Drug development, Life science, Antibody design, Database

# Elucidation of antibody recognition mechanism by quantum chemical calculations

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## Abstract

For the design of antibody drugs, it is important to understand the interaction between antigens and antibodies. The FMO method evaluates the interaction energy of each amino acid residue quantitatively based on the three-dimensional structure of protein complexes, and identifies important residues to provide clues for drug discovery. For example, the interaction analysis of the complex structure of spike protein and antibody with 12 types of antibodies for the novel coronavirus showed a good correlation with the experimental activity value ($IC_{50}$) and succeeded in identifying 9 residues that could be epitopes as antibody recognition sites (Fig.1).

## Background & Results

Drug discovery and development is also becoming increasingly digitalized. The FMO method enables large-scale quantum chemical calculations by treating macromolecules such as proteins as fragments. It also enables quantitative evaluation of inter-fragment interaction energies, which can be used for molecular design based on an understanding of molecular interactions. The FMO Drug Design Consortium is working to develop the FMO method as a practical drug discovery method by using the supercomputer "Fugaku" (project number: No. hp220143). The FMO database (FMODB) is being constructed and made available to the public. In novel coronaviruses, comprehensive FMO calculations have been performed on the complex structures of spike proteins and antibodies. In the example of the receptor binding domain (RBD) of the spike protein and 12 antibodies, a good correlation was obtained between the antigen-antibody binding energy and $IC_{50}$ ($R^2$=0.540). The antibody recognition site is similar to the human ACE2 receptor recognition site, and in all complexes, nine specific residues on the RBD surface contribute to the stabilization of the interaction with the antibody (Fig. 1). A similar approach can be used in the analysis of mutant strains, indicating that the FMO method is useful for epitope prediction. Comprehensive FMO calculations for other novel coronavirus-related proteins are also available from the FMODB (Figure 2). We are currently performing FMO calculations for various antigen-antibody complexes published in the Protein Data Bank and accumulating basic data for prediction of antibody modification by integrating FMO and AI.

## Significance of the research and Future perspective

Today, computational science and AI are beginning to be used everywhere to reduce the enormous cost and time required for drug discovery and development. Our research is expected to elucidate the molecular recognition mechanism of antibodies related to diseases through precise calculations based on quantum mechanics, and to be useful for the efficient design of modified antibodies. The same approach can be applied to various drug discovery modalities, and is useful for rational and efficient molecular design that is effective not only for conventional small molecule drug discovery, but also for the design of new modalities such as nucleic acid drugs and lipid nanoparticles.

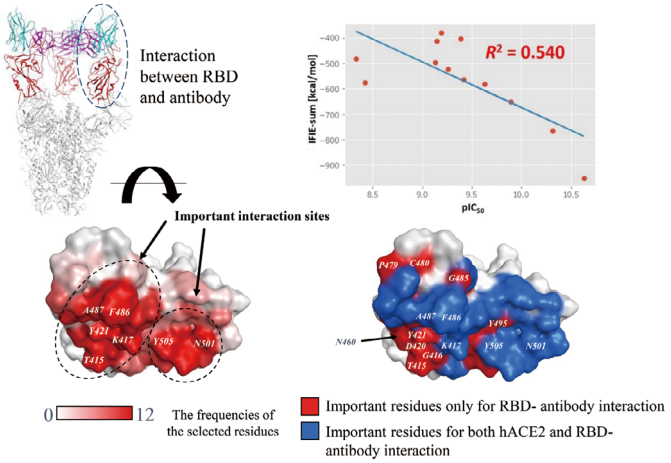


Figure 1. Interaction between spike protein and antibody

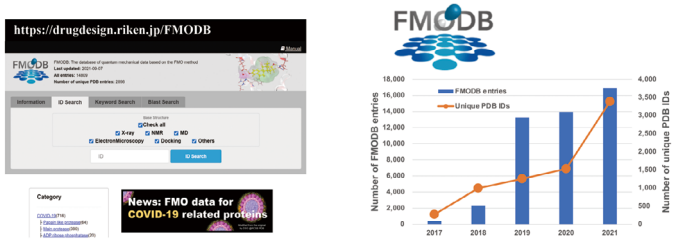


Figure 2. Top page of the FMO Database (FMODB) (left) and the number of registered structures (right)

**Patent**

**Treatise**

Watanabe, Kazuki; Watanabe, Chiduru; Honma, Teruki et al. Intermolecular Interaction Analyses on SARS-CoV-2 Spike Protein Receptor Binding Domain and Human Angiotensin-Converting Enzyme 2 Receptor-Blocking Antibody/Peptide Using Fragment Molecular Orbital Calculation. J. Phys. Chem. Lett., 2021, 12, 4059–4066. doi: 10.1021/acs.jpclett.1c00663

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**URL**

https://fmodd.jp/
https://drugdesign.riken.jp/FMODB/

**Keyword** In silico drug discovery, antibody design, computational life science, fragment molecular orbital (FMO) method, supercomputer Fugaku