Discovery by Design

Advancing Drug Discovery — Beyond Design

Drug discovery based upon high-throughput screening, combinatorial chemistry and rational drug design faces not a practical but a conceptual hurdle: the redundancy inherent to biological systems.

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An unexpected phenomenon challenges the pharmaceutical industry. While global research funding has doubled since 1991, the number of new drugs approved has fallen by 50% (1). Different reasons have been given to explain this trend. One reason puts the blame squarely on the "blockbuster" mentality, where the industry focuses only on a few profitable lifestyle diseases. As these diseases affect millions of people in industrialized nations, a single drug can serve a large clientele, though the underlying causes remain unaddressed. Nonetheless, this mentality might explain why fewer than 50 proteins are targeted by the 200 most profitable drugs. Fifty is a surprisingly small number given the total number of genes in the human genome (about 35,000), the estimated number of gene products (about 120,000 proteins, as estimated from messenger RNAs) or the even larger number of gene product interactions (probably two to four times larger, according to the number of interactions found in protein interaction networks). Thus, a quarter-million targets could be expected, at least in theory. Why then the small number of actual targets? Some have suggested that the scientific community seems to suffer from a genomics information overload, unable to decide how and where to look for the "good stuff." But is such an explanation sensible? It seems there is a valid biological explanation of why it is difficult to find novel targets using the approaches of the past few decades.

It might just be that the good stuff is not that plentiful. Despite the enormous progress made in computational chemistry, bioinformatics and rational drug design, the most successful drug candidates that end up on the pharmacist's shelf still are discovered by a good dose of luck. Combinatorial chemistry and high-throughput assays, too, have failed to improve the success rate dramatically, and the industry is rediscovering the value of searching for and screening natural products. So why does it appear that the number of good drug targets is relatively small compared to the number of human genes and protein interactions? It can hardly be for lack of trying, so I would like to point at a conceptual barrier. A barrier in the form of a structural and functional redundancy of metabolic pathways, signaling networks and protein complexes in living organisms. All are based upon the combinatorial use of a limited set of structural motifs and domains in proteins.

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Accounting for Redundancy

Not every mutation causes a disease, and not every disease is caused by a single mutated gene. Nature is enormously selective, yet not restrictive. Biological systems have built-in backup systems and redundant features that ensure that accidental changes (mutations) are not always bad. Biological systems have room to change, adapt and absorb defects. The large number of hereditary diseases is a good example of this principle. If diseases simply were detrimental, natural selection foretells their extinction. But redundancy does not mean that there are many parts that are produced but never used. As it happens, proteins in modern organisms have evolved into protein families, where members with recognizably similar features can function in subtly different contexts, contributing to a variety of physiological mechanisms. Functional redundancy is a hallmark of many protein families, as their members participate in a variety of distinct physiological processes. Cyclooxygenases are a good example. They form an enzyme family involved in both normal physiological regulation and in temporary immune responses to infection and stress. Consequently, aspirin and related cyclooxygenase inhibitors serve as painkillers and turn out to help in preventing cardiovascular and neurological diseases related to chronic over-activity of cyclooxygenases.

This functional redundancy easily can be traced back to the way protein structures are formed. At the molecular level, function follows form. Single mutations often can change a similarity (i.e., a conserved feature) into a different (or dysfunctional) one. Often, proteins might not be highly specific and can bind many ligands and substrates, although with varying efficiency. Just think of the number of cholesterol-lowering statins or cyclooxygenase inhibitors. Each class of drugs is defined by a pharmacophore structure common to several molecules with closely related but distinct chemical structures. Molecules with the same pharmacophore are functionally redundant in that they all have the same pharmacological effect. The observation that several drugs can bind the same target is the direct result of the flexibility and adaptability of proteins. This flexibility at the macromolecular level translates into robustness at the level of the organism. Such robustness also has been evident from knockout experiments designed to identify the involvement of genes in physiological processes. A majority of genes tested this way proved neither critical for the expected function nor essential for survival of the organism. This can only mean that organisms have back-up mechanisms to compensate for any loss in function that might result from a mutation. Quantitative trials in bacterial systems have attempted to determine the minimal number of genes necessary for a single cell's existence. So far, these studies have showed that more than half of all genes in bacterial genomes are not required for survival in a controlled environment (2).

Considering Multiple-target Drugs

What does this mean for the pharmaceutical industry? In my opinion, drug discovery has reached a threshold beyond which a simple cause and effect scenario no longer holds and that recognizes that most physiological systems and diseases are multi-factorial. Individual genes rarely are solely responsible for a particular phenotype, and changing the activity of a gene product simply might not change the course of a disease. Accordingly, the diminished output of new molecular entities (NME) despite increased R&D efforts — financially and technologically — could be addressed by shifting the view from single-target to multi-target drugs. We learned this lesson from the successful use of drug cocktails to suppress the spreading of HIV.

Could a single drug take the place of a drug cocktail? One structure–one target is a simplistic paradigm, for we know that a single drug molecule can and must bind to multiple proteins while avoiding interactions with others. The challenge is obvious: a drug should bind to its target as well as to transporters in the gut and the blood serum, but it should not bind to detox enzymes in the liver, nor transporters in the kidney that would clear the body of the drug molecule prematurely. And it certainly should not bind to receptors on tissues unrelated to the disease. Understanding the biology behind diseases and infection mechanisms is crucial — but obviously difficult.

If a single molecular species requires such complex consideration during its existence as an efficient and non-toxic drug, addressing adsorption, distribution, metabolism, excretion and toxicity (ADMET) for a drug cocktail seems intractable, for we need to know what each component of a cocktail binds to, as well as what it shouldn't bind to. Our rudimentary understanding of the complexity and redundancy of organisms does not allow us to do so. Thus, we still depend upon animal models and clinical trials.

The proliferation of "-omics" in the life sciences attests to the readiness in biomedical research to tackle this problem head on and emphasize a "global-view" approach. Nowhere is this more apparent than in pharmacology, which envisions the search for individualized, efficient and non-toxic drugs. Having catalogued myriad bits and pieces of biological and medical information in databases, a relaxation of the reductionist mind holds promise to bear fruit, through metabolic reconstruction, modeling of signal transduction pathways and networks of molecular ensembles, and to better predict a target that rapidly leads to identifying structures of a new molecular entity.

Learning by Trial and Error

The challenge of bringing a drug to market is not a failure of rational drug design, high-throughput screening, combinatorial chemistry or the lack of high-resolution structures. These simply might not be of much help for the problem at hand, because they address the wrong hierarchical level of cellular organization. Finding novel ligand structures with superior binding qualities to a receptor or enzyme is not the issue (I think this problem has been solved); understanding why they fail the clinic trial phases, however, is. I believe that the fundamental obstacle to successful drug discovery is rooted in the inherent redundancy of biological systems. Life is based upon soft, adjustable "hardware" — the macromolecules of life. It is the ability of proteins to adopt different stable conformations that distinguishes these biological macromolecules from machine hardware. So we are left dealing with the way nature operates best, as if to underscore the point that life has not been designed, but rather is the result of trial and error.

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References

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2. E.V. Koonin, *Nat. Rev. Microbiol.* 1(2), 127–136 (2003).PG