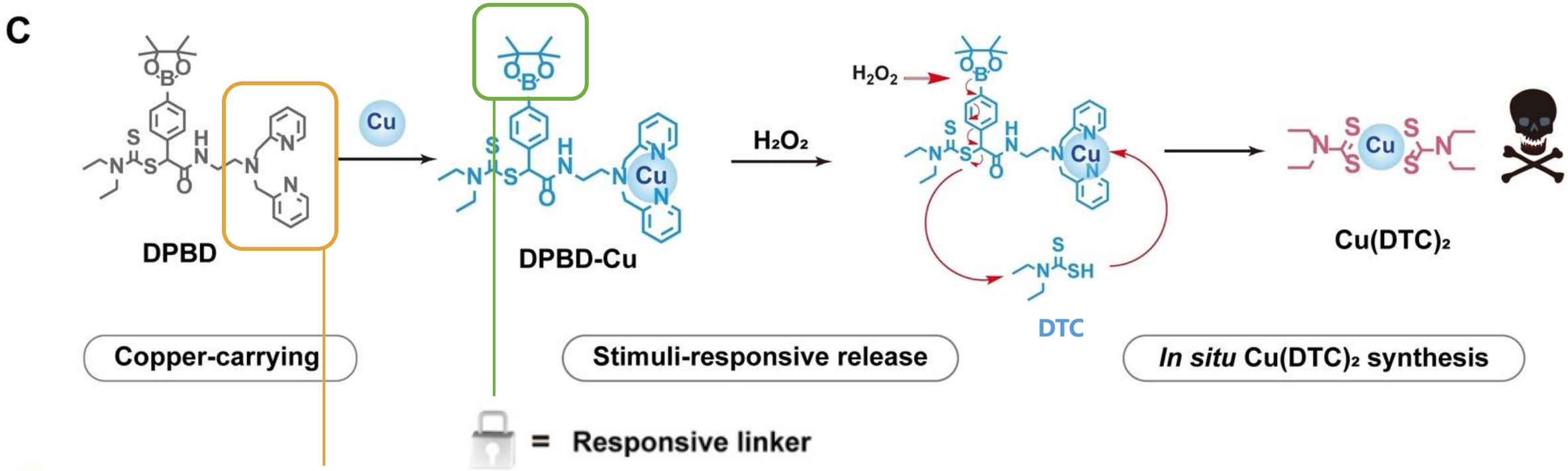
② High metal selectivity due to metal carrying

③ Higher target selectivity (than general prodrugs) due to greater structural changes

Zeqian H., *et al. Angew. Shem. Int. Ed.* **2022**, 61, e202203500

Metal-Carrying Prochelator

Mechanism and Design



2,2′-dipicolylamine (DPA) :

- Weaker than DTC
  ※logK：18.35(DPA-Cu) < 25.0 ($Cu(DTC)_2$)
- Stronger than other molecule in physiological environment

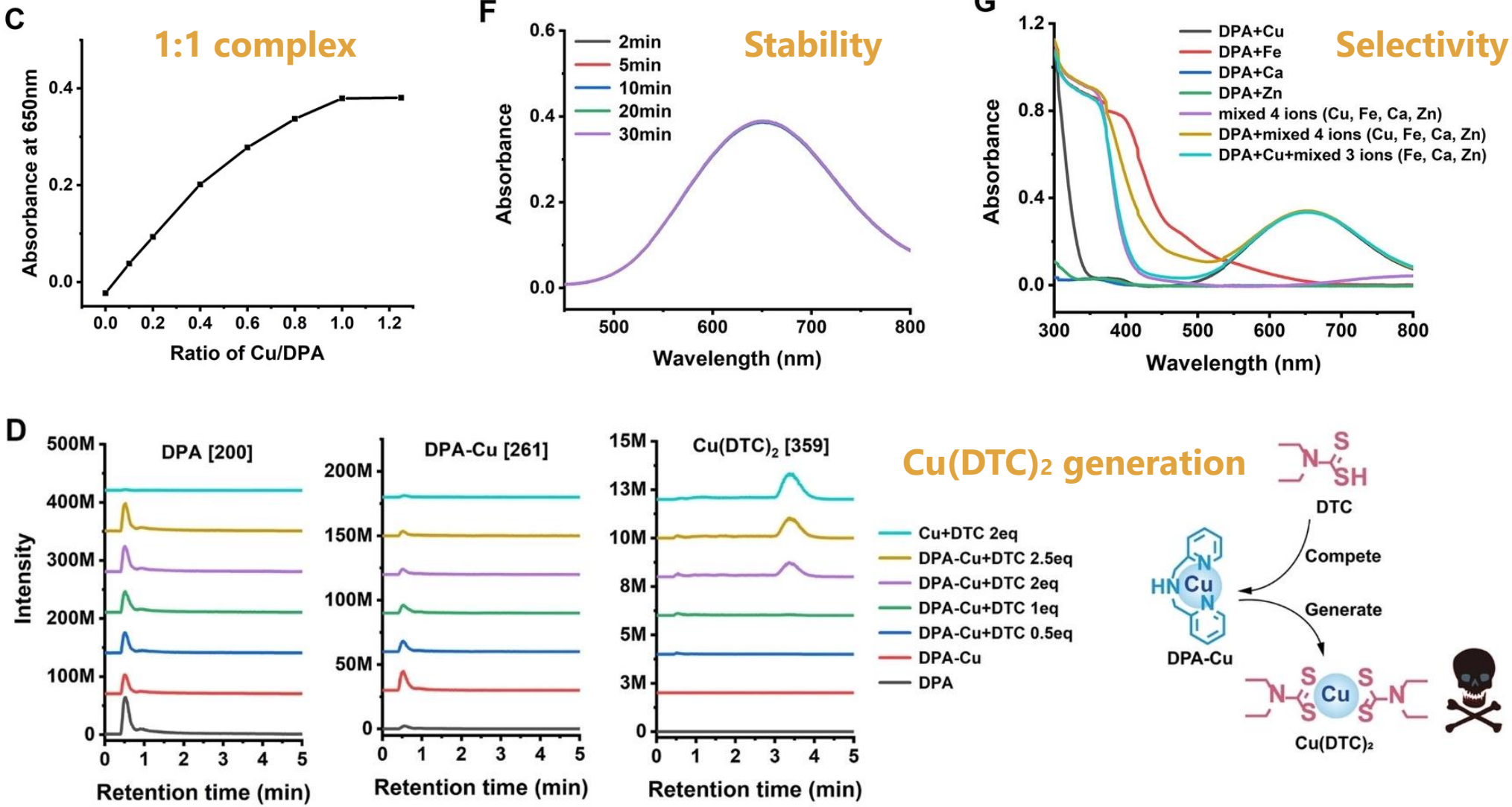
Phenylborate ester :

- H_2O_2 dependent cleavage and release of DTC
  ※ H_2O_2 conc. : 100uM (tumor) ≫ 20nM (normal)

Zeqian H., *et al. Angew. Shem. Int. Ed.* **2022**, 61, e202203500

Metal-Carrying Prochelator

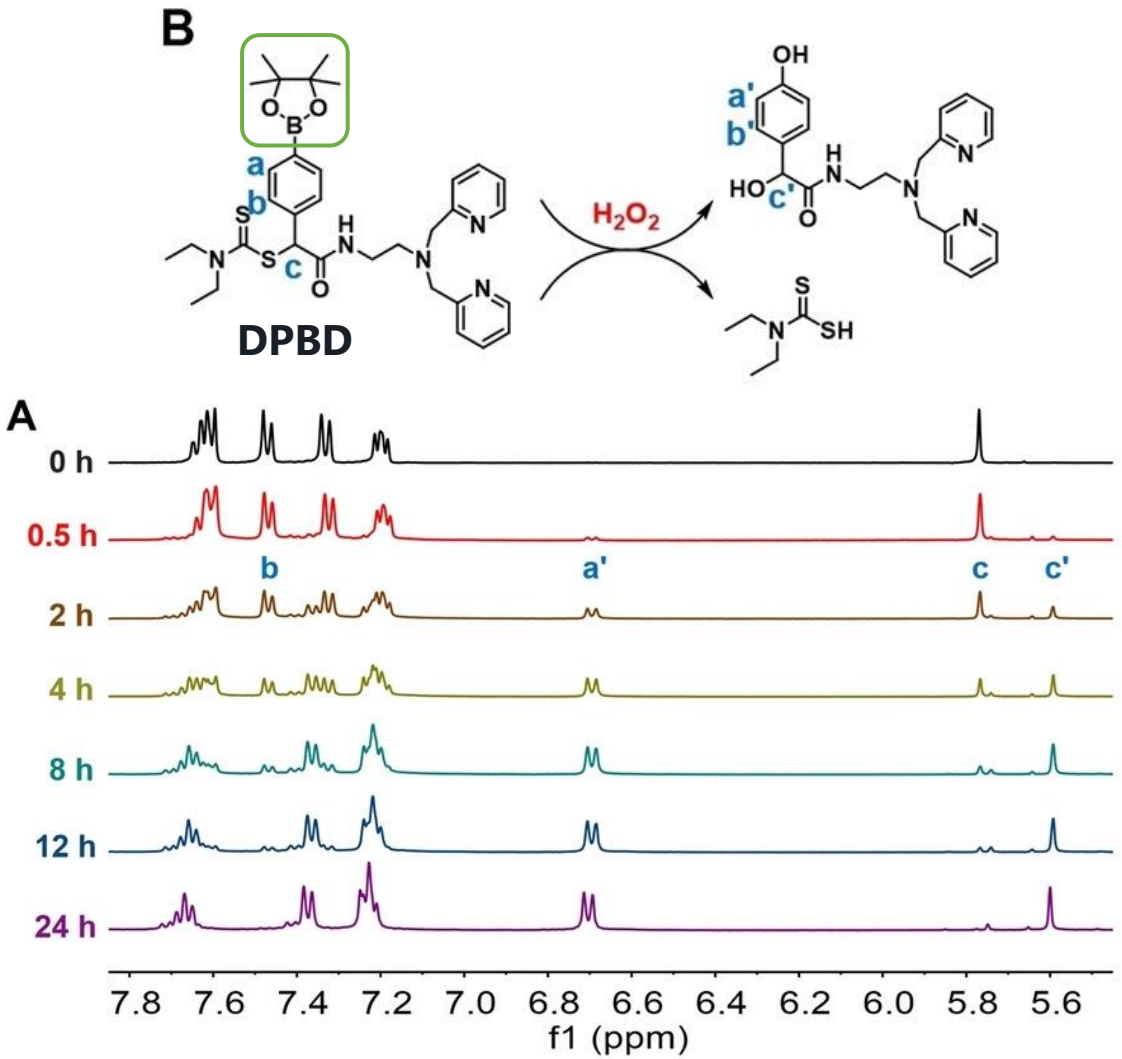
Properties：DPA moiety

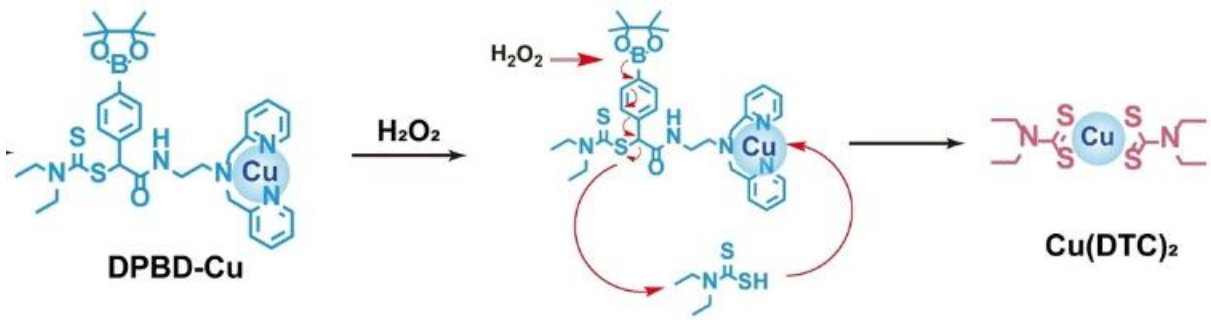


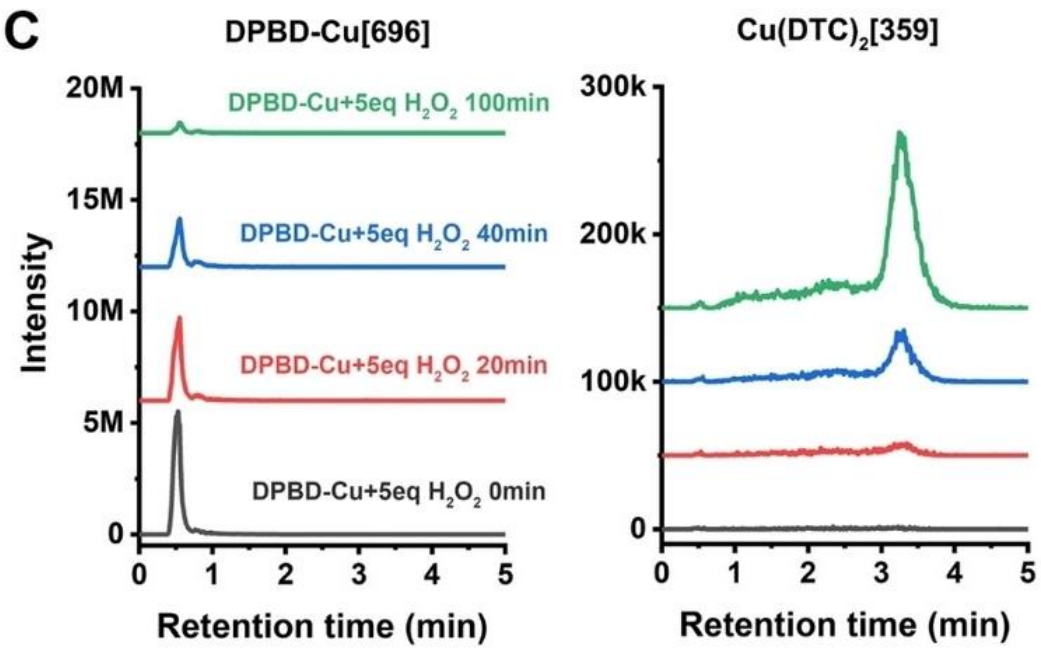
Zeqian H., *et al. Angew. Shem. Int. Ed.* **2022**, 61, e202203500

