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GENERAL REVIEW

Combining bioinformatics, chemoinformatics and experimental approaches to design chemical probes: Applications in the field of blood coagulation☆

Association d'approches bioinformatiques, chémoinformatiques et expérimentales pour la conception de sondes pharmacologiques : applications dans le domaine de la coagulation sanguine

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Summary Bioinformatics and chemoinformatics approaches contribute to the discovery of novel targets, chemical probes, hits, leads and medicinal drugs. A vast repertoire of computational methods has indeed been reported over the years and in this review, I will briefly introduce some concepts and approaches, namely the analysis of potential therapeutic target binding pockets, the preparation of compound collections and virtual screening. An example of application is provided for two proteins acting in the blood coagulation system. Overall, *in silico* methods have been shown to improve R and D productivity in both, academic settings and in the private sector, if they are integrated in a rational manner with experimental approaches. However, integration of tools and pluridisciplinarity are seldom achieved. Efforts should be

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done in this direction as pluridisciplinarity and a true acknowledgment of all the contributing actors along the value chain could enhance innovation and reduce skyrocketing costs.

MOTS CLÉS
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Poches de fixation de ligands ;
Criblage virtuel ;
Coagulation sanguine

Résumé Les approches bioinformatiques et chémoinformatiques contribuent à la découverte de nouvelles cibles, de sondes chimiques et de médicaments. Un vaste répertoire de méthodes a été développé ces dernières années et dans cette revue seront brièvement présentés quelques concepts et certaines approches, notamment l'analyse des poches des cibles thérapeutiques, la préparation des chimiothèques et le criblage virtuel. Un exemple d'application est donné et concerne deux protéines impliquées dans la coagulation sanguine. Globalement, il a été démontré que les approches *in silico* améliorent la productivité dans les milieux universitaires et instituts de recherche académique et dans le secteur privé, si elles sont intégrées de manière rationnelle avec des approches expérimentales. Toutefois, cette intégration de méthodes et la pluridisciplinarité se produisent encore assez rarement. Des efforts doivent être faits dans ce sens car la pluridisciplinarité associée à une véritable reconnaissance de tous les acteurs qui contribuent le long de cette chaîne de valeur pourrait stimuler l'innovation et contribuer à la réduction des coûts de manière significative.

Introduction

Bringing new drugs (e.g., low-molecular-weight chemical (LMW) compounds, biologics, vaccines) to market is a long and costly process, generally characterized by a very low probability of success [1—12]. As such, all the relevant technologies and skills should be used in a rational manner to increase the chance of success.

Different experimental approaches are being used today to discover novel LMW (the focus of this review) probes and drug candidates, such as target-based high-throughput screening (HTS) [13], phenotypic screening [14], fragment-based screening [15,16], among others. The choice of the approach will often be linked to the level of knowledge, technologies and assays available at the beginning of a project bearing in mind that all approaches have strengths and weaknesses. As an example, the traditional target-based small molecule drug discovery workflow [3,4] begins with target(s) identification. This step involves: analysis of the disease mechanism, genomics to rank genes with respect to physiological functions and proteomics to identify candidate proteins and protein networks that could be modulated by a drug [17]. In a second step, the target is validated as much as possible using genetic engineering, transgenic animal models, antisense DNA/RNA or chemical probes among others. Once some targets are expected to be important in a disease process, it is necessary to find and then optimize small molecules that can act on them. This step requires experimental screening of a usually large compound collection, the so-called HTS approach [13]. These initial hits have to be optimized in terms of potency/efficacy, selectivity, ADME-Tox (absorption, distribution, metabolism, excretion and toxicity) and pharmacokinetics (PK) properties to achieve relevant therapeutic effects. Along the process, it is important to align the target, clinical goals and chemical properties in such a way that a target product profile gets defined (i.e., a listing of the essential attributes required for a specific drug to be a clinically successful product and to be of substantial benefit over existing therapies) [4]. After years of research (e.g., 5—7 years or more), if the small molecules are deemed appropriate, clinical trials can start. From this short overview of the process, it is clear that developing a new drug from the original idea to the launch of the final product is a very complex endeavor. Such projects thus require many different skills, some luck and the use of several ever-evolving technologies [18].

In this review, as mentioned above, I will focus on small molecules and on *in silico* methods that can assist the process or in some cases drive the process. There are indeed many methods and databases that usually require years of development (not mentioning maintenance) that can be used in a drug discovery project (many tools are listed at http://www.vls3d.com [19]). Novel algorithms and new hardware advances have also led to an impressive improvement in the time needed to complete a calculation allowing in some cases to process millions of compounds in just a few minutes. The application of several computational approaches, if used in a rational manner and fully integrated in the discovery process, as estimated by Pricewaterhouse-Coopers (a consultancy) could save up to 2—3 years over the whole process and about 200 million dollars. In fact, *in silico* approaches can definitively help drug discovery as recently reported in two reviews published by scientists from pharmaceutical companies [20,21] but it is also known that there is room for improvements. Indeed numerous opportunities to optimize the methods are present given

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