S-01

date and time: October 25, 2022, 15:30–17:00
venue: 5F Big Hall

代謝酵素を対象とした SBDD 手法の開発
Structure Based Drug Design against CYP enzyme

Purpose of the Meeting

After being taken into the body, many drugs are metabolized by various metabolic enzymes mainly in the liver and small intestine and eliminated from the body. This metabolic reaction not only changes the activity of the drug itself, but also affects the efficacy and side effects of concomitant drugs. In particular, if an adverse effect on a drug-metabolizing enzyme is identified late in the development process, the search for a different compound is forced to return, resulting in a significant delay in the development process. The most important enzymes in the drug metabolism process are the Cytochrome P450 (CYP) superfamily. For general enzymes and receptors, SBDD, a method for rationally designing compounds from protein structures, can be applied. However, since CYPs are metalloproteins containing heme iron, it is extremely difficult to predict the binding and reaction mode of CYPs with substrates based on their three-dimensional structures because of the overwhelming lack of accurate structural information, including their charge and hydration states. Therefore, it is urgently needed to establish strategies and various measurement and structural analysis methods to obtain accurate structural information for SBDD utilization in order to develop drugs. In this symposium, we will introduce the development of rational drug design methods for Vitamine D3 metabolizing enzymes, CYP24A1 and CYP105A1, by integrating X-ray, neutron, and electron beam analysis with computational science.

Moderator : **Midori Takimoto-Kamimura**
Shiro Kondou
(CBI Research Institute
Quantum-Structural Life Science Labolatories)

1. **Why we are focusing on CYP as a project of the Institute for Quantum-Structural Lifescience Labolatories ? Midori Takimoto-Kamimura**
（CBI Research Institute）

2. **CYPs as predictors of drug metabolism and targets for drug discovery**
Toshiyuki Sakaki (Toyama Prefectural University)

The human genome contains 57 cytochrome P450s (P450s), which play a major role in the biosynthesis of steroid hormones and the metabolism of drugs. The present status, challenges, and future prospects of P450 research are discussed.

3. **Synthetic chemistry of VD3 derivatives that resist CYP24A1 metabolism**
○Atsushi Kittaka、Masashi Takano、Fumihiro Kawagoe (Teikyo University)

Our laboratory has been conducting synthetic chemical research on 2-position substitutions of active vitamin D3, especially those characterized by chemical elongation of carbon chains 1-3 in the α-direction. In the process, we have obtained several derivatives that have stronger binding affinity to the vitamin D receptor, which functions as a transcription factor, than the naturally active form of vitamin D3. They also acquired metabolic resistance to CYP24A1, the enzyme responsible for the metabolism of active vitamin D3. Synthetic methods for these VD3 derivatives and their representative biological activities for the treatment of diseases will be presented.

4. **Cryo-EM for CYP**
○Koji Yonekura、Tasuku Hamaguchi、Kiyofumi Takaba、Keisuke Kawakami、Saori

Maki-Yonekura (RIKEN/Tohoku University)

Single particle analysis of cryo-electron microscopy and electron diffraction are being used to study CYPs. Since the former is a challenging subject due to the molecular weight and the latter due to the thickness of the crystal as a limitation, analytical techniques are being developed in parallel. Electron beams are scattered by the Coulomb potential of the sample and have high sensitivity to valence electrons, which is different from that of X-rays and neutron beams. Various promising technologies for drug discovery applications have been developed, such as visualization of hydrogen atoms, acquisition of charge

5. Xray/neutron Crystallography Analysis for CYP

○Taro Tamada、Yu Hirano
National Institutes for Quantum Science and Technology

X-ray crystallography is common method in structural biology, accounting for about 90% of the PDB-registered structures. On the other hand, neutrons interact with nuclei, making it possible to determine the position of hydrogen atoms, which is difficult with X-ray crystallography at normal resolution. In addition, neutrons have about 6 orders of magnitude lower energy than X-rays, making them suitable for structure determination of metalloproteins because they are irradiation damage- and reduction-free. In this talk, we will introduce our X-ray and neutron crystallography efforts for CYPs.

6. Development of Solution Structure Analysis of CYPs by Solution Scattering

Masaaki Sugiyama
(Kyoto University)

Solution scattering (small-angle scattering) can be combined with exclusion volume chromatography and ultracentrifuge analysis to obtain unprecedentedly accurate data. Currently, we are using this data to derive the average structure in solution using Normal Mode Analysis (NMA). By comparing the solution structure with the crystal structure, we aim to elucidate the relationship between the structure modulation in solution and the CYP function. In this presentation, we will also introduce the results of this study and the solution structure analysis that can be developed by using molecular dynamics simulations and neutrons.

7. Expectations for Computational Chemistry Analysis Methods for CYPs

○Kinya Toda (MOLSIS Inc.)
Noriyuki Kurita (Toyohashi University of Technology)

In recent years, various analytical methods have been developed in the field of computational chemistry that can be applied to CYP research, and there are growing expectations for computational chemistry-based analytical methods in CYP research, which have been difficult to apply in the past: characterization of CYP reaction centers, evaluation of accessibility and affinity of metabolite compounds to the reaction centers, and analysis of electronic states around heme iron and the electronic structure around heme iron.

8. Closing

Shiro Kondou
CBI research Institute