Metal-Carrying Prochelator

Properties：DPBD (w/ Phenylborate ester)



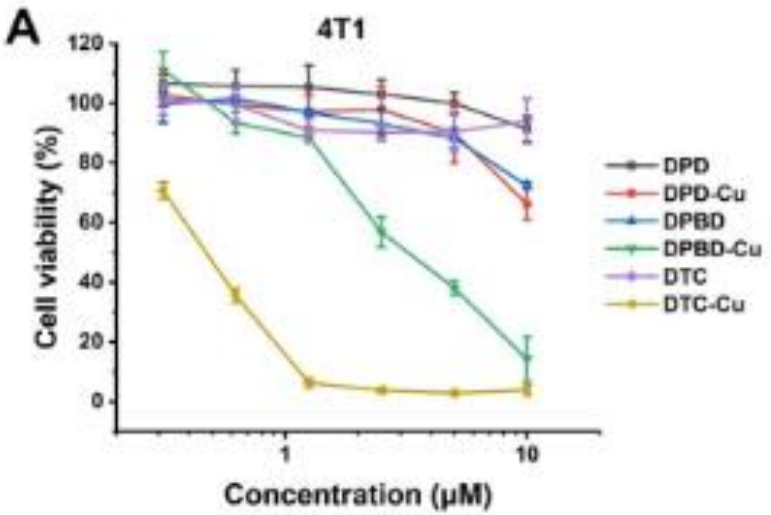


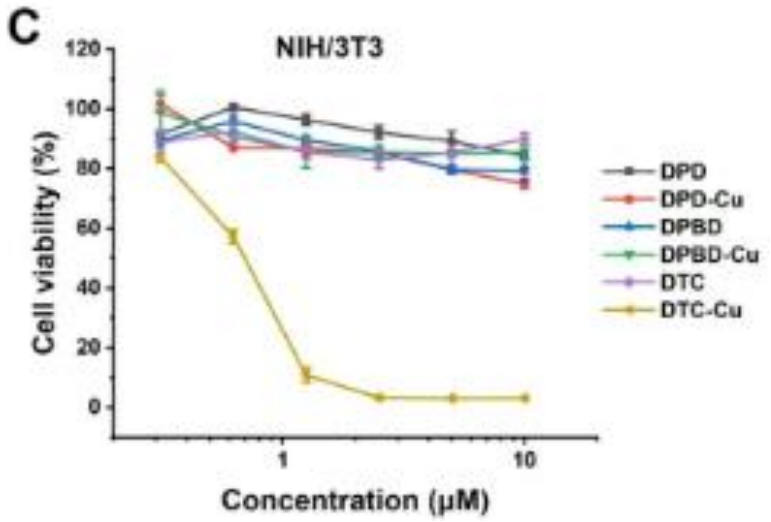


Zeqian H., *et al. Angew. Shem. Int. Ed.* **2022**, 61, e202203500

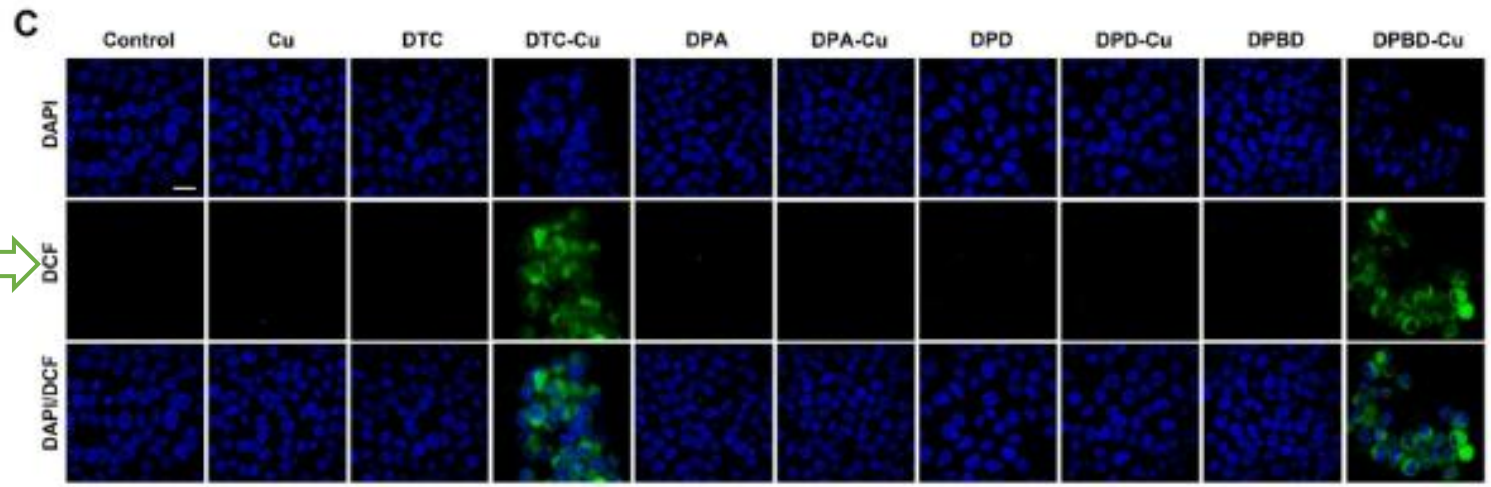
Metal carrying prochelator

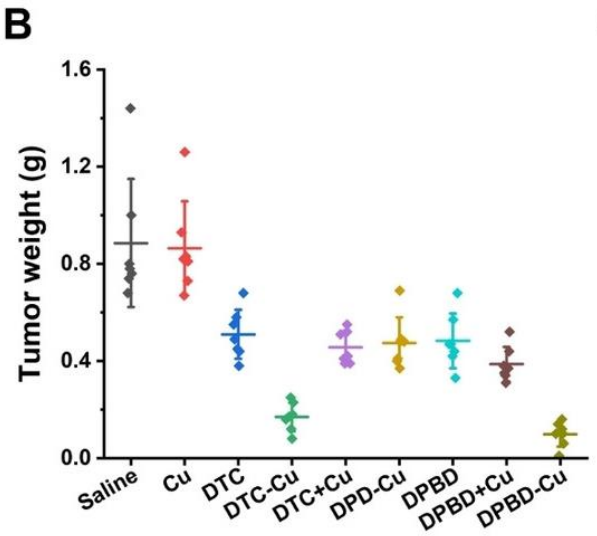
cellular / *in vivo* test

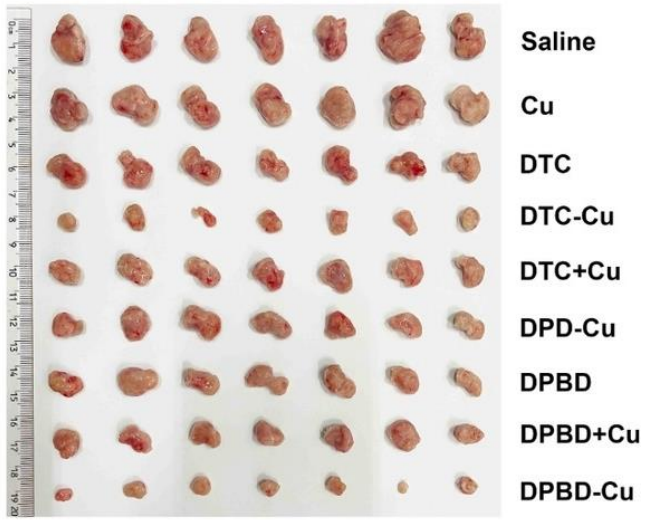




$^1O_2$







Zeqian H., *et al. Angew. Shem. Int. Ed.* **2022**, 61, e202203500

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   ii. Conventional Application

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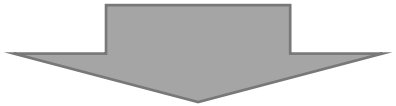
The role of copper in AD

Dyshomeostasis of copper in Alzheimer's disease

e.g, 0.4mM accunmulation of Cu in Aβ plaque

- Disfunction of physiologically essential enzyme
- ROS (reactive oxygen species) production through free or Aβ bound Copper
- Promotion of Aβ aggregation and stabilization of Aβ oligomer
- Promotion of tau phospholylation



Cu chelator can Alleviate the pathology of Alzheimer's disease

Charlène Esmieu, *et al*. *Inorganic Chemistry*. **2019** *58* (20), 13509-13527.
Kehinde D. Fasae, *et al*. *J. Trace. Elem. Med. Bio.* **2021** *67*, 126779.

History of chelators toward AD

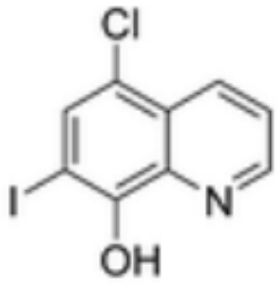
Clioquinol (CQ) :

- The 1st metal ligand (Ionophore) explored in neurodegenerative diseases
- Moderate affinity for Cu and Zn

✓ It permeated the BBB, facilitated clearance of Aβ deposits and improved cognitive function

✕ Adverse effects such as neurotoxicity were observed in a Tier II study (failure).

✕ Toxic di-iodo impurities were found in the manufacturing process.



L1 (PBT1, CQ)

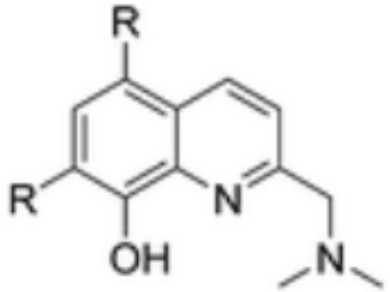
PBT2 :

- Compound with the same 8-hydroxyquinoline backbone

✓ It did not show any serious side effects

✓ It restored cognitive function in AD mice.

