ACS Medicinal Chemistry Letters

Viewpoint

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Fragonomics: The -Omics with Real Impact

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ABSTRACT: Fragonomics is the process of using small, relatively simple molecules to generate chemical starting points for hit generation. Fragonomics has come of age and is now one of the major concepts in hit generation. What is its future?

Fragment-based drug discovery (FBDD), or more appropriately fragment-based hit generation (FBHG), has been around as a concept for over 30 years, and in practice for almost 20 years. In the beginning, FBHG fought for acceptance, as with any new method entering a highly dogmatic industry. I have fond memories of explaining to project leaders why they should work on these 500 μM compounds because they were better starting points. After laughing at the young kid who did not understand drug discovery, they would go with the 1 μM lead-like (large and complex) compound and start chopping pieces off to explore the SAR. They would come back when the project was dead, or nearly so, looking for a "Hail Mary". Eventually, internal success lead to wide adoption. Not every company was slow to adopt the "smaller is better" concept. Companies were set up to exploit this concept; extant companies created teams from whole cloth. Today, the concepts of FBHG have become incorporated into a majority of hit generation processes.

At the turn of the century, -omics were all the rage: genomics, chemogenomics, metabonomics, and so on. Hoping to ride this wave and gain acceptance, fragonomics was coined to convey the nature of the process: "a highly integrated lead generation approach using small, relatively simple molecules".[1] This simple statement encompasses the four guiding principles of the field: (1) greater sampling of the available chemical space, (2) greater probability of finding a starting point than "conventional" (high throughput screening, HTS) methods, (3) deliberate and efficient medchem, and (4) a highly integrated process. In practice, this leads to certain specifications, but in contrast to what many people think, these are meant as guidelines and should not be viewed as rules.

The fewer the number of atoms in a given set of molecules, the fewer the number of potential molecules that can exist. There is no hard and fast rule for the size of a fragment; most practitioners limit them to 18 heavy atoms. A thousand fragment library samples the same amount of available chemical space as 10 trillion molecules do for a lead-like library. Fragments are also relatively simple, i.e., one or two substitutions. Limiting the degree of substitution on fragments has two purposes. First, limited substitutions allow quick and rapid testing of structure−activity relationship (SAR) hypotheses. Because of the simple nature of fragments, this testing can be done with the analogue by catalog/corporate collection approach. Analogue by catalogue finds similar easily accessible fragments that help define and test potential SAR hypotheses. Second, limited substitutions mean that beyond the core interaction, there is only one or two possible interactions with the target. This leads to fewer, or no, potential bad interactions and the possibility of at least one good one. This is a very important point that many people new to the field miss: its not the size of the molecule that makes it a fragment, it is its ability to make a good interaction while not making any bad interactions.[2] Lead-like molecules have multiple good interactions (higher affinity) and can tolerate some bad interactions. However, the cost of higher affinity (and the need for less sensitive assays) is these bad interactions and the necessity of early medchemist engagement. The physicochemical properties of fragments have been widely discussed with most libraries adhering to the Rule of 3 (Ro3).[3] The Ro3 has become dogma; (almost) every commercial fragment library adheres to this rule. Its applicability to a wide range of targets is suspect and its usefulness is in question. Like any dogma, its adherents are staunch and it will take time, and solid data, to break its grip.

Having at least, or sometimes only, one good interaction while eliminating bad interactions requires sensitive biophysical techniques to find these weak binding (micromolar to millimolar) fragments. Nuclear magnetic resonance (NMR) and surface plasmon resonance (SPR) are the two most popular direct screening methods for fragments. There are a variety of indirect biophysical techniques, which can be used as screening methodologies, but direct methods are vastly preferred. Once a weak binder is found it needs to be confirmed and tested as part of a SAR hypothesis. This can happen very quickly (days) and allows for robust testing of all fragment actives. Once confirmed as a hit, medchem engagement finally is needed in contrast with HTS-derived hits where the medchemist is engaged early and often. With a fragment, every atom added is done by choice. Despite appearances, delaying medchemist engagement is good for the medchemist, allowing them to focus their creativity and experience on validated and solid SAR hypotheses with more chemical space to work in. The final fragonomics principle is that all of the individual pieces must be highly integrated. Be denecessitating early medchemist engagment, the speed of testing SAR hypotheses is greatly increased. This is a key advantage of fragonomics: speed and efficiency of hit generation. With a well-designed fragonomics process, the library can be screened, actives confirmed, and SAR hypotheses developed and tested though several iterations in weeks. Oftentimes, the entire

