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Molecular Drug Targets and Drug Delivery

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Abstract

The ultimate goal of Precision Medicine Initiative is to generate therapies tailored to individual patients. Such therapies will need targeted precision drugs. Challenges involved in this task are discussed, and approaches to developing such drugs are suggested.

Keywords: Precision Medicine Initiative; Molecular Drug Targets; Drug Delivery; Targeted Precision Drugs

Introduction

Precision MedicineInitiative (PMI), a research project created by President Obama in 2015 with $215 million in funding, aims to collect genetic and other health data on a vast scale and use it to understand the way individuals respond differently to treatments and therapies. Further intention is to develop a medical model for customization of healthcare, with medical decisions, practices, and products being tailored to the individual patient.

Here I focus on the "product" of PMI which by necessity must be a targeted drug. The subject of this article is to consider the challenges faced by the process of utilizing the anticipated new knowledge into developing the PMI's ultimate outcome – precision drugs.

Targeted Precision Drugs

The term "targeted drugs" has been used broadly to describe drugs that act on general pathways that have been found to be associated with disease (but that also remains functional in normal cells), but it has also been used to refer to drugs approved for a selected and limited "target" population. In here, our interest focuses on drugs that interact specifically with a molecular structure, i.e., its target that has been clearly identified and validated as being uniquely associated with a given disease; therapeutic antibodies are probably the best example of targeted drugs.

Oncology is a therapeutic area that illustrates well the challenges in defining efficacy targets. According to the NIH National Cancer Institute [1] there are many different targeted therapies that have been approved for use in cancer treatment. These include hormone therapies that slow or stop the growth of hormone-sensitive tumors, signal transduction inhibitors that interrupt communications between a cell and its environment, gene expression modulators that modify the function of proteins that are involved in the process of gene expression, apoptosis inducers, angiogenesis inhibitors, and others. Most of these do not act solely on specific molecular targets of the disease as defined in the previous paragraph.

A landscape of molecular drug targets has been comprehensively discussed recently by Santos, et al. [2]. The authors examined a total of 893 human and pathogen-derived biomolecules that have so far formed a basis for 1,578 US FDA-approved drugs. These biomolecules include 667 human-genome-derived proteins targeted by drugs for human disease. It would seem that there is enough basic material on which to

develop targeted drugs until the PMI generates new actionable information.

So how can this information be used to develop site / cell-specific drugs? Korcsmaros, et al. [3] reported that "despite improved rational drug design and a remarkable progress in genomic, proteomic and high-throughput screening methods, the number of novel, single-target drugs fell much behind expectations during the past decade".

What does it take to define a drug target?

The initial basic research, primarily originating from academia, generates data on basis of which a hypothesis can be generated that inhibition or activation of a protein or pathway may result in a therapeutic effect in a disease state [4]. A prospective target will require further validation before it can be used to initiate a lead-discovery phase of drug-development process. Search for targets typically focus on proteins, genes and RNA. A target of use for drug development needs above all to be 'druggable', meaning that it is accessible to the putative drug molecule, and upon binding it elicits a measurable biological response relevant to the disease under investigation. In this phase, effort is made to find small molecule or biological therapeutic molecules that could be examined further at pre-clinical (initial target identification and validation, assay development, high throughput screening, hit identification, lead optimization) stage. Provided a compound becomes a candidate molecule for clinical development, its safety and efficacy needs first to be shown in animals before it is progressed to testing in tightly-controlled human clinical studies. Such efforts, when successful ultimately generate marketed medicines.

Development of Targeted Precision Drugs

Validation techniques used include *in vitro* tools, the use of whole animal models to establish safety and efficacy (phenotypic screening, gene association studies, chemo proteomics, transgenetic organisms, imaging, biomarkers, etc.) ultimately aiming to modulate the desired target in disease patients.

The conventional process of selecting new compounds as drug candidates has been using solubility and permeability assessments to evaluate the potential of a compound to be a drug. The reason is that in the conventional process of drug development, solubility plays a critical role in drug's bioavailability (e.g., access to a patient's circulation, absorption from the digestive system). Insoluble drugs have either been modified or formulated to increase their solubility, or discarded. As discussed in [5], drugs having low solubility but exhibiting *in vitro* high target selectivity (e.g., as determined by binding to specific disease-relevant molecular structures) should not be rejected; instead, it should be recognized that, for pharmacokinetic reasons, such drugs may be ideally suited to be "targeted", i.e., delivered to, and released in their active form at sites of disease [5]. For such new drugs, appropriate delivery system would need to be selected from the existing "armory" of delivery systems. It is likely that none of the existing systems proves to be adequate; hence, new, appropriately "tailored" combinations of drug and delivery system may need to be invented. Future development of site / cell-targeted drugs should adopt this broader approach to new drug selection.

The advents of mapping of the human genome, discoveries in molecular biology, and now hopefully new information generated by the PMI may eventually lead to stimulating and accelerating drug development towards the realization of targeted, precision drugs. So far, only few diseases (e.g., cancers) have benefited from developing drugs on the basis of our understanding of the genetic and biochemical basis of a disease in patient subgroups [6].