✕ It did not significantly reduce Aβ plaques (clinical trial failure)



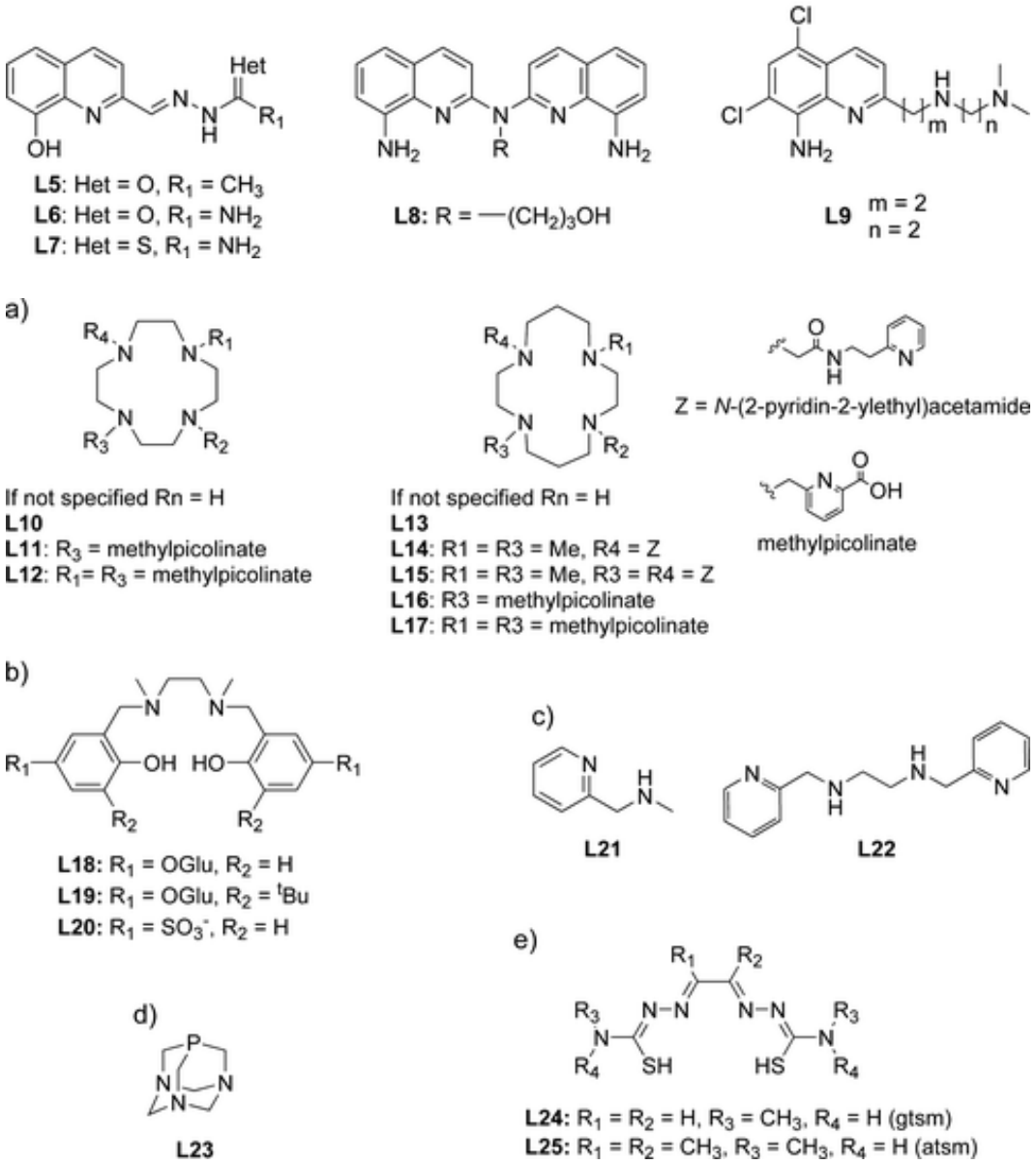
L2: R = Cl (PBT2)
L3: R = H

Charlène Esmieu, *et al*. *Inorganic Chemistry.* **2019** *58* (20), 13509-13527.
Kehinde D. Fasae, *et al. J. Trace. Elem. Med. Bio.* **2021** *67*, 126779.
Valentina Oliveri. *Coord. Chem. Rev.* **2020.** 422,213474.

Other Examples

- **Hydroxyquinoline(HQ) Derivatives (L5-L7)**
  higher affinity than 8-HQ parent compound
  due to tetradentate binding motif.
- **Aminoquinoline Derivatives (L8, L9)**
  high affinity to Cu(II)
- **Tetraazamacrocycles (L10-L17)**
  high selectivity for Cu(II) over Zn(II), low MW
- **Aminophenol Derivatives (L18-L20)**
  multifunctional agents
  - phenolic moiety：ROS scavenger
  - carbohydrate：solubility, low toxicity, BBB penetration

  high selectivity for Cu(II) over Zn(II)
- **Aminopyridine Ligands (L22)**
  L21 cannot compete with Aβ.
- **Phosphine Derivatives (L23)**
  first Cu(I) ligand able to retrieve both Cu(I/II) from Aβ
- **Bis(thiosemicarbazonato) Derivatives (L24, L25)**
  Ionophore



Charlène Esmieu, *et al*. *Inorganic Chemistry*. **2019** *58* (20), 13509-13527.

"2-in-1" bifunctional chelator

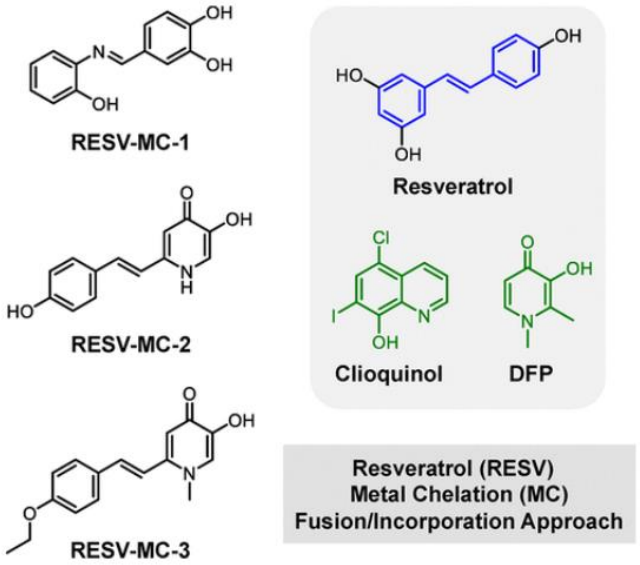
Incorporate structural elements
known to interact with Aβ species
→ improve **selectivity**
(Another way to increase selectivity than prochelators)

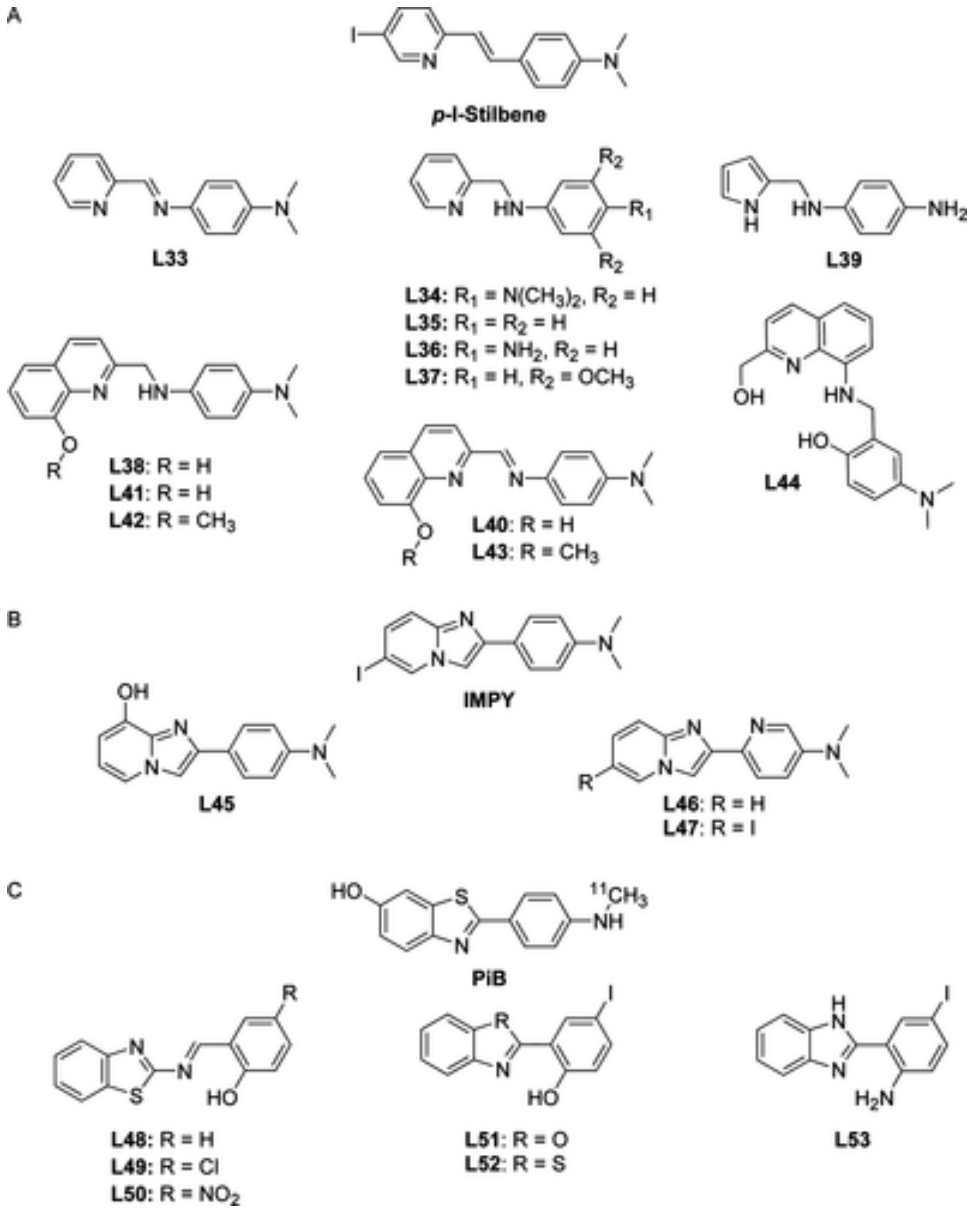
Aβ interaction scaffold

(A) Stilbene-like (L33-L44)
including resveratrol derivatives (RESV-)

(B) IMPY-like (L45-L47)

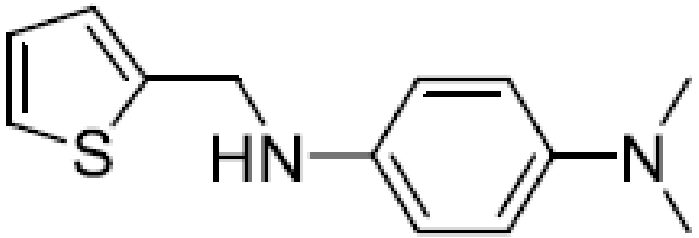
(C) PiB(ThT)-like (L48-L53)





Charlène Esmieu, *et al*. *Inorganic Chemistry*. **2019** *58* (20), 13509-13527.
Masha G. Savelieff, *et al. Chemical Reviews* **2019** *119* (2), 1221-1322

New Type Chelator：Design



(L1)

Stilbene-like
"2-in-1" bifunctional chelator

① Accommodation of the coordination geometries

S and N donor atoms in thiophen-2-ylmethanamine: for **Cu(I) and Cc(II)** (respectively∵HSAB rule)
N,N-dimethylaniline (DMA) moiety: for **Aβ amyloid**

② Redox Potential

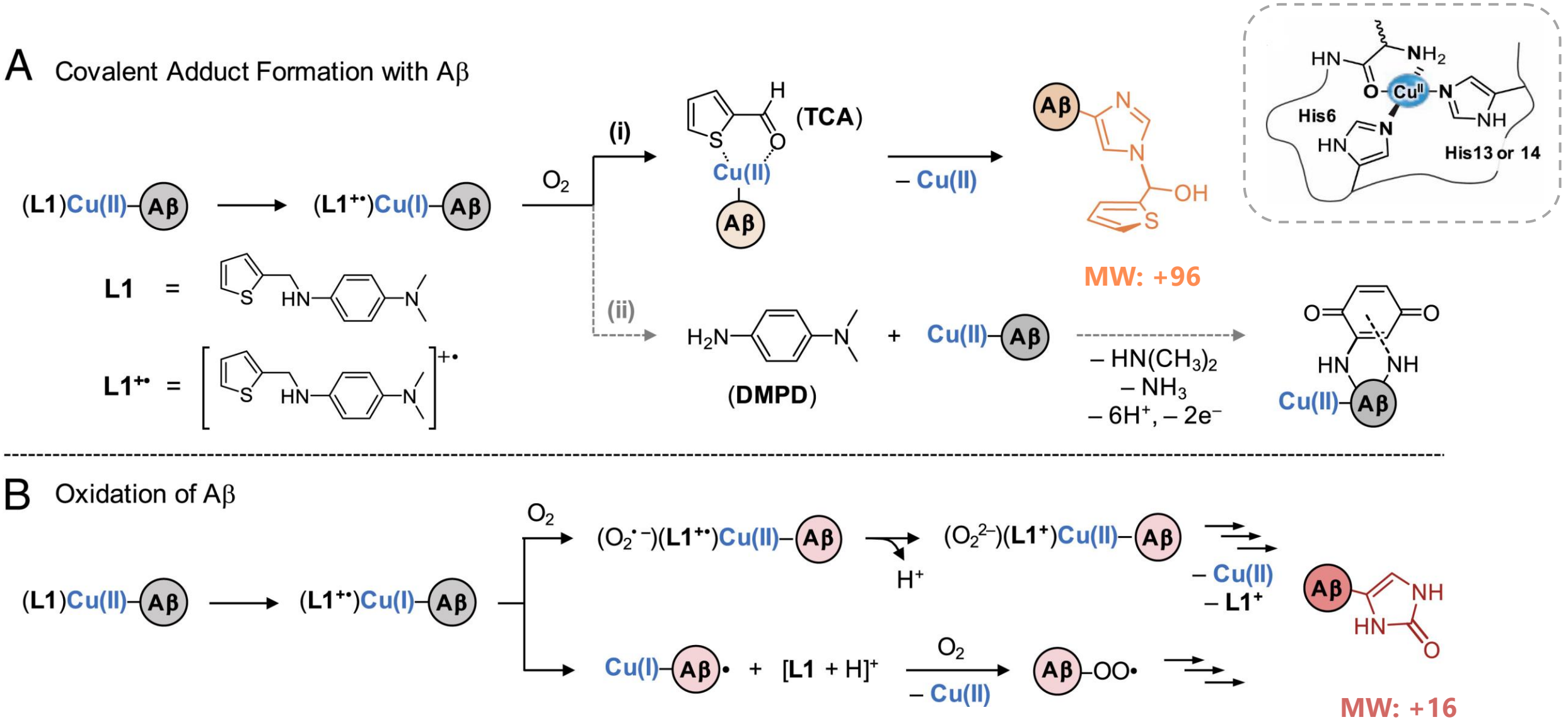
N,N-dimethyl-p-phenylenediamine (DMPD) moiety in L1：{$E_{1/2}$: **0.11 V** vs. Ag/Ag(I) in H_2O}
Cu(II)–Aβ：{E_0: approximately **0.083 V** vs. Ag/Ag(I) in H_2O}
→ critical in L1 capacity as a reducing agent

