Drug Discovery Chemistry

Cambridge Healthtech Institute Drug Discovery Chemistry

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The fragment-based drug discovery (FBDD) track was part of the larger Cambridge Healthtech Institute Drug Discovery Chemistry conference, which also included HCV drug discovery, kinase inhibitor chemistry, protein–protein interactions (PPIs), anti-inflammatories and combating drug resistance. The FBDD track had many interesting talks that covered experimental and computational approaches in FBDD. The conference lasted for 3 days and there were approximately 100–200 people in the room at any given time. The experimental approaches included NMR, x-ray crystallography, capillary electrophoresis, surface plasmon resonance (SPR) and MS.

The ^{19}F NMR spectroscopy method presented by Anna Vulpetti is a highly sensitive technique for fragment-based screening; ^{19}F chemical shifts and protein–fragment interactions were shown to correlate. The authors identified fluorophilic subsites in proteins in the PDB database with similar local environments: shielded fluorines are usually located near the hydrogen bond donors and deshielded fluorines next to the hydrophobic side chains and carbon of the carbonyl groups. This may be very useful for designing specific fluorine chemistry for lead optimization.

Target-immobilized NMR screening technology, presented by Gregg Siegal from ZoBios showed successful fragment screening for membrane proteins and was able to identify allosteric modulators of G-protein-coupled receptors. Target-immobilized NMR screening allows for fragment hits to be detected relatively efficiently. Binding is detected as the difference between the control (fragment in solution) and the target (fragment flowing over immobilized target). ZoBios typically screens 2000 fragments in a week using a single NMR machine.

X-ray crystallography is another technique used in FBDD to identify novel ligands. It has been shown to guide the discovery of β -secretase and ketohexokinase inhibitors by Ivan Efremov from Pfizer and Marta Abad from Johnson & Johnson. In these studies, the structural information helped direct the structure–activity

relationship (SAR) studies. X-ray crystallography is also a powerful technique to identify allosteric binding sites in proteins as described by David Strout. His group identified fragments that bind to the HIV protease exo site. They expanded these fragments by virtual screening of a library of 700,000 compounds against fragment-induced crystal structure.

Capillary Electrophoresis was presented by Carol Austin from Selcia as a tool to detect weak binding fragments. A successful application to Hsp90 was presented. SPR was presented by Per Kallblad from Beactica as a tool to identify fragment binders and help guide optimization. MS was presented by Denis Zeyer from Novalix as a way to detect intact protein–fragment complexes and can be used together with NMR and SPR. These experimental approaches laid the foundation for the future computational presentations, which all depend on experimental approaches for validation and prospective studies. The computational approaches presented are detailed below.

Charles Reynolds from Ansaris presented their fragment screening studies based on free energy of binding, which involves systematic sampling of fragments in protein environments and clustering. They found that free energy correlates to affinity better than enthalpy. Energetically favorable fragments are then assembled to form molecules that are synthesized and tested. The authors showed that, using their FBDD platform, they were able to identify a novel p-38 inhibitor with improved properties, such as higher selectivity against other kinases.

Chris Williams from CCG presented their computational approach to generate novel candidates from known active compounds using molecular transformations, based on medicinal chemistry rules such as bioisosteric transformations, heterocycle substitution and homologation. Their FBDD platform includes 2D and 3D filters, applying pharmacophore features and refinement in a flexible receptor.

Woody Sherman from Schrödinger presented Schrödinger's FBDD platform, which encompasses every stage in FBDD, from fragment

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generation/preparation to docking, fragment joining and scoring. In addition to tools for modeling fragments, Schrödinger offers a wide variety of tools to prepare the target proteins and characterizing binding sites. Furthermore, the software offers many tools to generate novel compounds from known binders, by either modifying the molecule's core or R-groups. Sherman described the modified XP Glide scoring function, which is better suited to screen fragments. This includes subtracting Glide rewards term, which is more appropriate for larger molecules, addition of vdW efficiency to reward good packing and desolvation terms to penalize overabundance of polar atoms. Testing of this scoring function on Abbott's FKBP test set showed improved early enrichment.

