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On Rational Design of Precision Drugs

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Perspective

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Abstract

The rational design of perfect precision drugs must be based on a precise definition of the disease's molecular target. This article offers a perspective on how the current drug development process needs to change to respond to this demand. This is not a review. However, the article refers to the past drug development to illustrate what needs to be done to progress to the next stage, namely the development of precision drugs–drugs that would act on diseases with no, or at least very much reduced side effects. To this end, unique molecular structures associated with diseases must be identified, followed by developing drugs that would bind specifically to such structures. Finally, future drug development must adopt this new paradigm.

Keywords: Precision Drugs; Rational Design; Molecular; Paradigm; Pharmacodynamic

Introduction

The creation of "perfect" drugs that would cure diseases without side effects has been contemplated now for over one hundred years; not a long time, given that, according to the current guestimate, it has taken some 4 billion years for "a freak accident" of simple cells to give rise to a complex life form.

Most drugs distribute freely throughout the body regardless of the disease location. Consequently, relatively large doses of conventional drugs need to be used to reach the drugs' pharmacodynamic concentration at the disease sites. Countless attempts have been made to deliver drugs close to their intended place of action, hoping to improve the efficacy and reduce side effects. For example, for targeting cancer, the rationale is that more potential drug targets are expressed on the cancer cell surface than healthy cells. Hence, anti-cancer drugs would accumulate preferentially at the disease sites when delivered locally. Marginal improvements in efficacy have been made with some delivery systems. But in most cases, such as with cancer, the overall outcome is that both normal and cancer cells are acted on by drugs, leading to significant and often life-threatening side effects.

Many ingenious approaches have been designed and tested to deliver drugs to selected sites for both therapeutic and diagnostic purposes; when combined, the application is referred to as theranostic. A PubMed search on Jan 1, 2022, for "cancer drug targeting" identified 265,363 publications; this extensive research effort has produced little to contribute to developing precision drugs.

Theranostics tries to utilize the response of materials to the body's endogenous stimuli associated with the disease. Endogenous factors such as enzymes, pH, glucose, ATP, hypoxia, redox signals, and nucleic acids have been considered in disease conditions such as cancer, diabetes, vascular disorders, inflammation, and microbial infections [1].

Many attempts have been made to achieve spatial control using particles of various sizes, shapes, surfaces, etc., to avoid recognition by the immune system and localize to specific organs [2,3].

However, effective design needs to start when applied to drug delivery by defining the desired specific and unique molecular target of the given pathology and efficacy to guide the drug-development process (e.g., a route of administration, formulation, component characteristics, etc.).

Drug delivery of the existing non-specific drugs to a particular tissue often ignores that the drug's pharmacokinetics plays a crucial role and must be considered [4,5].

So, how successful are pharmaceutical drugs?

Antimicrobials are a very successful form of chemotherapy, having saved many lives by enabling us to control bacterial infectious diseases that were the leading cause of human morbidity and mortality. However, a similar breakthrough to treat viral infections is still to be achieved. Cancer caused nearly 10 million deaths in 2020 [6]. Apart from drugs, cancer treatments include localized therapies, such as surgery, radiation therapy, cryotherapy, heat or chemical ablation, and/or systemic therapies (e.g., chemotherapy). Therefore, it would be ungrateful to be overly critical of the limitations of drugs that have been made available so far. However, there are very few safe and effective treatments for many diseases, including cancer [7].

This article argues that specific drugs could be designed once a unique molecular target of a disease is known. Targeting ligands combined with delivery systems would not be necessary in this case.

Sometimes, madness is defined as "doing the same thing and expecting different results." For example, the quote "Repetition makes a fact seem more true, regardless of whether it is or not" also applies to scientific efforts. "Repeat a lie often enough, and it becomes the truth" law of propaganda often attributed to the Nazi Joseph Goebbels is in psychology known as the "illusion of truth" effect. Research in drug delivery has been repetitive. "Inventive" approaches are developed without considering the fundamental requirements of disease targeting [8,9].

Antibodies may be the closest current compounds to the ideal drug, but they are by no means without side effects. Taking cancer as our "test ground," the task is to find unique molecular structures associated with the disease [10]. Is this possible? We do not know, but we do know that this would be the most likely way to develop a "perfect" therapy [11].

The way drug "targeting" is defined contributes to the "fuzziness" efforts made so far in this direction. Again, I quote: "Targeted therapy is a type of cancer treatment that targets proteins that control how cancer cells grow, divide, and spread. As researchers learn more about the DNA changes and proteins that drive cancer, they are better able to design treatments that target these proteins" [12]. This means that at present, targets that are being addressed are likely far removed from the origin of cancer; further, there are equally present on normal, non-cancer cells.