③ Promotion of copper-O_2 chemistry

Thiophene moiety： weaker σ-bonding ligand
→ potential for O_2 binding at the metal center in Cu(I/II)–Aβ

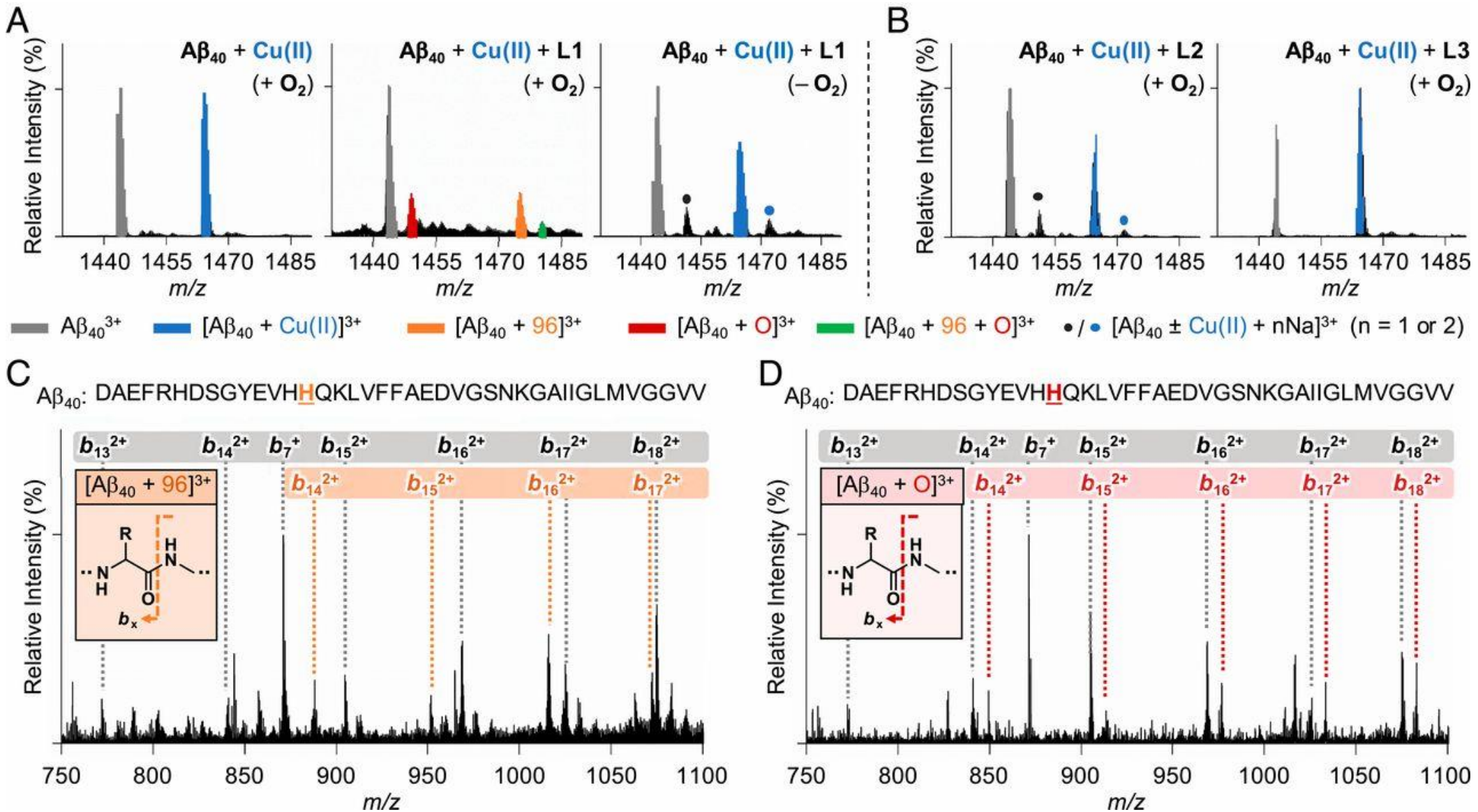
Marinary Y. C., Richard W. V. *J. Am. Soc. Mass. Spectrom.* **2002**. 13, 813-825.
Jiyeon Han, *et al*.PNAS. **2020.** *117* (10), 5160-5167.

New Type Chelator : Mechanism



Jiyeon Han, *et al*.PNAS. **2020.** *117* (10), 5160-5167.

New type chelator：Mechanism

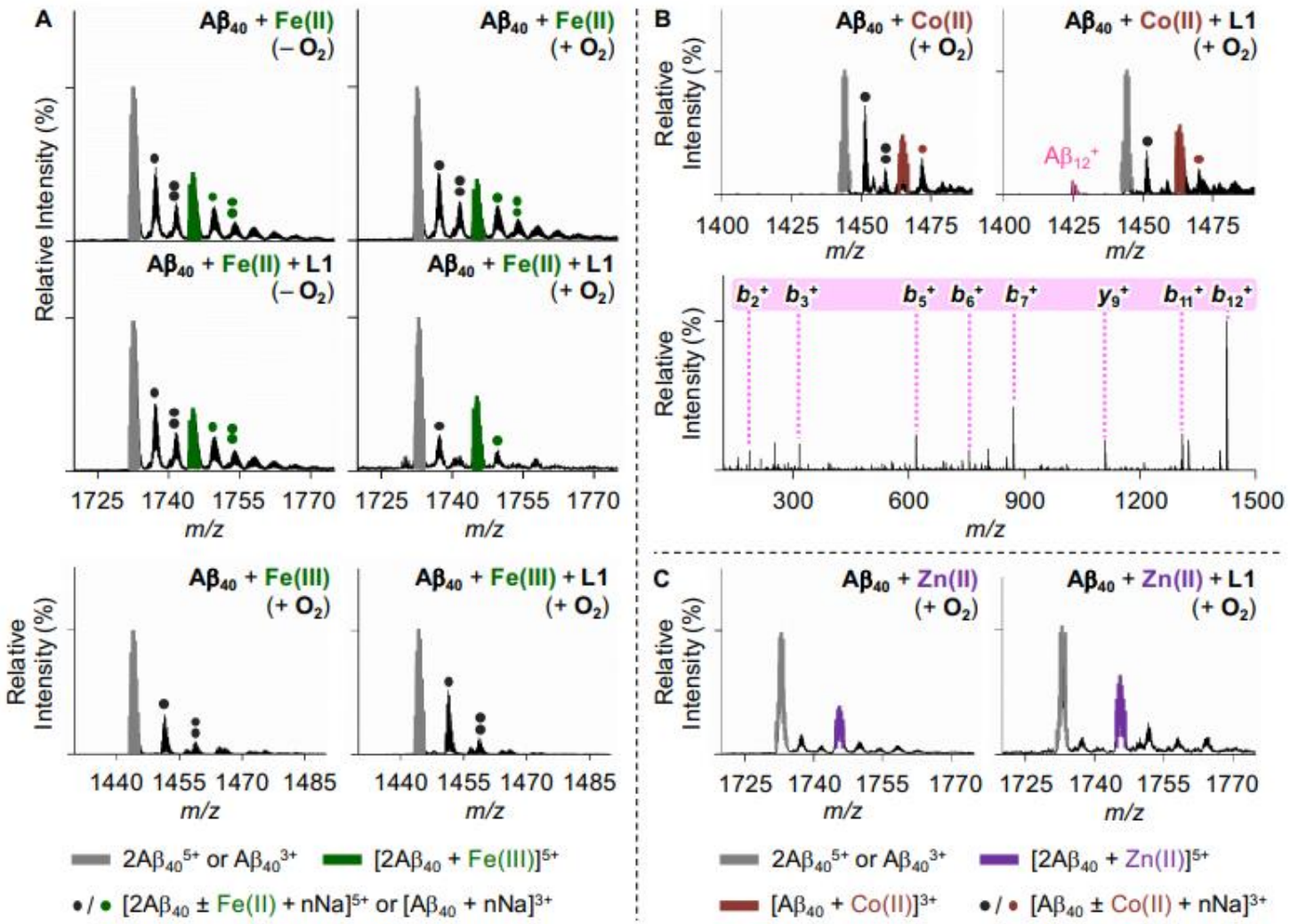


Jiyeon Han, *et al*.PNAS. **2020.** *117* (10), 5160-5167.

