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Early Drug Development Principles

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Perspective

A drug development programme begins when there is a disease or clinical condition for which there are no viable medicinal products and this unmet clinical need is the project's underlying driving motivation. The initial study, which is frequently conducted in academia, generates data to support a hypothesis that inhibiting or activating a protein or pathway will have a therapeutic effect in a disease state. The selection of a target is the result of this activity, which may require additional confirmation before moving on to the lead discovery phase in order to justify a drug discovery endeavour. During lead discovery, a comprehensive search is conducted to identify a drug-like small molecule or biological therapy, referred to as a development candidate, that will progress through preclinical testing, clinical development, and, if successful, commercialization.

Drugs fail in the clinic for two primary reasons: first, they do not work, and second, they are not safe. As a result, target identification and validation is one of the most crucial processes in the development of a novel medicine. A target is a general term that can refer to a wide range of biological entities, such as proteins, genes, and RNA. A good target should be effective, safe, suit clinical and commercial needs, and, most importantly, be 'druggable.' A 'druggable' target is one that is accessible to the potential drug molecule, whether it is a small molecule or a larger biological, and elicits a biological response that can be assessed both in vitro and in vivo after binding. Certain target classes, like as G-protein-coupled receptors (GPCRs), are more receptive to small molecule drug development, whereas antibodies are better at blocking protein/protein interactions. Good target identification and validation increases confidence in the target-disease link and allows us to investigate whether target modification will result in mechanism-based side effects [1].

Target identification has increased significantly as a result of data mining of available biological data. Data mining, in this sense, refers to the use of a bioinformatics technique to not only identify but also select and prioritise prospective disease targets [2]. Publications and patent information, gene expression data, proteomics data, transgenic phenotyping data, and chemical profiling data are among the data sources provided. Examining mRNA/protein levels to see if they are expressed in disease and if they are linked to disease exacerbation or progression is another method of identification. Another effective strategy is to look for genetic connections, such as if a genetic variant is linked to the risk of disease or disease progression, or whether the polymorphism is functional. For example, familial Alzheimer's Disease (AD) individuals frequently have mutations in the amyloid precursor protein or currently genes, which result in higher production and deposition of the Abita peptide in the brain, which is a hallmark of AD [3]. In humans, there are also phenotypes where mutations can negate or over activate receptors, such as the voltage-gated sodium channel NaV1.7, where both mutations cause pain phenotypes of insensitivity or oversensitivity [4].

Phenotypic screening is an alternate method for identifying disease-relevant targets. Employed a phage-display antibody library to isolate human Monoclonal Antibodies (MAbs) that bind to the surface of cancer cells in an elegant experiment. Immunohistochemistry was used to screen individual clones, and those that stained the cancer cells preferentially and strongly were chosen. Immunoprecipitation was used to isolate the antigens recognised by those clones, and mass spectroscopy was used to identify them [5]. They found 21 different antigens significantly expressed on numerous carcinomas among 2114 mAbs with unique sequences, some of which may be viable targets for corresponding carcinoma therapy and some mAbs that may become therapeutic agents.

The target must then be fully prosecuted after being identified. Validation methodologies span from in vitro tools to complete animal models to illness patient manipulation of a targeted target. While each strategy is valid in its own right, a multi-validation approach considerably boosts confidence in the observed conclusion [6].

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