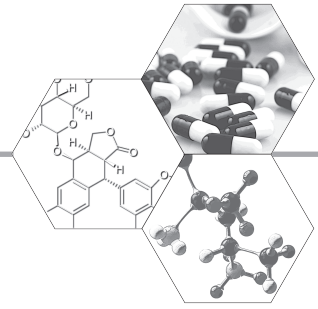

Pharmacophores for medicinal chemists: a personal view

"…the gap between computational chemists and medicinal chemists can only be bridged if there is a common language between them that allows for easy communication."

Keywords: pharmacophore elucidation ■ 3D database search ■ structure-based pharmacophore

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Designing and synthesizing the next blockbuster drug molecule is the holy grail of nearly every medicinal chemist actively involved in pharmaceutical research. Some of them have succeeded, and a compound imagined by their brain and made by their skilful hands has been introduced onto the market as a new chemical entity, after a long and tedious process full of hurdles, potential pitfalls and drawbacks. A few of these drugs have reached blockbuster status, that is, have generated revenues in the multibillion dollar range. A team of hundreds of scientists in different fields have contributes their expertise and their commitment to the development of such a drug. But at the very beginning there is the imagination, the intuition, the knowledge of a medicinal chemist or a team of medicinal chemists who guide the first steps on the ladder: the hits obtained in the initial screen; the leads obtained in the hit to lead transformation; and finally the candidate obtained after the lead optimization process.

An enormous amount of information has been generated in recent decades of 'rational' drug discovery and development. Has this information been transformed into knowledge? Is there any chance that this information can ever be transformed into knowledge, which can be used by others in the field? Or is a successful medicinal chemist still a magician, an alchemist, able to transform anything into gold, knowing that a blockbuster is several orders of magnitude more worth than this metal.

Today, more than ever, pharmaceutical industry faces considerable challenges, both fiscally and politically. On the one hand, increasing R&D costs, impinging on productivity, almost correlate with increasing rates of attrition. On the other hand, governments around the world trying to contain costs in their healthcare budgets forces enterprises involved in drug discovery and development to enhance the output of new drugs significantly in order to maintain their shareholder value. Considering that only one out of three drugs reaching the market recovers the original investment made, and taking into account the number of compounds that undergo attrition in preclinical research, the average success rate of approximately one in ten from first-in-man to market is ridiculously low. Have computational methods in drug design helped so far to enhance the chance of success? And, if so, which methods have been proven to be especially suited for use directly by the ones implicated in the making of new bioactive molecules, the medicinal chemists?

In the author's view and experience, the gap between computational chemists and medicinal chemists can only be bridged if there is a common language between them that allows for easy communication. A medicinal chemist who encounters a computational chemist who is using methods that the medicinal chemist does not fully understand, will not trust the results presented to him. Neither will he have confidence, if there is a magic black box used for making predictions about the quality (and the faith) of the compounds he is designing and will be synthesizing. How can this gap be bridged? There have been numerous attempts to offer software programs to medicinal chemists to assist them in making decisions on prioritizing compounds over others. Many of these attempts have failed because of high complexity, low user friendliness and lousy prediction capabilities of different software solutions. Some have been more successful, especially when they were using concepts that medicinal chemists already use intuitively when thinking about their molecules. One of these successful approaches that can be considered is the pharmacophore modeling technique developed and refined over several decades.

