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Pharmacology Studies: Hints for a Change in the Paradigm

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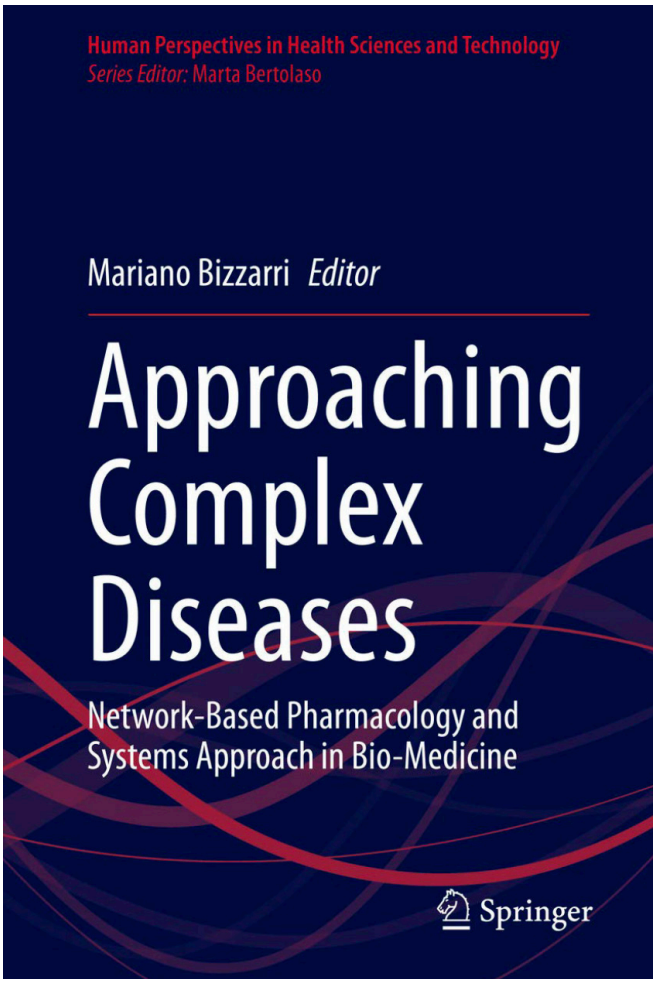

Approaching Complex Diseases: Network-Based Pharmacology and Systems Approach in Bio-Medicine
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The pharmaceutical industry is currently facing unparalleled challenges to develop innovative new drugs. Although the annual number of new drugs has not changed much, research and development (R&D) investment per drug is escalating at a marked rate. However, this relevant involvement in drug discovery is unfit to cope successfully with new challenges, as those provided by recent advances in basic and applied medical sciences.

While pharmacological research performed impressive results in treating cardiovascular, cerebrovascular and infective diseases, no proportional benefits have been recorded in the cure rates of neoplastic, metabolic and degenerative diseases.

Indeed, despite the increased investment in R&D by the industry, the number of new molecular entities achieving marketing authorization is not increasing. Contrary to expectations, high investment, development of technology and omics approaches - such as those based on proteomics and genomics - neither have reduced the R&D risk, nor have enhanced efficiency.

Three drug-discovery fads have driven the industry's R&D programs in the past thirty years: computer aided drug design, combinational chemistry linked to high throughput screening and genomics.

Until the 1990s, drug discovery and development was largely based on a phenotypic approach or observation-based ('empirical') approach. However, the accumulation of knowledge in biochemistry and molecular biology, led to a shift toward the target-based model, which entirely rely on a reductionist-based theoretical framework. Consequently, target-based drug discovery has been the main research paradigm used by the pharmaceutical industry during the last 30 years and billions of dollars have been invested into this approach. However, recent industry data strongly indicate that the

target-based approach is not an effective drug discovery paradigm and is likely to be the cause of the productivity crisis the industry is experiencing.

While drug-developing chemists and biologists in the 1990s mostly welcomed the transformation into a target-based approach (which was surmised more predictable and science-driven), two decades of experience shows that this model is failing to boost both drug discovery and efficiency. Selected targets were often not druggable and with poor disease linkage, leading to either high toxicity or poor efficacy. The off-target effect of a drug was much more difficult to predict in comparison to the phenotypic approach. Because the whole industry was using similar compound libraries for druggable targets, the diversity of pharmaceutical companies' portfolio has been spoiled. This has led to intense competition, where speed of clinical trials and marketing were the main attributes in determining the first-in-class or best-in-class.

