Fujitsu *in-silico* Drug Discovery Technologies for creating active novel compounds.

OPMF: Abstract fragment based *de novo* novel compound generation

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1. Introduction

OPMF (**O**ptimum **P**acking of **M**olecular **F**ragments) generates small molecules which have activity on a target protein with an original **abstract fragments based *de novo* design** approach.
OPMF generates highly novel and realistic compound structures which are difficult to create with usual experimental approaches in consideration of activity, certain properties such as polar surface area, logP and molecular weight, and synthetic feasibility which is estimated based on knowledge extracted from libraries of known chemical compounds. **OPMF can be used** not only for designing novel compounds but also **for searching candidate compounds from a library** of millions of compounds with designed abstract skeletons (scaffolds that are non-specific with reference to atoms) where **high hit rate** (not less than 4%) is achieved compared to high-throughput screening method.

2. Abstract fragments based de novo design approach

It is required to design a candidate structure which satisfies shape and electronic complementarities to the target, strongly binds to it and is expected to be strongly effective as a drug.
A combinatorial explosion occurs in case of constructing a drug molecule by combining sub-structures (fragments) such as hetero rings which are often found in drug molecules.
OPMF overcomes the combinatorial explosion by reducing the number of fragments to be considered **by introducing abstract fragments** whose kinds of atoms are abstracted with pseudo atoms (Figure 1).
Abstract skeletons which satisfy shape complementarities to the target are exhaustively searched with the pseudo atoms.
A candidate structure which is expected to strongly bind to the target is efficiently designed by assigning real atoms such as carbon or hetero atoms to an abstract structure considering electronic complementarities to the target.

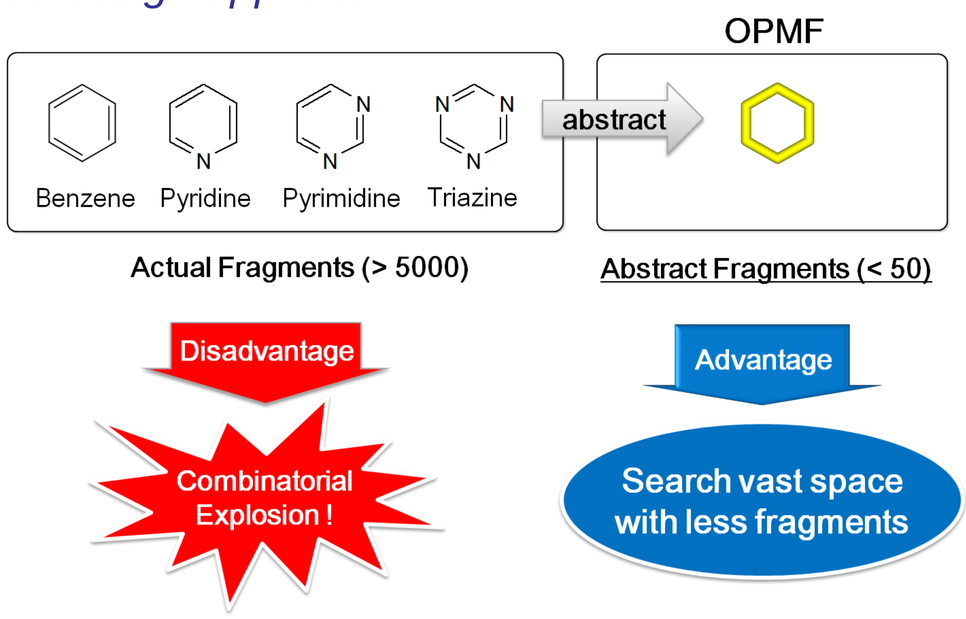

Figure 1 Abstract fragment and advantage

Designing a structure from scratch without information of known active compounds is called *de novo* design. **In *de novo* design with OPMF, structures with high novelty beyond one's imagination are produced** by generating structures exhaustively by connecting abstract fragments which are stably placed on a surface of a protein.

