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REVIEW ARTICLE

Application of computational methods for anticancer drug discovery, design, and optimization

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Computer-Aided Drug Discovery and Design (CADDD);
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Cancer

Abstract Developing a novel drug is a complex, risky, expensive and time-consuming venture. It is estimated that the conventional drug discovery process ending with a new medicine ready for the market can take up to 15 years and more than a billion USD. Fortunately, this scenario has recently changed with the arrival of new approaches. Many novel technologies and methodologies have been developed to increase the efficiency of the drug discovery process, and computational methodologies have become a crucial component of many drug discovery programs. From hit identification to lead optimization, techniques such as ligand- or structure-based virtual screening are widely used in many discovery efforts. It is the case for designing potential anticancer drugs and drug candidates, where these computational approaches have had a major impact over the years and have provided fruitful insights into the field of cancer. In this paper, we review the concept of rational design presenting some of the most representative examples of molecules identified by means of it. Key principles are illustrated through case studies including specifically successful achievements in the field of anticancer drug design to demonstrate that research advances, with the aid of *in silico* drug design, have the potential to create novel anticancer drugs.

PALABRAS CLAVE
Descubrimiento y diseño de fármacos asistidos por ordenador;

Aplicación de métodos computacionales para el descubrimiento, diseño y optimización de fármacos contra el cáncer

Resumen El desarrollo de un nuevo fármaco es un proceso complejo y arriesgado que requiere una enorme cantidad de tiempo y dinero. Se estima que el proceso estándar para producir un nuevo fármaco, desde su descubrimiento hasta que acaba en el mercado, puede tardar hasta

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Predicción de blancos;
Farmacóforo;
Identificación de hits;
Optimización de líderes;
Cáncer

15 años y tener un costo de mil millones de dólares (USD). Por fortuna, este escenario ha cambiado recientemente con la llegada de nuevas tecnologías y metodologías. Entre ellas, los métodos computacionales se han convertido en un componente determinante en muchos programas de descubrimiento de fármacos. En un esfuerzo por incrementar las posibilidades de encontrar nuevas moléculas con potencial farmacológico, se utilizan técnicas como el cribado virtual de quimiotecas construidas con base en ligandos o estructuras para la identificación de hits y hasta para la optimización de compuestos líder. En lo que respecta al diseño y descubrimiento de nuevos candidatos a fármacos contra el cáncer, estos enfoques tienen, a la fecha, un impacto importante y aportan nuevas posibilidades terapéuticas. En este artículo se revisa el concepto del diseño racional de moléculas con potencial farmacológico, ilustrando los principios clave con algunos de los ejemplos más representativos y exitosos de moléculas identificadas mediante estas aproximaciones. Se incluyen casos desarrollados en el campo del diseño de fármacos contra el cáncer con la finalidad de mostrar cómo, con la ayuda del diseño asistido por computadora, se pueden generar nuevos fármacos que den esperanza a millones de pacientes.

1. Introduction

The Nobel Prize in Physiology or Medicine 1945 was awarded jointly to Ernst Boris Chain, Sir Howard Walter Florey and Sir Alexander Fleming for the mass production of penicillin discovered by the latter almost two decades before. At that time, the average life expectancy at birth in Mexico was about 45 years.[1] Currently, life expectancy for newborns is around 75 years. This increase can be explained by many factors, including the significant amount of medication that physicians prescribe today to extend the life of a patient.

Most of the effects of medicines are based on the interaction between therapeutic chemical compounds (drugs) and proteins (targets), such as G-protein-coupled receptors, ion channels, proteases, kinases or nuclear hormone receptors, among others. Therefore, we might wonder how many new drugs are still to be discovered by researchers. The answer would be almost an 'unlimited' quantity. The number of potential targets remains unclear. However, recent estimates claim that the number of current targets is over an order of magnitude lower than it could be.[2,3] On the other hand, the number of organic molecules that can act as drugs is also a matter of debate. More than 100 million small chemical compounds have been already synthesized for their screening on specific targets in public and private laboratories.[4] In addition, it is not only a matter of quantity but also of quality. Until recently, medicines have been discovered either as a result of unexpected investigations—by inspection of natural substances traditionally considered as therapeutic—or in extensive experimental blind screening studies.[5] These drugs, although proven to be useful in the treatment of several pathologies, have significant downsides, like important side effects or low efficiency. As they were discovered, not designed, new drug generations have to overcome these difficulties.

The process of discovery and development of novel drugs is known to be time-consuming and expensive. On average, the standard process of discovery and development of drugs to marketing takes from 10 to 15 years. Furthermore, the average cost for research and development of each effective drug is estimated at $1.8 billion USD.[6] In this context, it is not surprising that the development of new strategies over the last decades has emerged to make the processes much more rational and efficient using new supercomputers combined with the knowledge and experience of researchers. To this day, physicians, biologists, chemists, physicists, and computer scientists work, hand in hand, with the goal of offering to patients better and more selective drugs to improve their quality of life. Nevertheless, there is still a long way to go in the field of drug discovery, or should we say, drug design?

In this article, we first introduce the concept of computer-aided drug discovery and design with a summary of the leading computational techniques that include drug-repositioning approaches and lead optimization techniques. In the second section, we describe how these approaches have been successfully applied. In addition, we review the concept of rational design and present some of the most representative examples of molecules identified by its means. Key principles are illustrated through case studies exploring the field of anticancer drug design to demonstrate that research advances, with the aid of *in silico* drug design, have the potential to create novel anticancer drugs.

2. Computer-aided drug discovery and design

Since the advent of the X-ray diffraction to unveil the chemical composition and three-dimensional (3D) geometry of a small organic molecule in 1932,[7] a large number of proteins have been solved either by X-ray or by nuclear magnetic resonance (NMR) spectroscopy and are available at open access protein databases (http://www.rcsb.org). This information allows researchers to understand and characterize many physiological processes based on interactions between proteins or between proteins and small molecules (ligands), as the case of the drug-target binding.

In 1962, Max Perutz and John Kendrew were awarded the Nobel Prize in Chemistry for the first solved high-resolution structure of protein (myoglobin). Since then, several other

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