One of the challenges in FBDD is low specificity of fragments; small molecules have high probability of binding to a target. According to Isabelle Krimm this is not always the case; she showed that fragments could be selective. In general, hydrophobic fragments are more unselective as they lack directionality and bind in different modes to several proteins. Fragments generated from known binders do not retain their affinity. Fragment-based screening is a better approach for finding fragments that bind.

Another challenge in FBDD is the fragment libraries that are composed of simple aromatic compounds, which makes it difficult to identify active fragments that are diverse. Roman Kombarov from Asinex described their approach in building a diverse fragment library, inspired by natural products that are sp^3 -enriched fused, spiro and bridged ring systems. These fragments present a combination of lipophilicity and solubility at physiological conditions.

In the topic 'Challenges for successful FBDD', it was found that fragment diversity is a problem. Small fragments cover larger chemical space but large molecules are found to be more diverse. One problem is that most fragments consist primarily of small heterocycles. Adding sp^3 centers would add diversity but might make chemistry more challenging. Also, a lot of fragment libraries have been designed for kinases, which typically have planar heterocycles binding at the hinge. However, this might not be ideal for other targets. Another issue is that it is often hard to get chemists to work with fragments. If a chemist has a 10-nM hit, from high-throughput screening or a 100- μ M fragment, in most cases they will go with the hit, even if it is large and unlikely to result in a drug. Much of this stems from the incentives in industry, where

people are rewarded for the number of active compounds that are synthesized. Starting with a more potent compound increases the chances that modifications will also be active. Most companies find that it is necessary to have a dedicated fragment group to make fragment-based discovery successful.

During the discussion in 'Using FBDD on membrane proteins', there was a complaint about underutilization of biophysical methods in FBDD: "Structure-based drug design did not play a significant role in drugs in market, yet customers still require structure." However, this was before the age of fragment-based discovery. Most people consider crystal structures to be essential to the FBDD process. It is hard to understand SAR with fragments, since they can change binding modes along the optimization. If crystal structures are not available, homology modeling can be useful. Recent publications have shown that homology models of membrane-bound proteins can now be made accurately enough to have significant value in FBDD.

In the kinase inhibitor chemistry track discussions, Kiyoyuki Omoto from Pfizer and Nels Thornstein from CCG presented computational approaches in building kinase databases from the available x-ray structures, to facilitate structure mining and homology modeling. Xuemei Zhang presented their SAR studies, which combined experiments with computational approaches.

The PPIs as drug targets track included several talks on hot topics such as macrocycles and staples peptides. Small molecules cannot mimic PPIs and large peptides suffer from poor cell permeability and oral bioavailability. Macrocycles and stapled peptides can remedy these problems. Nick Terrett from Ensemble Therapeutics presented their library of approximately 1.6 million DNA-tagged discrete macrocycles that can be used for screening. DNA-tags act as a barcode to track the behavior of each compound in a mixture used in screening.

Tomi Sawyer from Aileron presented their stapled peptide technology to design peptides that mimic PPI and are stable in physiological conditions. This technology results in substantial stabilization of helices, which thereby produces improved therapeutic properties, such as enhanced affinity and cell permeability. Successful computational predictions of helical stability were made using the Schrödinger molecular modeling tools. This work was published in *Chemical Biology and Drug Design* in 2010 [1].

Ilya Vakser presented their Genome Wide Docking Database, which includes data from experimental studies as well as models built using docking techniques. It allows searches of binding partners using an input sequence or structure. Sandor Vajda presented their FTMAP server, which can be used to identify binding sites for small organic molecules that can be used as building blocks for fragment-based design.

In summary, this was a very good conference that covered a wide range of topics. The fields of fragment-based drug design and chemical biology are coming together and there are a number

of synergies. In addition, successful applications of both computational and experimental approaches were presented. In many cases, the combination of computational and experimental techniques was the key to success.

Financial & competing interests disclosure

Woody Sherman is an employee of Schrödinger. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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