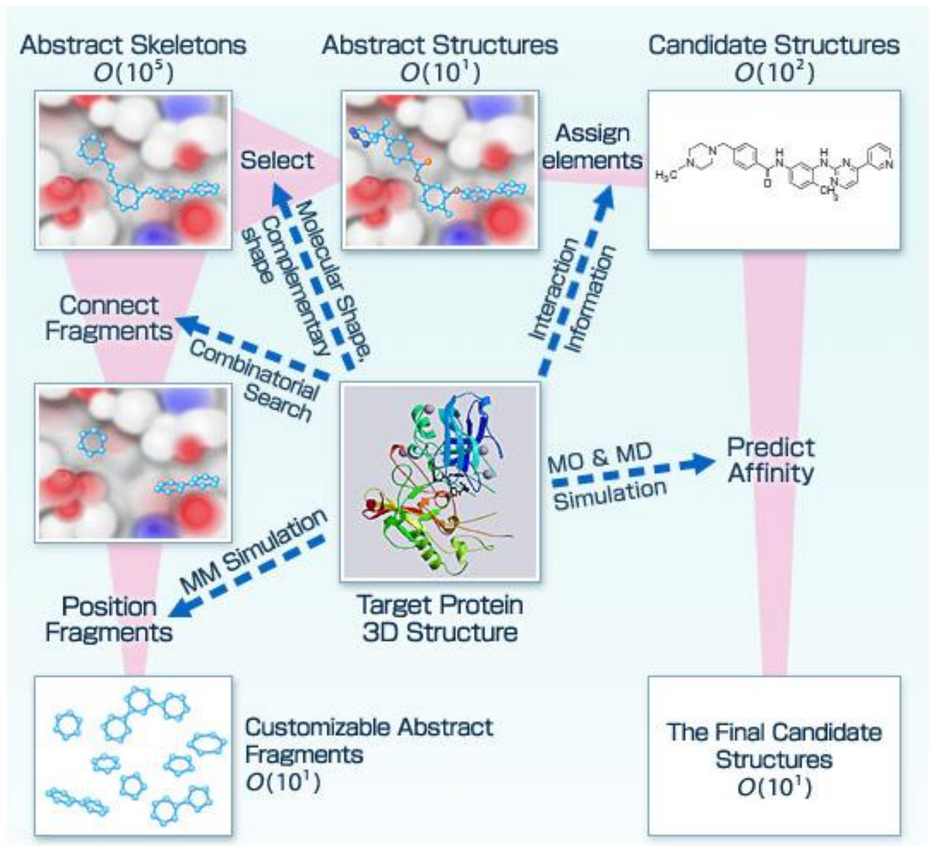

Figure 2 Protocol of *de novo* design of novel structures

Figure 2 shows hierarchical design process of OPMF where candidate structures are efficiently searched.

1. Position Fragments: Determine stable positions of each abstract fragment on an active site of a protein.

2. Connect Fragments: From abstract fragments which are placed in a stable position, find combinations of them by which an abstract skeleton can be formed. Connect the fragments in the combination by adding abstract atoms as linkers in chemically feasible manner.

3. Selection: Narrow down the abstract skeletons generated in step 2 based on structural requirement as a molecule and shape complementarities to the protein.

4. Assign Elements: Assigning elements considering the formation of hydrogen bonds, the electrostatic interaction and the possibility of synthesis.

5. Predict Affinity: Predict affinity of compounds with computer simulation techniques such as molecular dynamics (MD) or molecular orbital (MO) method.

3. Practical use in creating small molecule inhibitors

(1) Inhibition of binding of IgE and its high affinity receptor FcεRI

Immunoglobulin E (IgE) is an antibody which plays an important role in allergy. Prevention of IgE from binding to its high-affinity receptor, **FcεRI**, leads to blocking IgE-mediated signaling on mast cells and release of chemicals such as histamine which causes allergy. We designed abstract skeletons which should bind to FcεRI.
114 compounds were selected from a library of 4.5 millions of commercially available compounds with an original search algorithm in OPMF which uses an abstract structure as query. 5 of the 114 showed inhibition of binding of IgE to FcεRI with ELISA (**hit rate=4.3%**).
In addition to the 5 known compounds, novel compounds were also designed, synthesized and tested. Figure 3A shows one of the novel compounds which has the highest activity (IC_{50}=1.8μM). In this way, we proved our technology, **OPMF**, as **practically useful in designing small molecules to inhibit protein-protein interaction**.

