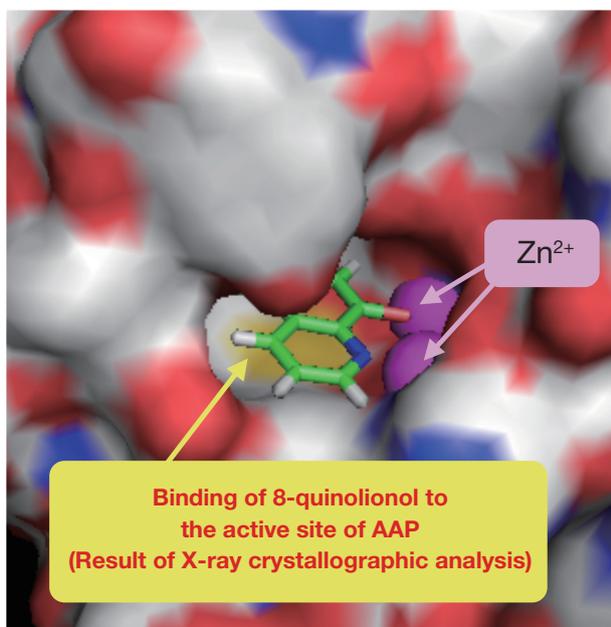## Bio

Solution for multi-drug resistance bacteria

Shin AOKI (Professor, Department of Medicinal and Life Science, Faculty of Pharmaceutical Sciences, Tokyo University of Science)

Purpose of Research

With the introduction of antibiotics, it was thought that the battle against infection had ended. However, antibiotic-resistant microbes (drug-resistant bacteria) have appeared and is now an issue of global challenge since there are no effective therapeutic methods against them. In addition, the appearance of multi-drug resistant bacteria has become a new threat and effective countermeasures are required. Recently, inhibiting "metallo-β-lactamase," an enzyme that leads to multi-drug resistance in pathogens, is gaining interest. At our laboratory, through research on metallic zinc complexes, we have focused on enzymes that selectively inhibit enzymes that contain zinc and are developing drug agents to inhibit the activity of enzymes that contain zinc such as metallo-β-lactamase. At the same time, we are designing molecules with lower toxicity and developing a reactivation method.

Summary of Research

Zn²⁺

Binding of 8-quinolionol to the active site of AAP (Result of X-ray crystallographic analysis)

Points

- Search for compounds that bind to the active site of dinuclear zinc enzymes and analyze mechanism of binding in detail using X-ray crystallography
- This compound was found to inhibit the dinuclear zinc enzyme AAP (Amino-peptidase from *Aeromonas Proteolytica*)
- A protective group was introduced to reduce toxicity of these compounds and we developed a method to eliminate the group under physiological conditions
- Knowledge, techniques and know-how which are related to complex chemistry in water

Metallo-β-lactamases are considered to be the most dangerous among β-lactamases and degrade almost all antibiotics that include penicillins, cephams and carbapenems. Bacteria (*Pseudomonas aeruginosa*, *Acinetobacter*, *E. coli* and *Klebsiella pneumoniae*, etc.) that carry the gene for this enzyme on a transmissible plasmid have strong pathogenicity and may cause infection not only in the hospital, but also to the general public.

Among metallo-β-lactamases, there are dinuclear zinc enzymes with two zinc molecules in the active center (Class B) and there are currently few drugs (inhibitors) that effectively inhibit these enzymes.

Our laboratory is applying basic research on metallic zinc complexes to develop dinuclear zinc enzyme inhibitors. Specifically, we have analyzed the structure of the active site of these enzymes in detail and searched for inhibitors that can bind to the zinc ions. However, inhibitors to metal enzymes are metalloligands which lead to toxicity. Therefore, we are investigating prodrugs that protect the ligand site to lower toxicity but can also be deprotected and reactivated at the right time and place.

Through these activities, we are aiming to develop a novel antibacterial agent against dinuclear zinc enzymes such as β-lactamase while avoiding multi-drug resistance.

Future Developments

- Selection of optimal compound from those known to bind to the active site
- Evaluation of enzyme inhibitory potency of the selected compound *in vitro*
- Molecular design and synthesis to lower toxicity (prodrug)
- Safety and efficacy evaluation *in vivo*
- Collaborative research with domestic and global partners

- Research Organization: This research is a collaborative study with Kengo Hanaya at the Faculty of Pharmacy, Keio University.

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