New type chelator：Selectivity

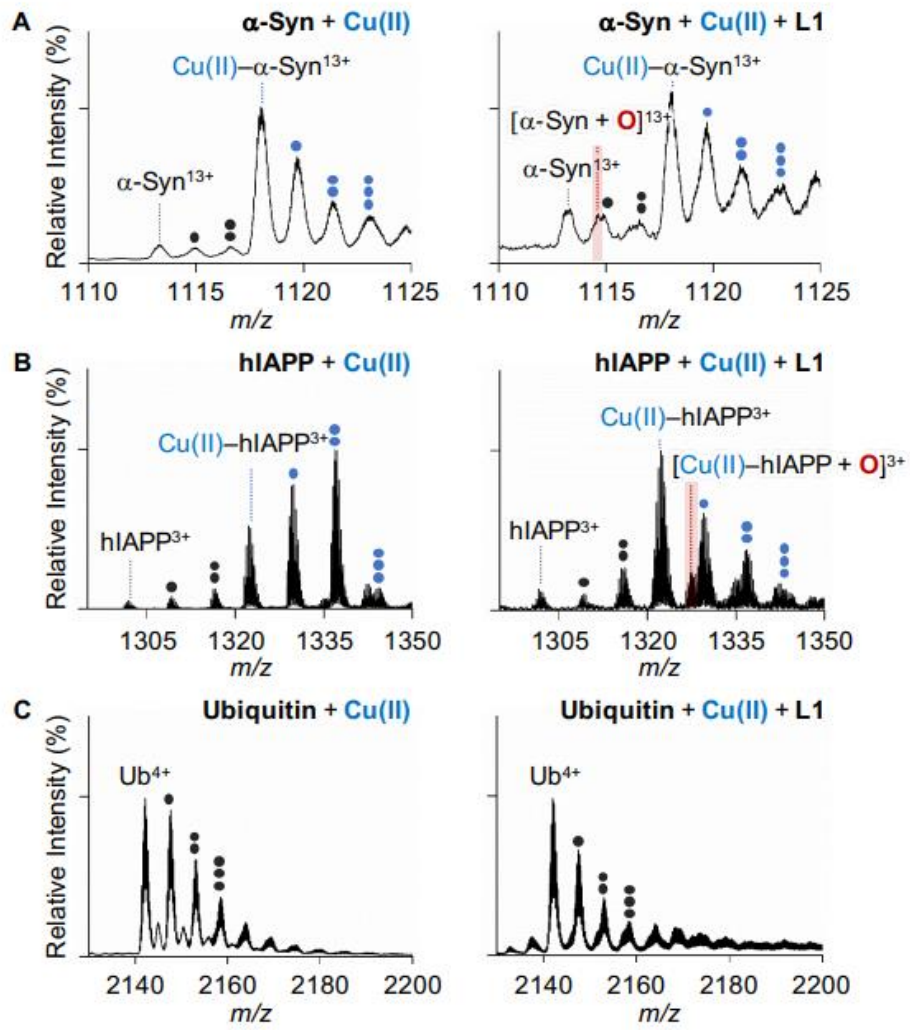
Metal ion selectivity

※Zn: non-redox



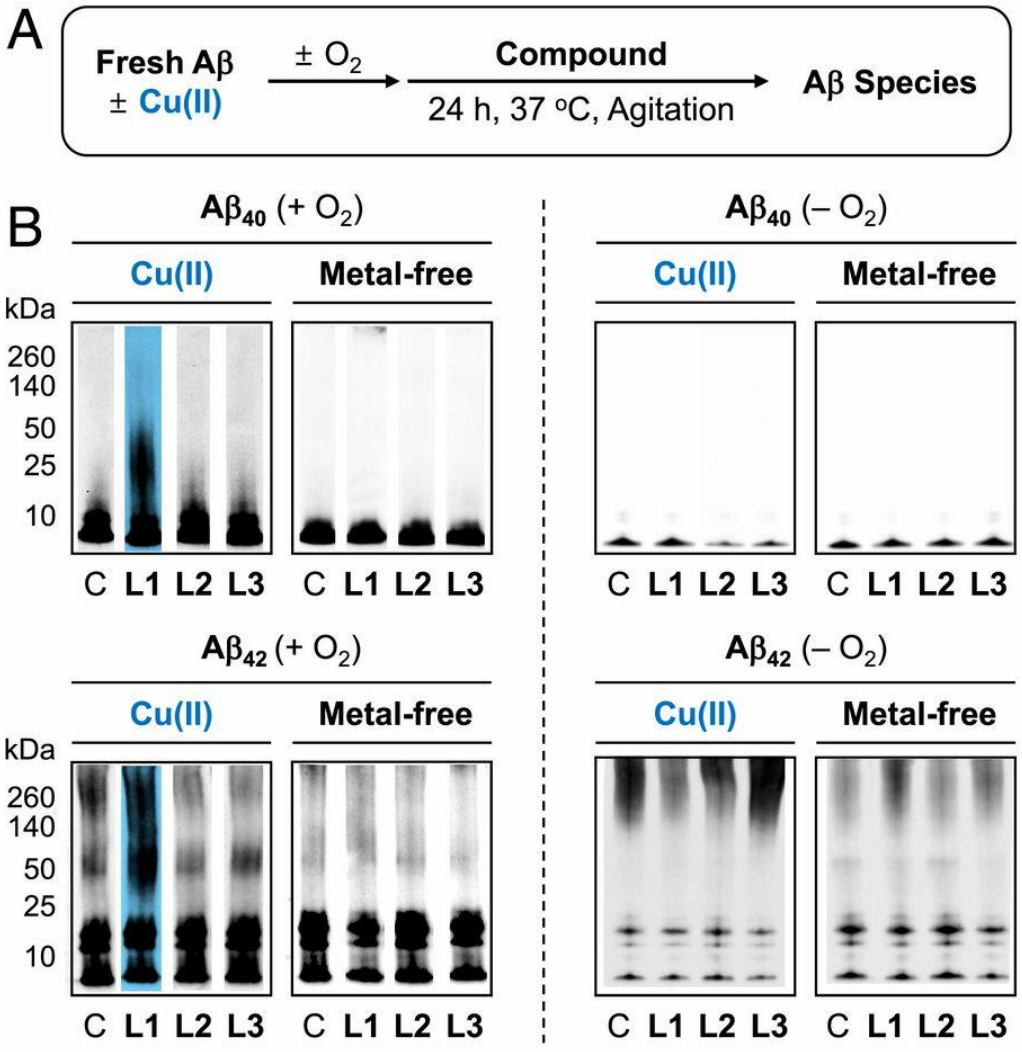
Protein selectivity

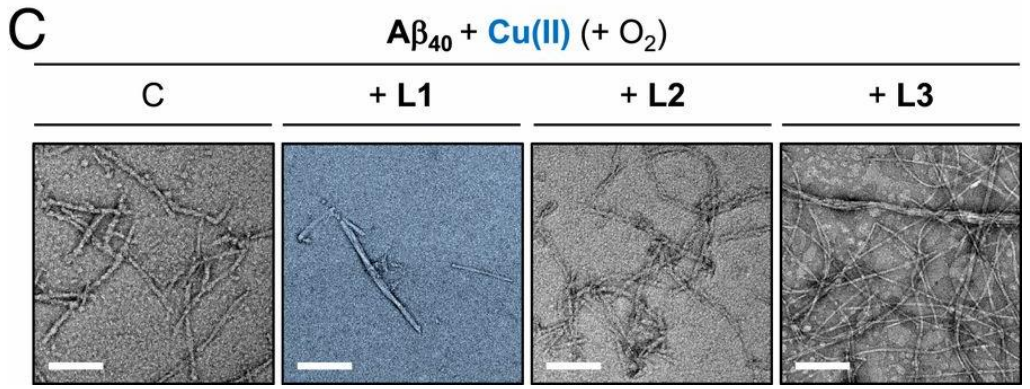
※Ubiquitin: non-amyloidogenic

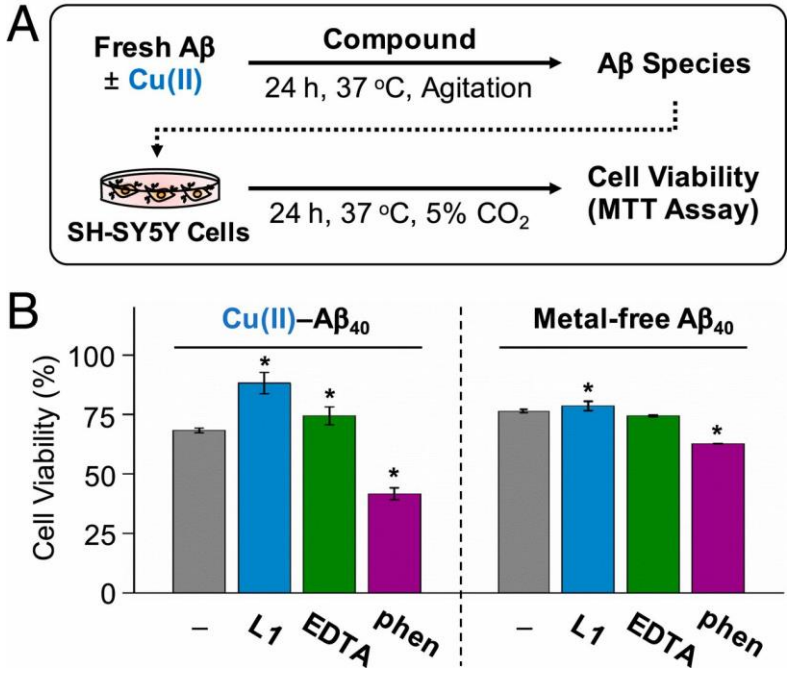


Jiyeon Han, *et al*.PNAS. **2020.** *117* (10), 5160-5167.

New type chelator : Efficiency







※ L2,L3: L1-like non-reactive compounds

Jiyeon Han, *et al*.PNAS. **2020.** *117* (10), 5160-5167.

Outline

1. **Introduction**
   i. Concept
   ii. Conventional Application

2. **Recent Attempts**
   i. Application to cancer
   ii. Application to Alzheimer's disease

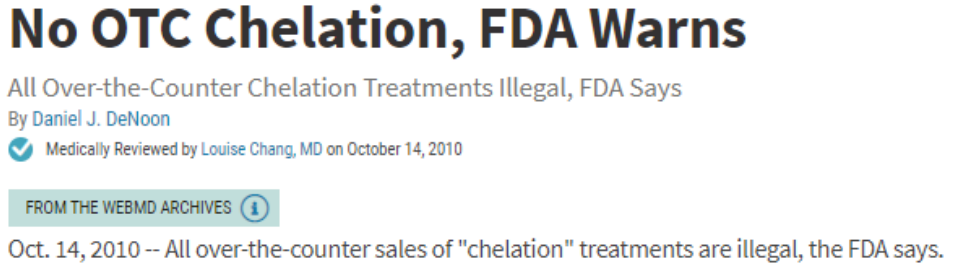
3. **Perspectives & Summary**

Challenges

- Not much relevant data due to short history of the field
  - Even the advantages of chelation is controversial.
  - The role of metals in pathology is also ambiguous.
- Variability of the experimental condition or usage of term
- Many criteria to be met for clinical use

  chelation ability, redox inertness, BBB or membrane permeability, solubility

  good affinity, selectivity, kinetic property, stability property, low toxicity
- Negative impression
  - EDTA toxicity
  - FDA waring in 2010
  - Chelation therapies as alternative medicine



No OTC Chelation, FDA Warns

All Over-the-Counter Chelation Treatments Illegal, FDA Says

By Daniel J. DeNoon

Medically Reviewed by Louise Chang, MD on October 14, 2010

FROM THE WEBMD ARCHIVES

Oct. 14, 2010 -- All over-the-counter sales of "chelation" treatments are illegal, the FDA says.

Anne Robert, *et al*. *Accounts of Chemical Research.* **2015** *48* (5), 1332-1339.
Charlène Esmieu, *et al*. *Inorganic Chemistry.* **2019** *58* (20), 13509-13527.
Kehinde D. Fasae, *et al. J. Trace. Elem. Med. Bio.* **2021** *67*, 126779.

Summary

- Recent findings on chelation-based therapy in cancer and Alzheimer's disease (focusing on Cu ions) were outlined.
- .Although there are still some issues to be solved, this treatment method is expected to be a new modality.
- There may be room for consideration of a copper-triggered switch mechanism ?

Appendix

安定度定数 K (logK)

ブリタニカ国際大百科事典 小項目事典「安定度定数」の解説

安定度定数
あんていどていすう
stability constant

錯体の安定度を示す平衡定数。金属イオン M と配位子 A が段階的に反応して MA_n のような錯体を生成するとき，それぞれのモル濃度 (*mol/l*) ［ ］によって，各段の平衡定数は，

$$k_1 = [MA]/[M][A]$$

$$k_2 = [MA_2]/[MA][A]$$

$$\cdots\cdots\cdots\cdots\cdots\cdots\cdots$$

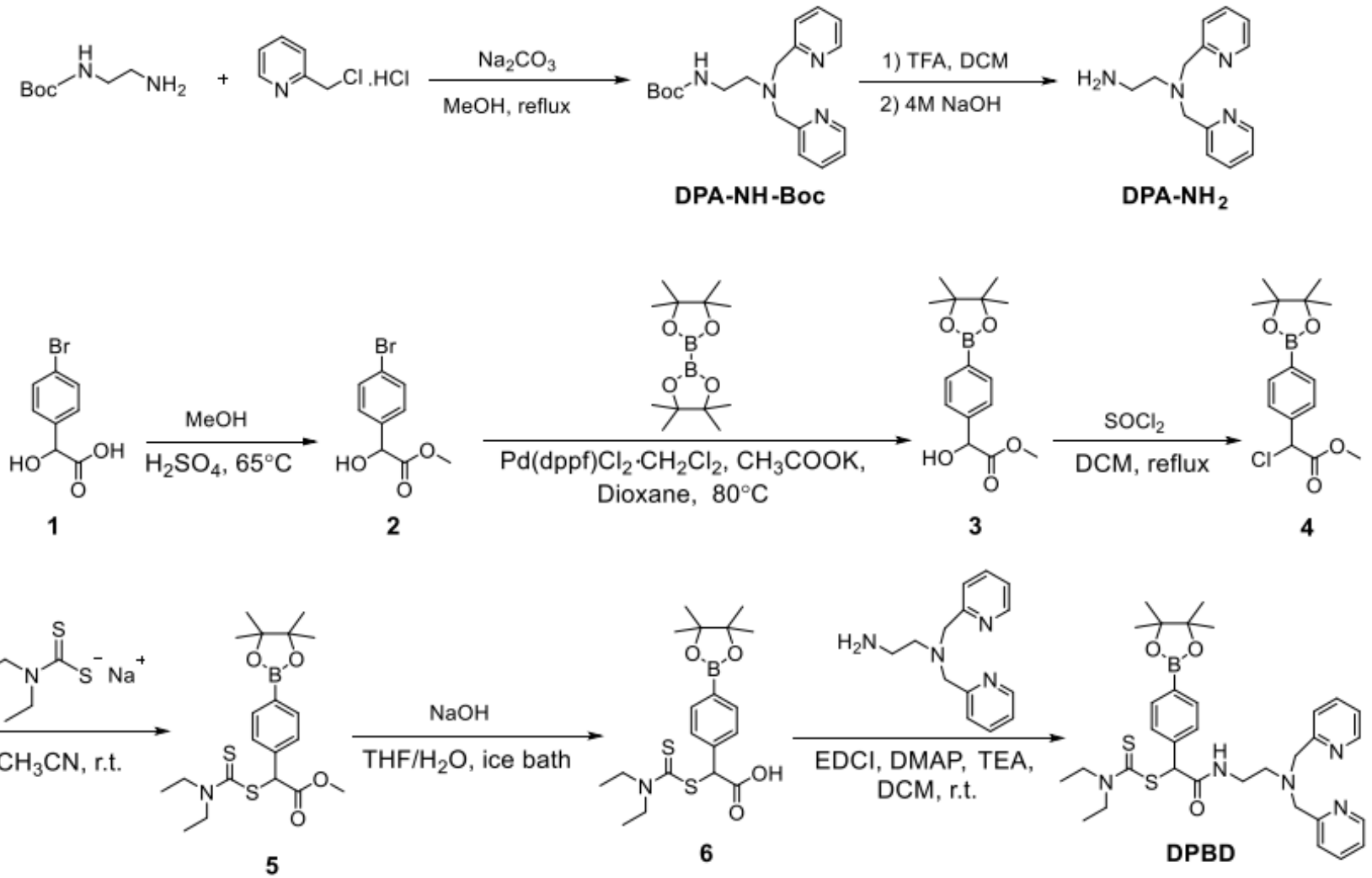
$$k_n = [MA_n]/[MA_{n-1}][A]$$

となり，k_1，k_2，…，k_n を逐次安定度定数という。また，

$k_1 \cdot k_2 \cdot k_3 \cdots\cdots k_n = K = [MA_n]/[M][A]^n$ として，K を全安定度定数という。錯体の生成しやすさを示す尺度で，大きい値ほど安定性が高い。電位差法，分光光度法，ポーラログラフ法，イオン交換法，溶媒抽出法などを利用して測定される。

