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Commentary

Screening and Design in Drug Discovery

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ABOUT THE STUDY

Drug discovery is the process through which innovative candidate pharmaceuticals are discovered in the fields of medicine, biotechnology, and pharmacology. In the past, drugs were discovered accidentally, like penicillin, or by extracting the active ingredient from therapies that were already in use. In more recent times, a method called classical pharmacology has been used to screen chemical libraries of synthesised small molecules, natural products, or extracts in intact cells or whole organisms in order to find substances that had the desired therapeutic effect [1]. Since the sequencing of the human genome made it possible to quickly clone and synthesise huge quantities of purified proteins, it has become standard practise to use high throughput screening of large compound libraries against isolated biological targets that are hypothesised to be disease-modifying. This technique is known as reverse pharmacology. The efficiency of the hits from these screenings is subsequently examined in cells and then on animals. Modern drug development processes include the identification of screening hits, medicinal chemistry, and optimization of those hits to increase their affinity, selectivity, efficacy/potency, metabolic stability, and oral bioavailability. Once a molecule has been discovered that meets each of these requirements, drug development can start. If successful, clinical investigations are developed [2].

Screening and design

In order to locate a new drug against a predetermined target for a particular condition, High Throughput Screening (HTS), in which enormous chemical libraries are examined for their capacity to modify the target, is commonly used. Chemicals will be tried to see if they can stimulate or inhibit a target, such as a novel GPCR [3]. Likewise, if the target is a protein kinase, chemicals will be tested to see if they can inhibit that kinase. Another goal of HTS is to show how selective the compounds are for the chosen target, as the goal is to develop a molecule that will only interact with the chosen target and no other, related targets. In order to accomplish this, cross-screening is the process of detecting if "hits" against the selected target would interfere with other related targets. Cross-screening is advantageous because the more unrelated targets a medicine hits after it enters the clinic, the greater the likelihood that it may cause off-target toxicity [4]. There is a low probability that the optimum medicine candidate will emerge from these initial screening runs. Screening for compounds that are unlikely to be used as drugs is one of the first steps; for example, compounds that are hits in almost all assays and are referred to as "pan-assay interference compounds" by medicinal chemists are eliminated at this stage, if they haven't already been removed from the chemical library. Multiple chemicals with different levels of action are common. If these chemicals share chemical characteristics, a pharmacophore or more can be built [5]. In order to improve particular qualities of the lead chemical, such as activity against the chosen target, activity against unrelated targets, drug similarity or ADME properties, medicinal chemists will now attempt to use Structure-Activity Relationships (SAR) [6].

Phenotypic screens have also enabled the discovery of novel chemical starting points for medication development. Models of all kinds have been used, including those based on yeast, zebrafish, worms, primary cell lines, patient-derived cell lines, immortalised cell lines, and whole animals [7]. These screening techniques are used to find compounds that counteract disease characteristics including mortality, protein aggregation, mutant protein expression, or cell proliferation in a more complete cell model or organism. Smaller screening sets are typically employed for these screens, especially when the models are expensive or time-consuming to run. Long target deconvolution tests may be necessary because it is frequently uncertain how exactly these screens' hits work. The growth of the science of chemoproteomics has enabled a variety of approaches to identify therapeutic targets in these circumstances. If a lead chemical series has been created with adequate target potency and selectivity as well as favourable drug-like properties, one or two compounds will then be recommended for drug development [8].

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