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Cancer cells are considered to be very different from healthy cells [13-16]. The differences include cell shape, nucleus shape and form, chromatin form, nucleoli, blood supply, cytoplasm, growth, maturation, oxygen use, location, and perhaps others. None of these differences uniquely define the disease cells.

Cancer cells behaviour also differs from normal cells by
- Growing in the absence of signals to grow.
- Not responding to signals to stop dividing or to die (programmed cell death, or apoptosis).
- Invading adjacent areas and metastasizing to more distant areas.
- Promoting angiogenesis to generate blood vessels to supply tumors with oxygen and nutrients.
- Becoming inconspicuous to the immune system, avoiding removal.

Although some research has utilized some of the above differences in developing therapies, these differences are not sufficient to allow exclusively targeting cancer cells. A more progressive notion of cancer origin and development argues that cancer is a genetic disease; errors in genes may alter the way cells divide and grow. Such alterations may be inherited from one's parents or can be caused by harmful substances in the environment, such as the ultraviolet light from the sun.

Each person's cancer has a unique combination of genetic changes. As cancer continues to grow, additional changes will occur. Even within the same tumor, different cells may have different genetic changes. This picture of cancer does not offer an easy target for treating the disease unless one finds a way to silence the aberrant genes. A few of these treatments can be used by anyone with cancer that has the targeted mutation, no matter where cancer started growing [17,18]. Regardless of how complex an issue might be and how diseases such as cancer are initiated, it is reasonable to say that there must be a starting point. If so, can we find it?

Changing the Paradigm

If we have the starting point, we might be able to act on it and stop the disease. Treating any disease involves dealing with a complex network of interactions between chemical agents, their targets, and effects on numerous biological

pathways that could be utilized for drug discovery and development. Reaching an understanding of interactions will no doubt require combined efforts of medical sciences, biology, biochemistry, and related disciplines pulling and pooling together all that information by a "very intelligent" artificial intelligence (AI), enabling the generation of an insight into the biological foundation of diseases and drug effects. The task will no doubt be very difficult and time-consuming but would at least "in principle" promise a better outcome compared to the existing "single target" and "shotgun" research paradigms, generating more disease-specific, more effective, and safer drugs. It might offer an opportunity to identify a single agent or at least a very narrow combination of agents acting on a single target associated with a disease.

After decades of unsuccessful attempts to realize the concept of the "magic bullet", network pharmacology was suggested to replace the current rational drug design paradigm of "one gene, one drug, one disease" by searching for multitarget drugs acting as "magic shotguns" [19-21].

It has been challenged that the increased understanding through network biology of biological processes would lead to identifying a single molecular target for drug discovery [22,23]. However, there must be a starting point, whether the disease origin requires single or multiple factors. Whether a "shotgun" approach can generate more effective therapies associated with fewer serious side effects remains to be demonstrated [24].

The network pharmacology approach has been applied to single synthetic therapeutic agents and natural compounds. Ma et al. identified 38 baicalein targets and 76 differently expressed genes (DEGs) following treatment with baicalein, including 55 upregulated and 21 downregulated genes. The DEGs were significantly enriched in the biological functions of apoptosis, endoplasmic reticulum stress, and PERK-mediated unfolded protein response. Protein-protein interaction (PPI) network construction and topological screening revealed a core module of PPIs, including two baicalein targets, TP53 and CDK1, and two downregulated DEGs, HSPA1A and HSPA1B. In the module derived from Gene Expression Profiling Interactive Analysis (GEPIA), expression and survival data for these genes were subjected to Kaplan–Meier analysis of overall survival and disease-free survival. Overexpression of CDK1, BRCA1, TUBB, HSPA1A, HSPA1B, and HSPA4 was associated with significantly worse overall survival, while overexpression of CDK1, CLU7, BRCA1, and TUBB was associated with significantly worse disease-free survival. These data suggest that baicalein exerts therapeutic effects against HCC via a PPI network involving TP53, CDK1, HSPA1A, and HSPA1B. In addition, the authors proposed that EEF1A1, MDM2, CUL7, and BRCA1 were linked strongly with HCC, taking part in cell growth, cell cycle regulation, and the maintenance of cell survival [25].

Network pharmacology helps systematic characterization of drug targets. Ideally, this might change the need for effective drugs acting on multiple (the disease and normal) cells, limiting the beneficial effects to single targets present on single cells, making the failure of drug-discovery projects due to unacceptable side effects less frequent [26-28].