DPBD synthesis

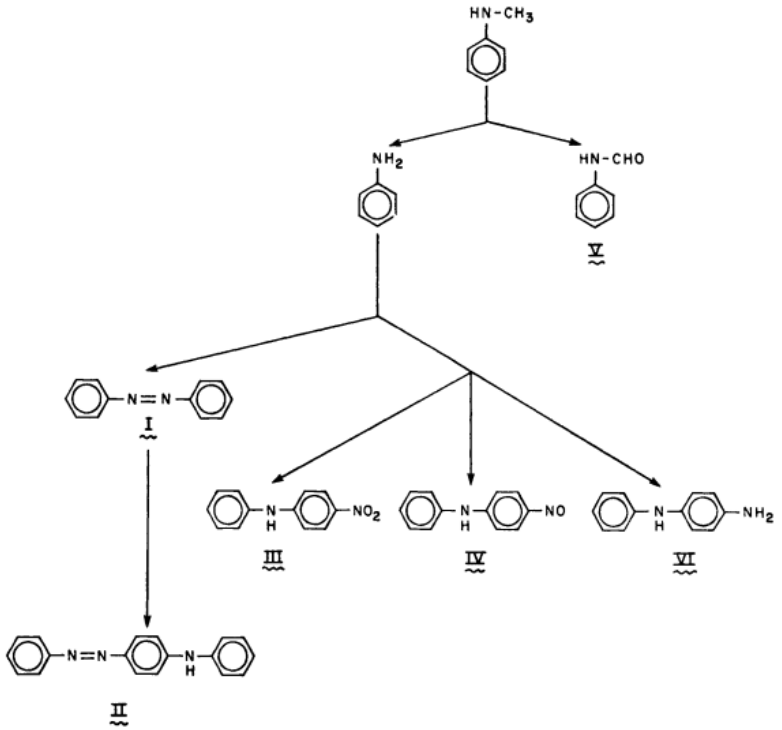
Synthesis of DPBD



N-dealkylation のところ

Oxidation Reactions of Aniline and *N*-Methylaniline J. Org. Chem., Vol. 50, No. 5, 1985 695

Scheme I. Products Isolated from the Aniline and *N*-Methylaniline Reaction with Superoxide



RETURN TO ISSUE ‹ PREV ARTICLE NEXT ›

Amine Oxidative N-Dealkylation via Cupric Hydroperoxide Cu-OOH Homolytic Cleavage Followed by Site-Specific Fenton Chemistry

Sunghee Kim†, Jake W. Ginsbach‡, Jung Yoon Lee†, Ryan L. Peterson†, Jeffrey J. Liu†, Maxime A. Siegler†, Amy A. Sarjeant†, Edward I. Solomon*‡, and Kenneth D. Karlin*†

View Author Information

Cite this: *J. Am. Chem. Soc.* 2015, 137, 8, 2867–2874
Publication Date: February 23, 2015
https://doi.org/10.1021/ja508371q

Article Views 5049 | Altmetric - | Citations 87
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Journal of the American Chemical Society

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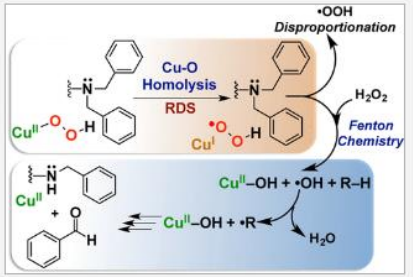
SUBJECTS: Bond cleavage, Hydroxyls, Ligands, Oxides, Reaction mechanisms

Abstract

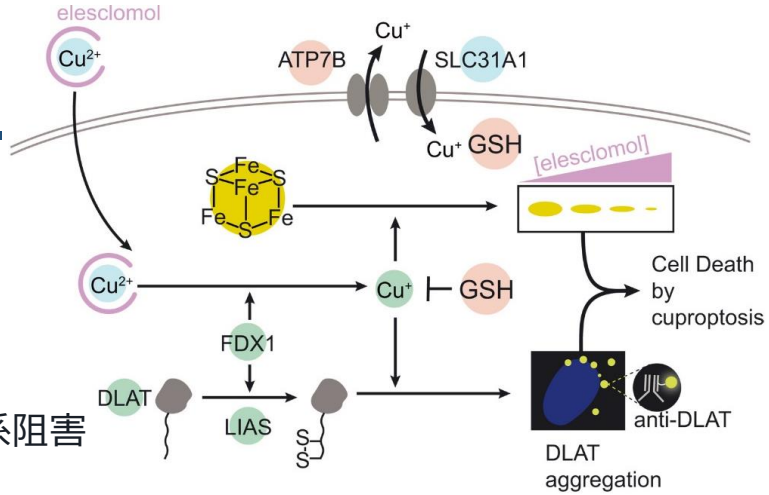
Copper(II) hydroperoxide species are significant intermediates in processes such as fuel cells and (bio)chemical oxidations, all involving stepwise reduction of molecular oxygen. We previously reported a Cu^{II}-OOH species that performs oxidative N-dealkylation on a dibenzylamino group that is appended to the 6-position of a pyridyl donor of a tripodal tetradentate ligand. To obtain insights into the mechanism of this process, reaction kinetics and products were determined employing ligand substrates with various *para*-substituent dibenzyl pairs (-H,-H; -H,-Cl; -H,-OMe, and -Cl,-OMe), or with partially or fully deuterated dibenzyl N-$(CH_2Ph)_2$ moieties. A series of ligand–copper(II) bis-perchlorate complexes were synthesized, characterized, and the X-ray structures of the -H,-OMe analogue were determined. The corresponding metastable Cu^{II}-OOH species were generated by addition of H_2O_2/base in acetone at −90 °C. These convert ($t_{1/2} \approx 53$ s) to oxidatively N-dealkylated products, producing *para*-substituted benzaldehydes. Based on the experimental observations and supporting DFT calculations, a reaction mechanism involving dibenzylamine H-atom abstraction or electron-transfer oxidation by the Cu^{II}-OOH entity could be ruled out. It is concluded that the chemistry proceeds by rate limiting Cu-O homolytic cleavage of the Cu^{II}-(OOH) species, followed by site-specific copper Fenton chemistry. As a process of broad interest in copper as well as iron oxidative (bio)chemistries, a detailed computational analysis was performed, indicating that a Cu^{I}OOH species undergoes O–O homolytic cleavage to yield a hydroxyl radical and Cu^{II}OH rather than heterolytic cleavage to yield water and a Cu^{II}-$O^{\bullet-}$ species.



↑ひいてたのはこれ

Cuproptosis

旧説：
・アポトーシスの誘導
・カスパーゼ非依存性細胞死
・活性酸素種（ROS）誘導
・ユビキチン-プロテアソーム系阻害

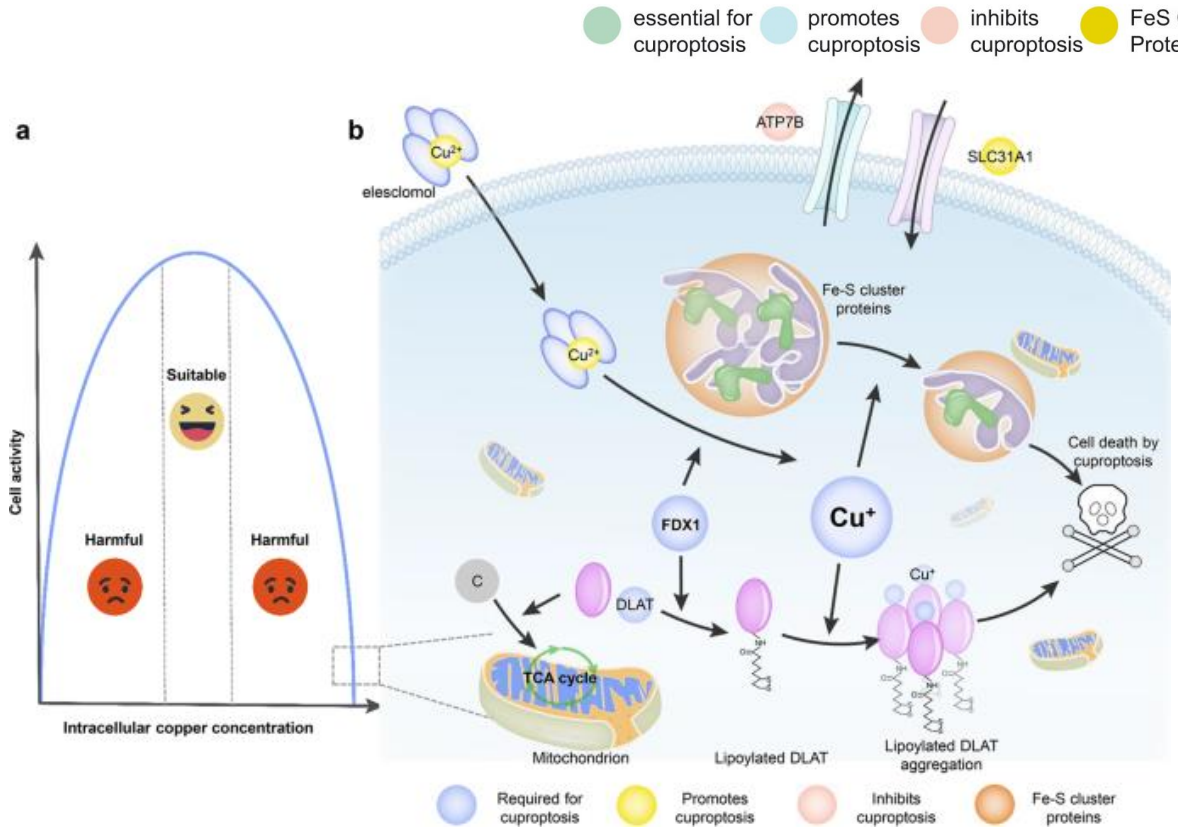


excess copper promotes the aggregation of lipoylated proteins and destabilization of Fe-S cluster proteins that results in proteotoxic stress and ultimately cell death

Copper induces cell death by targeting lipoylated TCA cycle proteins

PETER TSVETKOV, SHANNON COY, BORYANA PETROVA, MARGARET DREISHPOON, ANA VERMA, MAI ABDUSAMAD, JORDAN ROSSEN, LENA JOESCH-COHEN, RANAD HUMEIDI, [...] TODD R. GOLUB +9 authors Authors Info & Affiliations

SCIENCE · 17 Mar 2022 · Vol 375, Issue 6586 · pp. 1254-1261 · DOI: 10.1126/science.abf0529



Schematic illustration of cuproptosis mechanism. The effect of intercellular copper concentration on cell activity shows that cells maintain highly bioactive only within a suitable range of extremely narrow copper ion concentrations (**a**). Elesclomol, a copper ionophore, shuttles copper into the cells. FDX1 encodes a reductase to reduce Cu^{2+} to Cu^{+} and is a direct target of elesclomol. DLAT, a protein target of lipoylation, involves with mediating carbon entry to the TCA cycle. DLAT lipoylation was promoted by FDX1, and Cu^{+} enhanced lipoylated protein aggregation and iron-sulfur cluster protein reduction, which triggered proteotoxic stress and cell death (**b**).

Li, SR., *et al*. *Sig Transduct Target Ther.* **2022**. 7, 158.

自閉症スペクトラムに対するキレーション

- Main results
- We excluded nine studies because they were non-randomised trials or were withdrawn before enrolment. We included one study, which was conducted in two phases. During the first phase of the study, 77 children with ASD were randomly assigned to receive seven days of glutathione lotion or placebo lotion, followed by three days of oral dimercaptosuccinic acid (DMSA). Forty-nine children who were found to be high excreters of heavy metals during phase one continued on to phase two to receive three days of oral DMSA or placebo followed by 11 days off, with the cycle repeated up to six times. The second phase thus assessed the effectiveness of multiple doses of oral DMSA compared with placebo in children who were high excreters of heavy metals and who received a three-day course of oral DMSA. Overall, no evidence suggests that multiple rounds of oral DMSA had an effect on ASD symptoms.

Chelation for autism spectrum disorder (ASD)

Stephen James, Shawn W Stevenson, Natalie Silove, Katrina Williams Authors' declarations of interest

Version published: 11 May 2015 Version history

https://doi.org/10.1002/14651858.CD010766.pub2

- Authors' conclusions
- This review included data from only one study, which had methodological limitations. As such, no clinical trial evidence was found to suggest that pharmaceutical chelation is an effective intervention for ASD. Given prior reports of serious adverse events, such as hypocalcaemia, renal impairment and reported death, the risks of using chelation for ASD currently outweigh proven benefits. Before further trials are conducted, evidence that supports a causal link between heavy metals and autism and methods that ensure the safety of participants are needed.