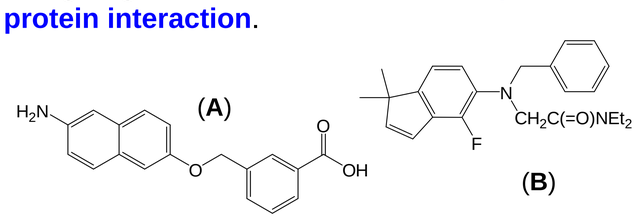

Figure 3 Molecules created with OPMF
(**A**) IgE - FcεRI antagonist (**B**) KSP inhibitor

(2) Inhibition of ATPase activity of mitotic motor protein KSP

Kinesin spindle protein (KSP) is known as a target for a new generation of antitumor compounds. KSP is essential for formation and function of mitotic spindle. Inhibition of KSP prevents formation of normal bipolar spindle, leads to cell cycle arrest at M-phase, inhibits cell proliferation and ultimately leads to apoptosis. We designed novel KSP inhibitors with OPMF.
12 compounds were synthesized and their ATPase activity was measured to test an ability to prevent the hydrolysis of ATP to ADP in the presence of microtubules. **3 of the 12 were active**. Figure 3B shows a molecule with the highest activity (44.5% inhibition at 10μM).

4. A framework which aims to replace an experimental approach in DD with IT

As described with practical application, OPMF itself produces novel compounds of activity in micro-molar range.

By **combination of OPMF and MAPLE CAFEE** (**MA**ssively **P**aral**LE**l **C**omputation of **A**bsolute binding **F**ree **E**nergy with well-**E**quilibrated system) which precisely predicts an activity of a compound, we are able to produce novel compounds of activity in nano-molar range with **an ideal structure and simulation based *in-silico* drug discovery** (DD) **system** which aims to replace a time- and cost-intensive, experimental trial-and-error approach in DD with IT (Figure 4).

Using the framework of OPMF and MAPLE CAFEE, we can get active compounds by creating novel compounds or by finding from a library of millions of compounds. Once we have active compounds, we can improve their activity or property through modification.

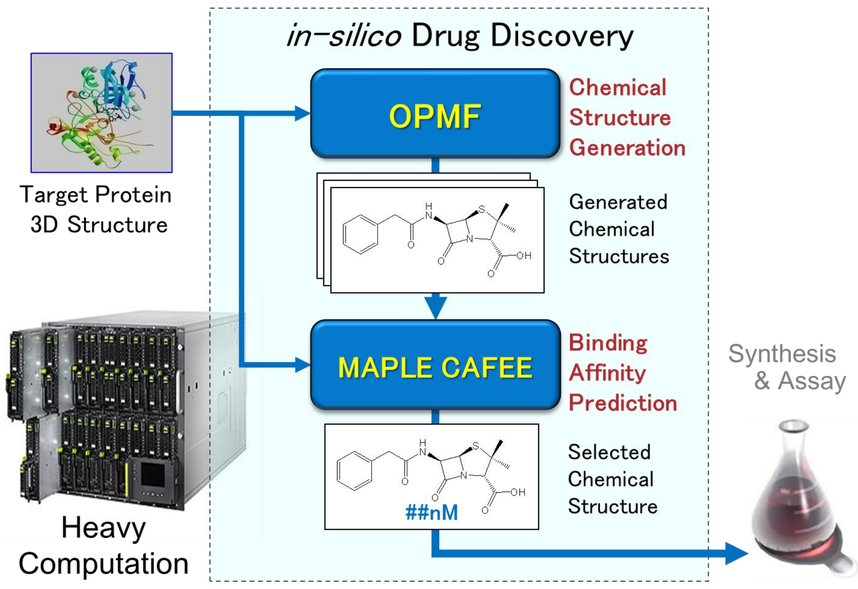

Figure 4 Two core technologies of Fujitsu's *in-silico* DD OPMF and MAPLE CAFEE

To validate our *in-silico* DD technology really practical, we have been **collaborating with the Experimental Therapeutics Centre** (Singapore) through development of inhibitors to anti-infective target proteins.