To generate a product tailored to individual patients, PMI will need to utilize or generate

- A clear, definitive diagnosis of a given disease,
- A clearly identified and defines molecular target of the disease – unique, not a general one. In other words, the target should not be a molecular pathway operating both in the basis of the disease as well as in non-disease state; the target needs to consist of specific molecular features associated solely with the disease.

Such clearly defined disease molecular target would then be used to develop a drug that very specifically interacts with the target and exert a pharmacological effect. If this is indeed achieved with a small molecule, there may not be much need for developing a delivery system for such a drug.

Currently, a vast majority of medicines derive their therapeutic activity from interacting with a protein target, either boosting or inhibiting its function. It is estimated that there are two million proteins in the human body. There is for PMI much to choose from, and a long way to make its mark.

There have always been many failures in the process of drug discovery and development, for a number of reasons. One of the reasons is surely our lack of understanding of the underlying causes or pathways of a disease. Developing drugs for Alzheimer's can be used as an illustration – to date, "promising" biomarkers (such as amyloid plaque), when tested, have all failed to predict clinical improvement.

Defining whether a drug is "targeted" should be based on data. The FDA categorizes anti-cancer approved drugs into three categories – a) cytotoxic agents that act on human DNA and/or RNA, b) cytotoxic agents that act at least partially through protein targets, and c) drugs that the FDA considers to be "targeted therapeutics" [1]. However, the actual assignment of a drug to the third group rather than the second group is complicated by the broad spectrum of targeting observed. Many of the drugs (such as topoisomerase inhibitors) are selective for their targets but are highly toxic. Some kinase inhibitors show a wide range of normally functioning kinases and their associated pathways, but also adverse reactions. Classifying drugs as being "targeted" to their structural focus of biological activity when the therapeutic activity of the drug is accompanied by side effects is highly questionable. Target definition is likely to become even more difficult in case of genetic variations in order to characterize clinical efficacy and safety, and predict drug utility in individual patients or in patient subgroups.

Future Challenges

PMI is likely to add information about the causes of complex disease. Considering that disease conditions may arise from a combination of environmental factors, genetic and epigenetic dysfunction, our true understanding of disease may not become any clearer.

Given such complexity, will the relative "simplicity" of targeted drug delivery, targeted therapy and precision drugs actually work? Thus, will a reductionist approach to targeted therapy still have a role in the future? Some argue that "an armory of mechanistically sophisticated and thoroughly experimentally annotated drugs that target this complexity is required", and envisage a role for drug combinations, network drugs [7] and "polypharmacology" [8]. To quote Aristotle: "The more you know, the more you know you don't know." So, it is quite conceivable that the "ideal", "perfect" precision drug as we would like to see it – with very high target selectivity, high efficacy and no side effects will remain in the land of Utopia.

It has been long recognized that an important part of drug discovery is serendipity. Developing targeted drugs should be a less unpredictable process as it should, and can be based on a more extensive, validated information, derived from new insights into disease and fundamental biology that are emerging, understanding of the associations between currently successful drugs, their efficacy targets, phenotypic effects and disease indications that have been reported [1]. All this should aid efficient discovery of a new generation of medicines. Selected drug targets should have a critical role in the disease process with less significant involvement in other important processes to limit potential side-effects, have an expression pattern allowing for drug efficacy by, for example showing tissue-specific expression, and have structural and functional properties allowing for drug specificity.

Two directions for developing "precision drug" would seem to emerge from the above considerations:

1. Developing molecular structures that bind uniquely to targets that have been validated to be associated solely with molecular targets of the disease origin, progression, or elimination. These are likely to be small molecules with an ability to reach the targets in various locations of the body. In this case, there may not be any need to employ drug carriers; an optimal formulation should suffice.
2. Genetic material needs to enter cells to interact with its intra-cellular target. In most cases it cannot do it by itself, (but naked DNA can be made to enter cells using electric current – i.e., by electroporation [9]) and hence a carrier needs to be employed. Carriers most commonly used in gene therapy are viruses, liposomes and nanoparticles. Clearly, vehicles to deliver genes must be able to recognize and deliver their "pay load" to specific cell types. However, none of the vehicles has so far been found entirely satisfactory.

Currently, there are 3541 genes listed in the UniProt database for which there is experimental evidence that the genes are involved in various disease conditions, including cancer, neurologic, systemic and cardiovascular disease. Some 1129 of these have been deemed as being of possible interest as potential drug targets because they belong to known drug-target protein classes i.e., enzymes, transporters, receptors and ion-channels, and as such have not yet been targets for FDA approved or experimental drugs [10,11].

Conclusion

It is apparent that there is no need to wait for the efforts of the PMI to produce new knowledge and new data. There is enough known for us to start working towards generating precision drugs. The past failures need to be recognized, avoided, and built on.

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