This development is further supported by the rapidly increasing computational biology capabilities that can guide scientific experimentation by realistic modeling and theoretical examinations. Network pharmacology can merge molecular networks integrating multidisciplinary biochemical, bioinformatics, and systems biology, additionally supported by steadily increasing capabilities of Artificial Intelligence (AI) [29]. However, a new paradigm needs to be introduced into network pharmacology that identifies molecular interactions and biological processes unique to a particular disease.

The processes involved in Network Pharmacology Research consist of

- Data collection and validation (the selection of original experimental data and experimental validation for the predicted network model) [30-32].
- Network Analysis and Visualization to establish a network using related technology and extract information useful for further studies [33-35].

Network pharmacology has been applied extensively to Traditional Chinese Medicine [36]. Results reported by Ma et al. provide a fitting example of what data might be generated using an *in silico* network pharmacology approach. Examining the anti-HCC effect of baicalein on hepatocellular carcinoma, the authors reported that it was related to endoplasmic reticulum stress, apoptosis, oxidative stress, and the p53 signalling pathway and involved 14 proteins. The study speculated that CDK1 and TP53 might be baicalein targets to downregulate the expression of HSP70 [37].

Many drug-activated targets associated with a number of diseases were identified using the disease gene networks and meta-analysis [38,39]. Networks examine databases to find modes or rules, detect the literature information, analyze selected data, and discover novel effects of various interactions [40,41]. However, network results are by no means simple and clear. Wu, et al., obtained information by text mining Chinese Pharmacopoeia and constructed the TCM formulation (slices)-symptom network. The authors reported 3,016 pairs of TCM slice-symptom correlations. Each TCM slice was correlated with 4.67 symptoms, and each

symptom was related to 7.47 TCM slices [41]. Examining the very extensive networks, such as herbal medicine interactions, may not be the best way forward.

Zhang, et al., proposed a computational framework for integrating protein-protein interactions, disease phenotype similarities, and known gene-phenotype associations to capture the complex relationships between phenotypes and genotypes [36]. The genome-wide prioritization of candidate genes for over 5,000 human phenotypes has been publicly released to facilitate the future discovery of disease genes. The approaches employed so far are unlikely to identify structurally unique molecular targets of disease. Further, the complexity of bioactive agents interacting with human biology suggests that the current drug safety evaluation may grossly underestimate and ignore potential, especially long-term risks.

Artificial Intelligence (AI)

AI has been defined (by Oxford Languages) as "the theory and development of computer systems able to perform tasks normally requiring human intelligence, such as visual perception, speech recognition, decision-making, and translation between languages [42]."

There are four distinct types of AI. Reactive AI is programmed to provide a predictable output based on the input it receives (e.g., Deep Blue, the chess-playing IBM supercomputer that bested world champion Garry Kasparov). Limited Memory AI learns from the past and builds experiential knowledge by observing actions or data. Theory of Mind AI has not been developed yet; it will give computers true decision-making capabilities that are similar to humans. Self-aware AI will be needed to implement the paradigm proposed in this article, having a level of consciousness and intelligence similar to human beings. This type of AI will have desires, needs, and emotions as well, and will be self-aware of their internal emotions and mental states. But it may not be enough. A super-intelligent AI that surpasses the current human intelligence may be needed to understand biological data and networks, make predictive analysis, design next experiments, interpret data, etc [43].

Recently, there has been growing interest in using artificial intelligence and big omics data to study the "network target" underlying traditional medicine. Hopefully, with the current progress in network pharmacology research techniques, more network-based analytical approaches could be assimilated into such a medical field in order to accelerate the comprehension of the nature of traditional medicine and divine the discovery processes of traditional medicine. Network pharmacology may facilitate the development of the future therapeutic strategy involving the integrated treatment of complex disorders through targeting a specific network. The boom in network pharmacology has prompted more clinicians and scientists to devote their attention and efforts to elucidate the possible mechanism of action underlying traditional therapeutics in recent years.

Numerous data sources are available from system pharmacology databases and analysis platforms (TCMSP) and SymMap databases to screen the active compounds and their targets. GeneCards, Therapeutic Target Database (TTD), and Online Mendelian Inheritance in Man (OMIM) databases have been used to find the targets corresponding to gout and hyperuricemia. Venn diagram was used to obtain the intersection targets of plantain and diseases. The interaction network of the plantain active compounds-targets-pathways-diseases was constructed by using Cytoscape 3.7.2 software. Finally, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were carried out [44].