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In fact, the concept of pharmacophores has been used in drug research for many years [1]. It is based on the assumption that the molecular recognition of a biological target shared by a family of compounds can be described by a set of common features that interact with a set of complementary sites on the biological target. Such features are quite general, as hydrogen-bond donors, hydrogen-bond acceptors, positively and negatively charged or polarizable, hydrophobic regions, or metal–ion interactions, and they are the same elements that medicinal chemists use in their imaginational design process. In addition to their nature, the 3D relationship between each of the features is another key component of the pharmacophore description, which sometimes is missing in the medicinal chemist's imagination, since most of them have been trained extensively in conceiving structures in 2D. However, as the feature-based pharmacophore concept is closely linked to the widely used principle of bioisosterism, it is quite understandable that medicinal chemists have largely adopted it when designing their bioactive compound series. Although the first definition of the pharmacophore as a concept had been attributed to Ehrlich, recently Van Drie [2] wrote that it was Kier who introduced it in a series of papers in the late 1960s and early 1970s [3,4] when describing common molecular features of ligands of important central nervous system receptors, followed by Höltje in 1974 [5]. In these early studies, the pharmacophore models were mainly deduced manually, assisted through the use of simple interactive molecular graphics visualization programs. Later, the diversity and steadily growing complexity of molecular structures that characterize drug discovery have led to the development of sophisticated computer programs for the determination, manipulation and use of pharmacophore models. A considerable number of books, book sections and reviews [6–13] on this approach exist today, the most recent comprehensive one published being that by Leach *et al.* [14]. Still, the basic concept of pharmacophore models as simple geometric representations of key molecular interactions remain unchanged. Such feature-based pharmacophore models have found extensive use in medicinal chemistry for hit-and-lead identification, and during the subsequent lead to candidate optimization. The simplicity of pharmacophore representations does also inevitably mean that it cannot explain everything about the binding of a ligand to its biological target. It is therefore crucial to understand the limitations of the concept as an essential pre-requisite for a successful application.

The author's group at Innsbruck University used a wide variety of different computational molecular design methods before entering into the design and implementation of new software prototypes [15,16]. It was no coincidence that they aimed at the development of new, more accurate, and more user friendly pharmacophore modeling tools later on. Most of the effort invested into the design of these tools, such as LigandScout [17] has been devoted to creating an intuitive graphical user interface, allowing users to get into a productive state very quickly. In the recent past, these tools have become widely used, not only by computational chemists, but much more by medicinal chemists, both in academia and in industry, who rely on them to support them in their daily work at the bench.

The large number of papers published in recent years, together with the increasing interest of researchers in the field of feature-based pharmacophore modeling in drug discovery is obviously a consequence of the fact that many other virtual screening approaches, such as structure-based docking, did not fully meet the expectations people had for them. The biggest issue of the latter is still remaining, the correct prediction of free binding energy. The scoring functions used for this task may work well each in special application cases for which they were tuned to. In other target families, they will likely fail. Since docking and scoring is computationally expensive and since ranking of hits is still not possible with satisfactory accuracy, the simple concept of 3D feature-based pharmacophores has again gained more than significant interest. The pharmacophore concept continued to consider the need to understand, explain, and predict molecular interactions with the targets as well as structure–activity relationships. Its practical applicability for medicinal chemists makes it an excellent communication tool between modelers and synthetic chemists. Pharmacophores are of unambiguous simplicity and usefulness for searching structural databases [18].

Accordingly, due to their computational efficiency in database mining, their importance will largely increase in parallel screening software based on pharmacophores together with publicly or commercially available collections of pharmacophore models covering important targets, as well as anti-targets. This, in fact, allows for rapid bioactivity profiling of compounds

even before they are synthesized and will also drastically enhance the library design process. Several studies about pharmacophore-based ligand profiling [19–22] and target fishing [23–25] have been published so far. The results indicate that these methods can compete well with other approaches based on scalar descriptors or on molecular docking and scoring [26,27]. However, with the advantage that information can easily be traced back from virtual space into molecular structure information, pharmacophore-based modeling enables a successful interaction between a computational chemist and his medicinal chemist counterpart.

In the pharmacophore perception area there is still a lot of room for research aimed at the improvement of methods or even the design of novel algorithms. In view of the growing quantity of chemogenomics data available, automated methods for pattern recognition-based pharmacophore generation are needed and currently being developed. On the other hand, enhancement of search efficacy is of utmost importance, especially when parallel (or inverse) screening for affinity profiling is envisaged. Applying a 'fail early, fail safe' strategy using a geometrically more accurate 3D alignment algorithm has recently been shown to improve virtual screening results over conventional incremental n-point distance matching approaches [28]. Including fingerprint descriptors as a first step of filtering before 3D conformation matching is likely to further enhance search performance.

Both in the pharmaceutical industry and software companies specialized in computer-aided molecular design, the demand for experts in the field interfacing medicinal chemistry and computer sciences will increase within the next decade. The concept of pharmacophores is truly a concept that has stood the test of time and is therefore likely to play an important role in drug research for many more years to come. There is no doubt that we will experience an exciting period of substantial progress in pharmacophore-based virtual screening technologies in the near future.

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