Published: August 13, 2014

   dx.doi.org/10.1021/ml5003212 | *ACS Med. Chem. Lett.* 2014, 5, 952−953

fragonomics process can be completed before the HTS has even finished its initial testing.

These four guiding principles are manifested in three practical components: libraries, screening methods, and the prosecution of actives. Libraries are a source of much debate: how big should they be, should they be maximally diverse or biased, and should they contain more 2D, more 3D, or a mix of molecules? The answers are yes. Libraries can be, and should be, whatever the practitioner needs them to be. Some libraries are as small as a few hundred molecules, while some are over 20,000. Most libraries are in the 2000 fragment range, which can be screened by NMR or SPR in a week or so. The choice of screening methods affects the choice of libraries, and *vice versa*. Optimally (and honestly who works in an optimal environment these days?), multiple orthogonal direct methods are used as primary screens. Biophysical characterization, mostly indirect methods, is then performed as follow up. In the end though, much characterization is of the "checking boxes" kind. The most important information is that which prospectively informs medchem decisions. Restrospective data makes us feel good, but does not advance the project. So, you might be wondering where does X-ray crystallography fall? Many people will not prosecute fragments without structure. It is of the nice to have, but not need to have category. Fragonomics is harder without it without question, but it is still very doable. If the target is important enough to be in the portfolio, then it is important enough to use all your tools against, not just the "easy to use" ones. Ultimately, the correct choice of library and screening method is dependent upon the resources available. Most practitioners are limited in their resources and have to compromise to implementing a good method that is obviously not ideal. Anyone who tells you that their way is the best, or even that there is a best way, is selling you something. This is another key advantage of fragonomics: it is highly adaptable to the target and resources available.

Early hit generation, and thus fragonomics, has historically been controlled by the availability of medchemists. They are the most precious resource, we are told repeatedly, and thus the hardest to get. Fragonomics delays medchemist engagement to much later in the hit generation stage. Initial active confirmation, hit identification, and hit expansion can all be done without any medchemist. Of course, having a medchemist involved from the beginning of the fragonomics process is ideal, it is just not always possible. Medchem input on library design, active triage, etc., can avoid many problems, unless the practitioner understands medchem well. Sometimes, the key molecule to test a SAR hypothesis does not exist and thus needs to be made. A nonmedchem-fluent practitioner can result in "pollution of the literature", like rhodanines as leads.

Fragonomics, once the young turks, is now the old guard, with its own dogma to assail. It is implemented in practice, or in principle, throughout the drug discovery arena from industry to academia. It has become an important deliverer of chemical equity, and there is a robust pipeline of compounds in the clinic due to fragonomics. It stands alone among the -omics as consistently delivering to the clinic. No one needs convincing of its utility anymore. There are still mountains to climb: difficult target classes like intrinsically disordered proteins and multiprotein complexes or nonstructurally enabled targets (which overlap with IDPs and multiprotein complexes significantly). What's the future for fragonomics? Current debate in the field centers around the mathematical validity of ligand metrics and 2D vs. 3D fragments. This is quibbling around the edges. Fragonomics has won the field. As a stand alone field, it has no future. That does not mean that it is a dead field; quite the opposite. Fragonomics is the reigning dogma for hit generation. The age of the medchemist is over; now is the time of the biophysicist.

AUTHOR INFORMATION

Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

The authors declare no competing financial interest.

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