The argument for why chelation therapy may be helpful for persons with ASD stems from the use of mercury in vaccines (Holmes, 2010). Mercury, as well as other metals, has been shown to be toxic to humans in high levels. Thimerosal, which contains mercury, was used in vaccines given to young children. Thus, the argument goes that ASD could be due in part to the presence of heavy metals in the body.

↑

Given the small amount of Thimerosal in vaccines, the fact that Thimerosal was eliminated from vaccines several years ago, and the continuing increasing incidence of autism, the believability of this premise is quite weak.

TAKING A CLOSE LOOK AT CHELATION THERAPY

January 18, 2011

By: Organization for Autism Research

Cardiovascular Disease に対するキレーション

- Background
- EDTA is an intravenous chelating agent with high affinity to divalent cations (lead, cadmium, and calcium) that may be beneficial in the treatment of cardiovascular disease (CVD). Although a large randomized clinical trial showed benefit, smaller studies were inconsistent. We conducted a systematic review of published studies to examine the effect of repeated EDTA on clinical outcomes in adults with CVD.

- Methods and Results
- We searched 3 databases (MEDLINE, Embase, and Cochrane) from database inception to October 2021 to identify all studies involving EDTA treatment in patients with CVD. Predetermined outcomes included mortality, disease severity, plasma biomarkers of disease chronicity, and quality of life. Twenty-four studies (4 randomized clinical trials, 15 prospective before/after studies, and 5 retrospective case series) assessed the use of repeated EDTA chelation treatment in patients with preexistent CVD. Of these, 17 studies (1 randomized clinical trial) found improvement in their respective outcomes following EDTA treatment. The largest improvements were observed in studies with high prevalence of participants with diabetes and/or severe occlusive arterial disease. A meta-analysis conducted with 4 studies reporting ankle-brachial index indicated an improvement of 0.08 (95% CI, 0.06–0.09) from baseline.

- Conclusions
- Overall, 17 studies suggested improved outcomes, 5 reported no statistically significant effect of treatment, and 2 reported no qualitative benefit. Repeated EDTA for CVD treatment may provide more benefit to patients with diabetes and severe peripheral arterial disease. Differences across infusion regimens, including dosage, solution components, and number of infusions, limit comparisons across studies. Additional research is necessary to confirm these findings and to evaluate the potential mediating role of metals.

Chelation Therapy in Patients With Cardiovascular Disease: A Systematic Review

Filippo Ravalli, Xavier Vela Parada, Francisco Ujueta, Rachel Pinotti, Kevin J. Anstrom, Gervasio A. Lamas and Ana Navas-Acien

Originally published 1 Mar 2022 | https://doi.org/10.1161/JAHA.121.024648 | Journal of the American Heart Association. 2022;11:e024648

Other version(s) of this article

Web MD のキレーションに関する記事

Autism：×

The use of chelation therapy to treat this condition is based on the idea that autism is caused by mercury in childhood vaccines. Studies have proven this idea to be false. But some health care providers also believe that removing metals from the body can improve autism symptoms.

The American Academy of Pediatrics (AAP) says there's no evidence that chelation is an effective treatment for autism, and it may be dangerous. One child with the condition died after having this treatment. The AAP doesn't recommend using chelation therapy for autism, except in a clinical trial.

Alzheimer's Disease：△

In patients who have this, abnormal proteins called tau and beta amyloid build up in the brain and damage it. To date, no treatment can stop or reverse this disease.

Some researchers think that a buildup of metals like copper, iron, and zinc might also play a role in Alzheimer's disease. If this is true, chelation therapy might have a place in treating it. So far, there's no evidence that it works.

Heart Disease：△ (糖尿病は〇？)

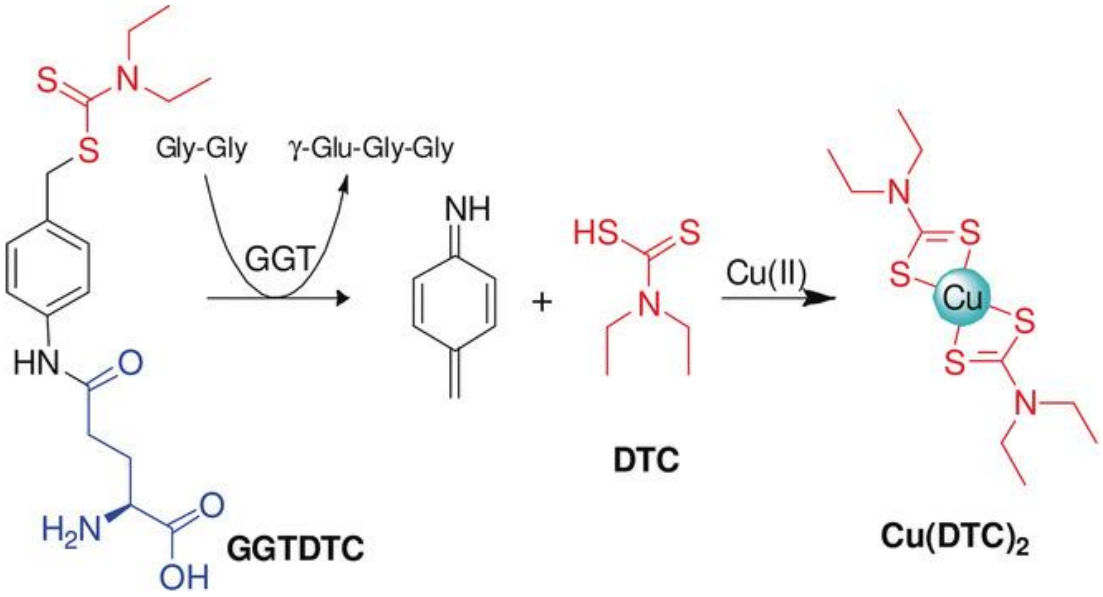
You get this when fatty deposits called plaques form in your arteries. These substances cause your blood vessels to narrow. They also make them less flexible, so less blood can flow through them. Artery plaques contain calcium. The chelating drug disodium EDTA binds to this mineral. The idea is that chelation therapy clears it out of the blood vessels. It removes plaques, too.

In 2002, the National Institutes of Health did a big study on chelation therapy, called TACT. It found that this treatment somewhat reduced the risk of heart attacks, strokes, and other heart problems. But it only worked in people with diabetes. The study didn't find enough proof that it treats heart disease. And so far, the FDA hasn't approved this treatment for the condition. A new study called TACT2 may yield more information.

About TACT：
https://www.nccih.nih.gov/health/questions-and-answers-the-nih-trials-of-edta-chelation-therapy-for-coronary-heart-disease

GCT prodrug

A prodrug approach is presented to direct copper-dependent cytotoxicity to prostate cancer cells. The prochelator GGTDTC requires activation by γ-glutamyl transferase (GGT) to release the metal chelator diethyldithiocarbamate from a linker that masks its thiol reactivity and metal binding properties. In vitro studies demonstrated successful masking of copper binding as well as clean liberation of the chelator by GGT. GGTDTC was stable to non-specific degradation when incubated with a series of prostate cancer and normal cell lines, with selective release of diethyldithiocarbamate only occurring in cells with measurable GGT activity. The antiproliferative efficacy of the prochelator correlated with cellular GGT activity, with 24 h inhibitory concentrations ranging from 800 nm in prostate cancer lines 22Rv1 and LNCaP to over 15 μm in normal prostate PWR-1E cells. These findings underscore a new strategy to leverage the amplified copper metabolism of prostate cancer by conditional activation of a metal-binding pharmacophore.



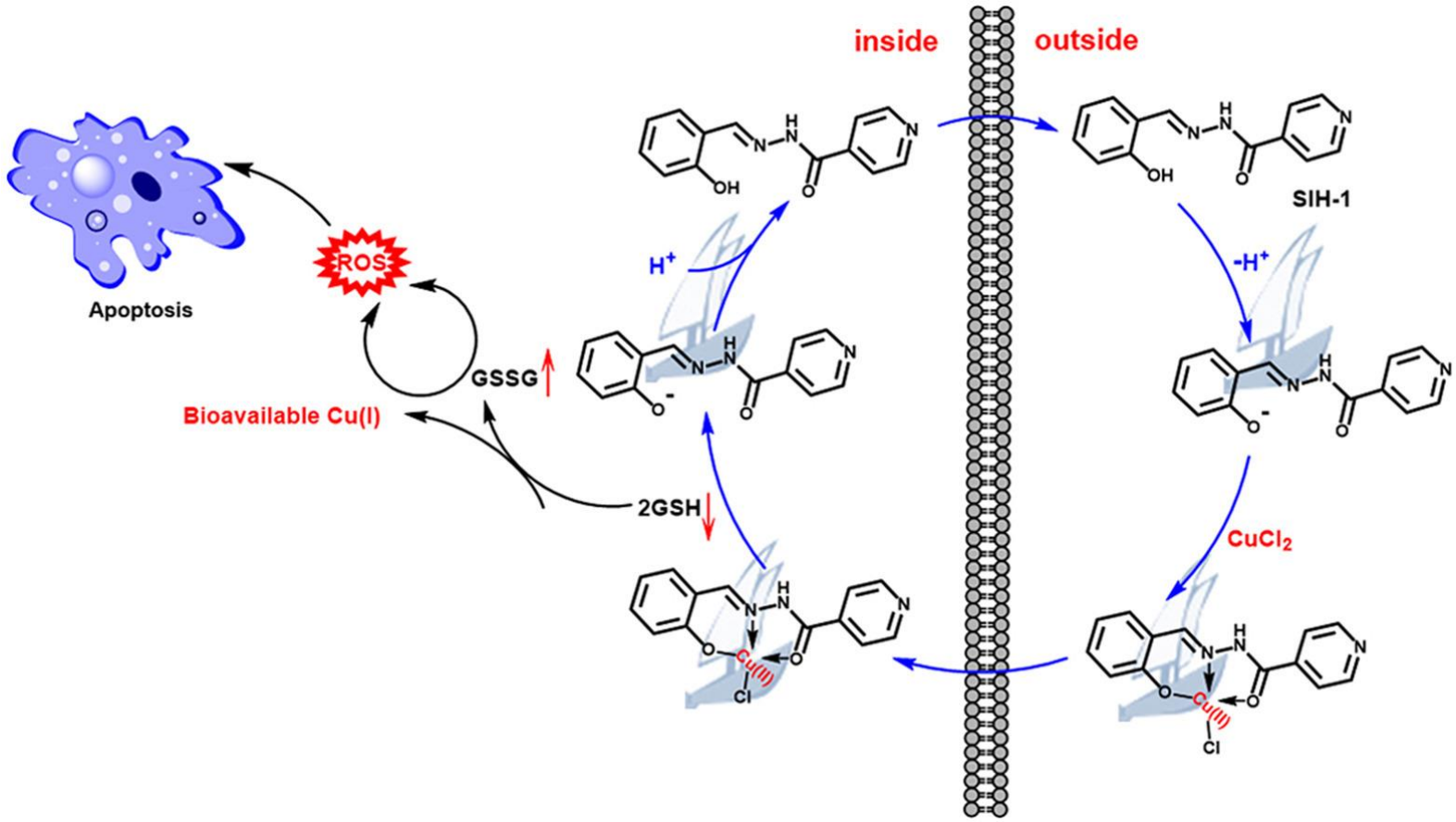
Communication | Full Access

Leveraging γ-Glutamyl Transferase To Direct Cytotoxicity of Copper Dithiocarbamates against Prostate Cancer Cells

Dr. Subha Bakthavatsalam, Dr. Mark L. Sleeper, Azim Dharani, Dr. Daniel J. George, Dr. Tian Zhang, Katherine J. Franz

First published: 19 July 2018 | https://doi.org/10.1002/anie.201807582 | Citations: 36