Moreover, this approach will likely focus on non-essential targets, thus producing more failures through lack of efficacy. However, there are no evidence that any of these is or will be capable of replacing the old techniques. Namely, the basic premises on which gene-based pharmacological approach is increasingly questioned, as no one of the bewildering results hitherto anticipated have been so far achieved. For instance, the possibility of finding so-called synthetic-lethal drug targets, which are only essential in cancer cells that carry mutations in so-called tumor suppressor genes, is attractive only in theory as many objections stand out against that hypothesis. Indeed, a classical genetic approach is unlikely to be a solution as this model underestimates the importance of environmental milieu in shaping health boundaries. The second reason is the great complexity of gene/gene, gene/environment interactions, and the third reason is the high individual variability.

The purpose of drug design is to find the optimal structure that possesses high specificity around the target and interferes less with other sites to decrease the likelihood of side effects. However, in many, if not in most diseases, such unique target simply does not exist. For instance, in cancer, several pathway are deregulated, none of which is as specific enough to be a 'hallmark of cancer'. Moreover, by utterly inhibiting/activating this/these target(s) would seriously impair also the functioning of normal tissues, which usually rely on the same pathways.

Some attempts have been made to deal with these challenging hurdles, even if a rational strategy is still lacking.

We need a conceptual revolution. This 'paradigm change' will have profound scientific and philosophical consequences, given that it implies the search for general principles on which a cogent theory of biology might rely. Because much of the logic of living systems is located at higher levels, it is imperative to focus on them. Indeed, both evolution and physiology work on these levels. A Systems Biology approach is needed to catch such a complexity. Accordingly, this new perspective will entail epistemological and methodological issues as well.

Industry synergy. Based on the R&D level and progress made, new small, molecular entities will still be dominated in drug innovation for the next decade. This strategy is primarily thought to reduce the burden of financial investments. However, still confusing is the class of compounds on which we have to focus. Currently, this approach mostly relies on perspective of 'industrial synergy', aimed at multichannel integration of small/medium size enterprises.

Nanotechnology. In recent years, nanotechnology has been increasingly applied in drug development throughout the drug development chain. Nanoparticle-based therapeutics can confer the ability to overcome biological barriers, effectively delivering drugs and biologics, and preferentially target sites of disease. However, despite the potential advantages of nanoparticles, only a relatively small number of nanoparticle-based medicines have been approved and marketed for clinical use. The safety and efficacy of nanomedicines can be influenced by minor variations in multiple parameters and need to be carefully examined and controlled in preclinical and clinical studies, particularly in reference to their biodistribution, pharmacokinetics and potential toxicity.

Natural products. Natural products and their derivatives have historically been invaluable as a source of therapeutic agents. Despite the disbelief that such class of potential drugs encompassed in the last decades, recent updates and technological advances, coupled with unrealized expectations from current lead-generation

strategies, have led to renewed interest in natural products in drug discovery. Indeed, many natural molecules, prone to be eventually engineered to amplify their efficacy, have already proven to be effective in the treatment of several diseases.

Network polypharmacology. The dominant paradigm in drug discovery is the concept of designing maximally selective ligands to act on individual drug targets. However, many effective drugs act via modulation of multiple proteins rather than single targets. Advances in systems biology are revealing a phenotypic robustness and a network structure that strongly suggests that exquisitely selective compounds, compared with multitarget drugs, may exhibit lower than desired clinical efficacy. This new appreciation of the role of polypharmacology has significant implications for tackling the two major sources of attrition in drug development—efficacy and toxicity. Integrating network biology and polypharmacology holds the promise of expanding the current opportunity space for druggable targets.

Tumor reversion. Tumor reversion, a new testable paradigm in drug discovery, constitutes a remarkable case in point of the aforementioned strategy. An increasing number of reports has ascertained the occurrence of cancer reversion, both in vitro and in vivo. This process encompasses mandatorily a change in the cell-stroma interactions, leading to profound modification in tissue architecture. As cancer can be successfully 'reprogrammed' through the modification of the dynamical cross talk with its microenvironment, the overall cell-stroma interactive network must be recognized as the 'target' for pharmacological intervention. This new approach bears huge implications, from both a theoretical and clinical perspective, as it may facilitate the design of a novel anticancer strategy focused on mimicking or activating the tumor reversion pathway.

What we have to do now? Clearly, the looming difficulties will be primarily on the premises on which therapies are planned. For these, the companies may well have to go back to academia or, at least, to academics studying new and unexplored paths. For instance, systems biology, which today is still largely an enterprise of "academic" interest may find itself increasingly incorporated into the research programs of industrial enterprises.

We believe that the needed approaches are not simply to flog individuals to try harder but to build systems and infrastructures that enhance creative effort. Lateral thinking can and should be taught. Indeed, time is gone to address such challenging issues and to restore both confidence and efficiency to the pharmaceutical industry.

The volume we are proposing herewith in the Springer series, points to address such questions, by providing a full assessment of the premises underlying a radical shift in the pharmacology paradigm.