For example, a network pharmacology-based strategy combined with molecular docking studies and in vitro validation was employed to investigate bioactive compounds, potential targets, and molecular mechanism of Zuo Jin Wan against colorectal cancer, identifying 36 bioactive ingredients and 163 gene targets. Quercetin, baicalein, wogonin, beta-sitosterol, and isorhamnetin were indicated as candidate agents acting on AKT1, JUN, CDKN1A, BCL2L1, and NCOA1 potential drug targets. The KEGG indicated that the PI3K-AKT signaling pathway might be involved in facilitating the effects against colorectal cancer. Molecular docking suggested that quercetin, baicalein, and wogonin combined well with AKT1 and JUN.

Applying network pharmacology to elucidate active ingredients, potential targets, and mechanisms of action underlies the complexity of biological systems. It also indicates what initial steps may need to be taken to unravel such complexity to identify unique molecular features and molecular targets that specific drugs could address.

How can we identify unique molecular features?

Studies have started to emerge to determine molecular features and clinical outcomes, for example, in non-small-cell lung cancer (NSCLC) harboring ALK fusion genes in young patients [45]. The study identified ALK fusions in 101 NSCLC patients. The most frequently occurring ALK fusion partner was EML4, identified in 80.8% (42/52) of young patients. It also identified rare ALK fusions, including CHRNA7-ALK, TACR1-ALK, HIP1-ALK, DYSF-ALK, and ITGAV-ALK; patients with these fusions responded well to crizotinib treatment. The study identified unique genetic characteristics of ALK-rearranged NSCLC patients.

Various forms of acute myelogenous leukemia (AML) are associated with many different translocations and genetic aberrancies. It has been generally accepted that AML consists of related but distinct diseases. Studies on leukemic stem cells (LSC) attempted to define LSC's shared developmental, cellular, and molecular features associated with different AML subtypes. Importantly, some features are unique to the leukemia stem/progenitor cells and are not present in normal hematopoietic stem cells (HSCs). The study concluded that "distinct molecular and cellular characteristics of the LSC population may provide new opportunities for AML therapy" [46].

Ramesha, et al., identified unique molecular features of Kv1.3-expressing CNS-MPs. The potassium channel Kv1.3 in brain myeloid cells is considered a possible therapeutic target for Alzheimer's disease (AD) [47]. However, the expression and functions of Kv1.3 channels in brain myeloid subpopulations and the microglial-versus-peripheral myeloid origin of Kv1.3-expressing cells in AD remain unclear. Kv1.3 has been shown in mice to be selectively upregulated in an Aβ-dependent manner by a subset of microglia-derived cells and expresses higher levels of pro-inflammatory genes. The presence of Kv1.3-expressing microglial subpopulations in human AD has been confirmed. Blocking Kv1.3 in an AD model reduced Aβ neuropathology, increased synaptic protein expression, and skewed the microglial transcriptome toward pro-phagocytic and protective phenotypes, offering preclinical rationales for targeting microglial Kv1.3 channels for AD therapeutic immunomodulation.

It would be unreasonable to expect or suggest that the conventional, somewhat "hit and miss" approach to drug discovery should be abandoned. Despite its inefficiency, it has produced therapeutic agents that have moderated the effects of many diseases, alleviating patients' suffering and even saving lives. However, too much information is available to identify a myriad of potential targets, providing a plethora of potential chemical candidates. At the same time, too few practical means are available for reducing candidates down to a manageable number. Serendipity has always been a part of drug discovery (Fleming, penicillin, for example).

However, with our increasing knowledge of disease biology and the availability of effective technology to analyze data and apply our knowledge, it is time to expand our paradigm and include the search for unique molecular features of diseases into our overall strategy. Developing a new drug involves the same process regardless of the disease. However, if the first step, selecting the drug target, is wrong, then the whole process is futile. This is the key reason why the average cost of advancing drugs to market approval is so high. According to Schlander, et al., the estimated total average capitalized pre-launch R&D costs range from $161 million to $4.54 billion (2019 US$), with the therapeutic area-specific estimates being highest for oncology drugs (from $944 million to $4.54 billion) [48].

Five key stages of drug development are needed to bring a new drug on the market: discovery, preclinical research, development (formulation, manufacturing, etc.), clinical research, and regulatory approval. Some 5,000–10,000 chemical compounds are screened for a new drug approved for use in humans, taking 10 to 15 years [49]. The first step is crucial in determining the eventual success of the drug.

Conclusion

It would be worth directing the huge current resource dedicated to conventional drug development to rational basic research identifying drug candidates based on unique molecular structures directly involved in the disease initiation and progression.

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