他のIonophore for がん



ELSEVIER

Free Radical Biology and Medicine

Volume 129, December 2018, Pages 215-226

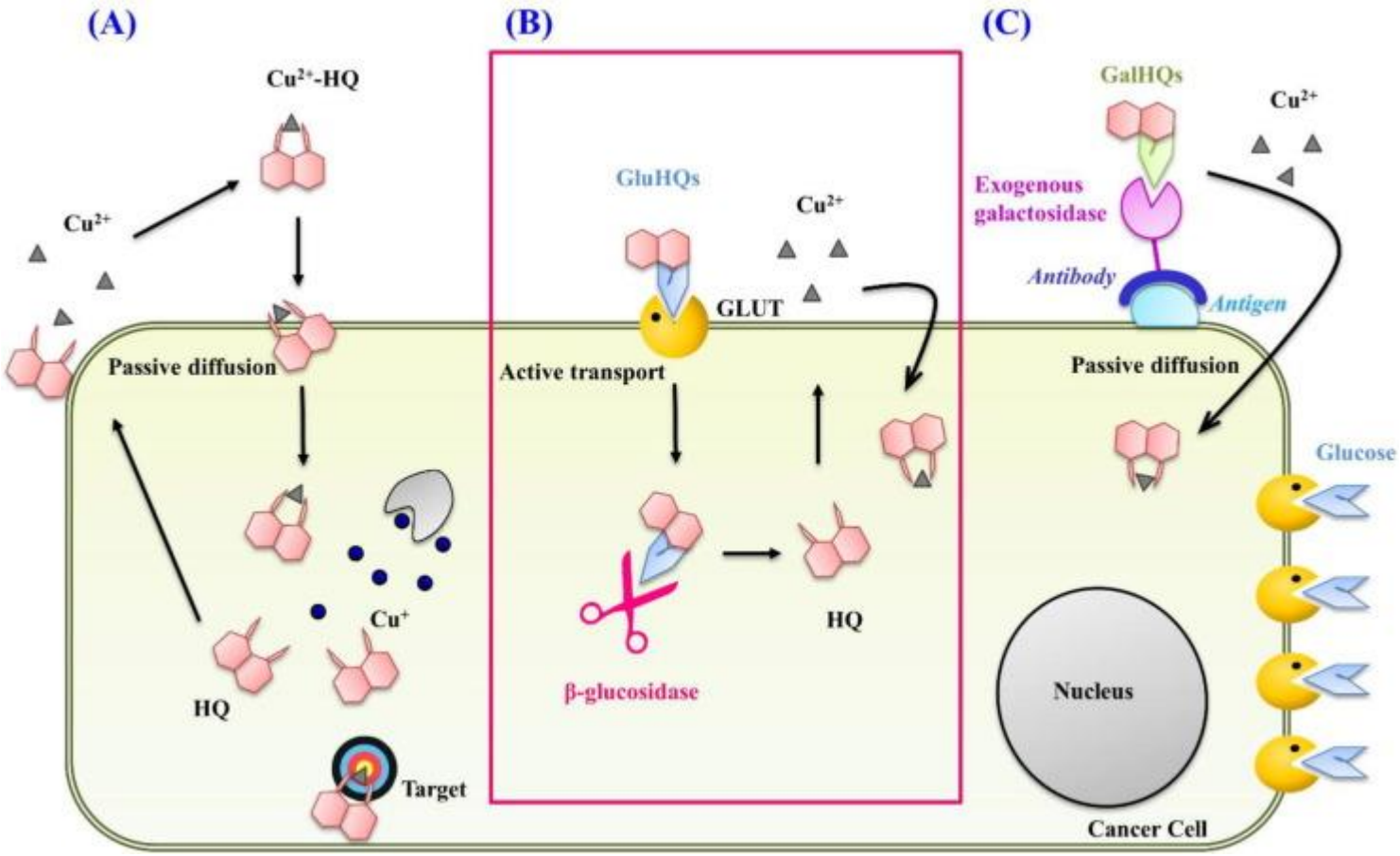
Original article

Designing salicylaldehyde isonicotinoyl hydrazones as Cu(II) ionophores with tunable chelation and release of copper for hitting redox Achilles heel of cancer cells

Yuan Ji, Fang Dai, Bo Zhou

他のprolonophore for がん

Mechanism of action of HQs and their proionophores GluHQs and GalHQs. Cu-HQs diffuse passively through the cell membrane into the cytosol and release Cu to their target or increase the intracellular pool of Cu (A). GluHQs and GalHQs cannot passively cross the cell membrane owing to the hydrophilicity. The targeting moiety of GluHQs is recognized by GLUT transporters that are overexpressed in cancer cells (B). Upon the internalization, GluHQs are hydrolyzed by the cytosolic β-glucosidase (B). The nontoxic GalHQs are administered systemically and hydrolyzed only in the presence of the exogenous β-galactosidase that is delivered to cancer cells exploiting an antigen–antibody interaction (C). In the latter cases, the released HQs function as Cu ionophores and release Cu to their target or increase the intracellular pool of Cu (for clarity, the release of Cu is not represented but is analogous to the mechanism represented in A).



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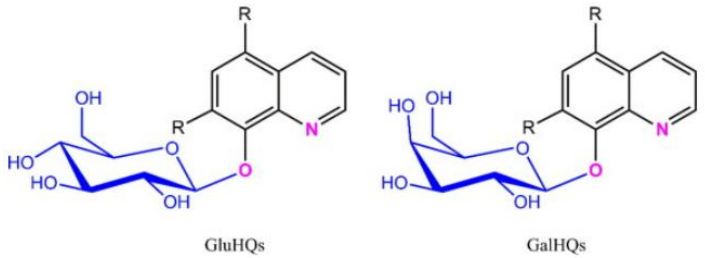
Volume 422, 1 November 2020, 213474

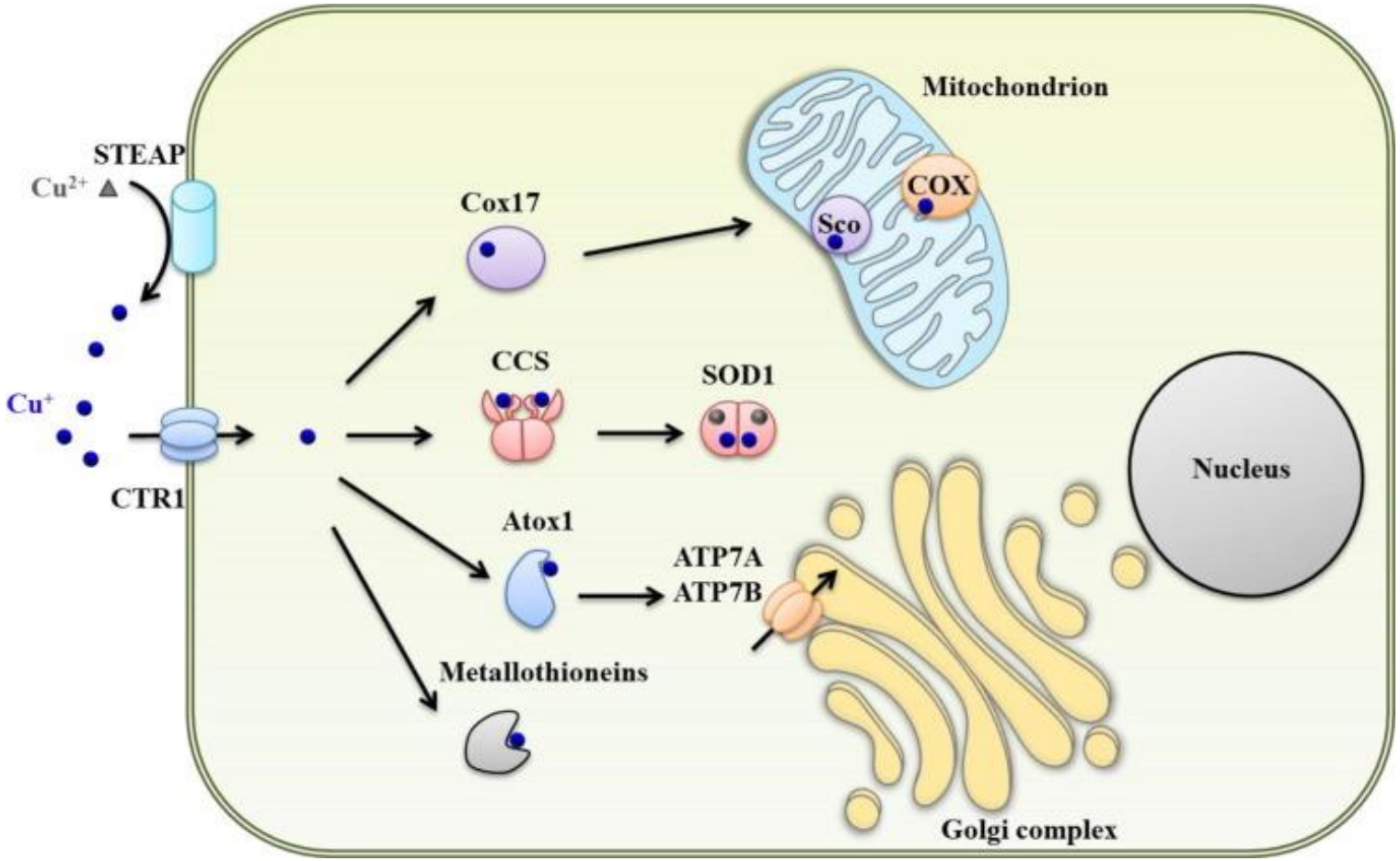
Review

Biomedical applications of copper ionophores

Valentina Oliveri



Cu homeostasis



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Coordination Chemistry Reviews
Volume 422, 1 November 2020, 213474

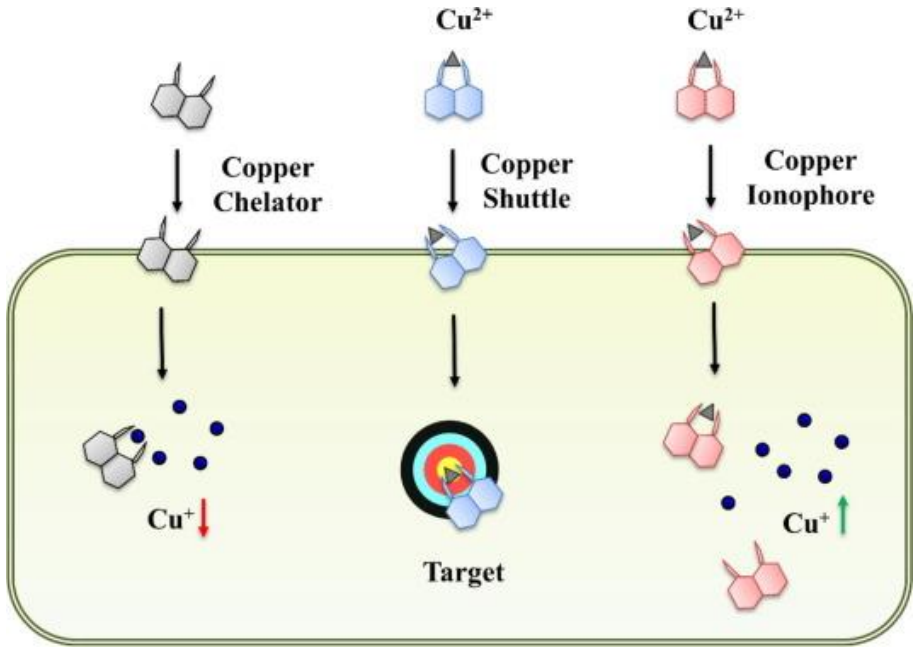
Review

Biomedical applications of copper ionophores

Valentina Oliveri

Fig. 1. Cu homeostasis in mammalian cells. Cu^{2+} is reduced to Cu^{+} by reductases on the cell membrane. Cu is transported into the cytoplasm by Ctr1. The imported Cu^{+} rapidly associates with other molecules such as metallothioneins, GSH, and metallochaperones, which distribute Cu^{+} to different cellular locations. Atox1 transports Cu to the ATPases, ATP7A, and ATP7B in the Golgi complex, whereas Cox17 and Sco proteins are involved in the trafficking of Cu to the mitochondria for incorporation into cytochrome *c* oxidase (COX). The Cu chaperone for Cu/Zn-superoxide dismutase (CCS) transfers Cu to Cu/Zn superoxide dismutase (Cu/Zn SOD/SOD1) that is involved in the detoxification of superoxide radicals. For clarity, only the oxidation state of Cu is represented in the figure, however Cu is always bound to biologically-relevant molecules.

Metal shuttle



Metal shuttles do not significantly affect the intracellular metal concentration but deliver the metal to a precise target, or the metal complex itself is the active compound

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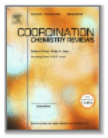
Coordination Chemistry Reviews

Volume 422, 1 November 2020, 213474



Review

Biomedical applications of copper ionophores

Valentina Oliveri

https://www.sciencedirect.com/science/article/pii/S0010854520303349?via%3Dihub

CQ の役割

CQ (or PBT2) sequester metal ions that are in equilibrium with amyloid-beta (Aβ) complexes and **promote plaque dissociation**.

CQ (or PBT2) can form ternary complexes with the metal ion and Aβ.

These complexes are internalized by neurons, where the metals and ligands dissociate and are addressed to different pathways.

The metal ions may **activate phosphoinositol 3-kinase (PI3K)**.

This leads to downstream activation of Akt, c-Jun-N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and consequently **matrix metalloproteinases (MMPs)**.

MMPs promote Aβ clearance, whereas **Akt pathway inhibits** the α- and **β-isoforms of glycogen synthase kinase 3 (GSK3**), a serine/threonine kinase.

GSK3β is considered a central target in AD as it is associated with the **hyperphosphorylation of tau protein.**

GSK3β is inhibited by phosphorylation at the regulatory site ser-9.

Overall, CQ (or PBT2) **reduces tau phosphorylation and mediate Aβ clearance** trough the activation of the above-described pathways.

Cu-AβからのROS発生

Ageing Research Reviews
Volume 77, May 2022, 101619

Review

Oxidative stress: The core pathogenesis and mechanism of Alzheimer's disease

Renren Bai [a, b, c], Jianan Guo [d, 1], Xiang-Yang Ye [a, b, c], Yuanyuan Xie [d], Tian Xie [a, b, c]