International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Predictive Modeling of Drug-Drug Interactions in Personalized Medicine Using Network Pharmacology

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Abstract: ***The goal of personalized medicine is to enhance therapeutic efficacy by customizing the treatment of each individual patient. As a consequence of the increasing incidence of polypharmacy (the simultaneous use of multiple pharmaceutical agents), a primary clinical concern is Drug Interactions (DIE), which may negatively influence both the effectiveness and safety of therapeutic agents causing adverse effects related to drug use and reduced effectiveness in patients with complex problems. Classic methods for identifying DEI are limited due to their inability to effectively scale to the number of agents used, and limited knowledge of the entire system's effects on drug action. Network pharmacology has developed into a useful framework for developing in silico, predictive models for DDI, through combining information regarding the relationship between Drugs & Targets, The Biological Pathways, and the various Disease Networks, as well as Multi-Omics Data (genomics, transcriptomics, proteomics), allowing researchers to model and/or predict the potential interactions of multiple drugs through Networks of Biological Interactions, rather than relying upon single drug to target models. The combination of Network Pharmacology with Personalized Medicine has provided many tools that improve clinical decision-making, ensure patient safety, and facilitate individualized treatment. Continued developments that utilize the integration of Network-based Models, Pharmacogenomics, Real-world clinical Data, and Artificial Intelligence to increase the precision and accuracy used in the prediction of DDI will likely accelerate the implementation of such models into clinical practice.***

Keywords: Personalized Medicine, Drug–Drug Interactions, Network Pharmacology, Predictive Modeling, Pharmacogenomics

1. Introduction

By 2030, personalised medicine (PM) is expected to revolutionise healthcare through a transition from reactive care towards more effective, fair and person centred care. According to the International Consortium for Personalised Medicine (ICPerMed), PM is expected to bring about the next generation of healthcare, based on more effective predictive, preventive and personalised therapeutic approaches that take account of individuals' differences. This transformation encompasses five core perspectives: empowering citizens to control and engage with their own health related data; equipping healthcare professionals with the knowledge and tools to safely use personalised health information in clinical decision making; enabling healthcare systems to deliver optimised and equitable promotion of health, prevention, diagnosis, and treatment; utilising comprehensive health information to enhance care and research; and establishing sustainable economic models that balance investment, innovation, and shared societal benefit. The implementation of these perspectives is expected to improve access to modern healthcare methods, enhance individual control over health data, and stimulate economic development in the health sector, thereby creating a more effective and responsive healthcare landscape for all citizens by 2030.(Vicente et al., 2020). Personalized medicine has shown that it can make healthcare systems better by improving patient outcomes, making disease management easier, and making better use of healthcare resources. The Charles River Associates report shows that personalized medicine can give patients better treatments by tailoring therapies to their unique biological profiles. This leads to higher response rates and fewer negative events. It also helps to better predict and prevent diseases, which makes it easier for healthcare systems to find and treat them. Personalized medicine could help lower the overall cost of healthcare by preventing or delaying the need for more expensive care and making better use of limited healthcare resources. This includes shortening hospital stays and getting rid of treatments that don't work, which will help healthcare systems run more efficiently and improve the health of the people they serve. (Ec, 2018)

Drug-drug interactions

Drug-drug interactions (DDIs) refer to the modification of the pharmacokinetic properties and/or pharmacodynamic responses of one drug due to the concurrent use of another drug. Against this backdrop, the challenge of DDIs is particularly reported to be real and of grave concerns within the clinical setting where patients are often on several medications at the same time due to comorbid conditions of a serious nature. Conversely, the drug interaction liability of one drug is often associated with the influence of drug-metabolizing enzymes and/or drug transporters, which interact with drug absorption, drug distribution, drug metabolism, and drug elimination. Specifically, as supported by available data on the drug remdesivir, it is evident that its metabolism is associated with enzymatic systems that belong to the CYP superfamily of enzymes, although the threat of DDIs appears low based on available evidence. However, it should be noted that the simultaneous use of this drug with an inducer or an inhibitor of such enzymes may pose this theoretical challenge of altering drug exposure.(Yang, 2020)

Drug-Drug Interactions (DDIs): Drug interactions resulting from concomitant administration of medications wherein one drug affects another's metabolic process and hence systemic exposure and drug response. Drug interactions in which medications are metabolized as a result of induction or inhibition of hepatic cytochrome CYP enzyme are most prevalent. Induction of CYP enzyme by other co-administered medications may lead to rapid removal of co-administered medications and subsequent reduced levels in plasma resulting in reduced effectiveness of medications. Factors such as differences in individual's CYP enzyme level as well as variations in nuclear regulatory factors for such medications affect predictions of induction of CYP enzyme and subsequent level of interactions. Conclusion: Understanding CYP induction mechanisms is thus critical in making predictions regarding individual-level DDIs to maximize benefits from drug therapy.(C. Tang et al., 2005)

DDIs are a clinically important and increasingly identified problem in oncology practice. Cancer patients often are exposed to many medicines simultaneously, including anticancer, support care, and treatments for premorbid conditions, which greatly increases the risk of DDIs. The risk is further exaggerated by the narrow therapeutic indices of many anticancer drugs. Therefore, even with minor changes in pharmacokinetics, there can be significant changes in drug response. Clinically significant drug-drug interactions may lead to increased toxicity and/or decreased drug effect and thus dose adjustment or drug discontinuation is necessary. One of the main reasons for drug-drug interaction is the mechanism of drug metabolism, primarily by the cytochrome P450 enzyme system. Many anticancer drugs depend on this system for metabolism. Inhibition or induction of these drug-metabolizing enzymes by other administered drugs may alter drug exposure in unexpected ways. Although they have serious potential, DDIs in oncology often go unrecognized in daily clinical practice.

Improved awareness and education will contribute to the safe and effective treatment of cancer.(McLeod, 1998)

Clinical importance in modern healthcare

The knowledge of pharmacokinetic and pharmacodynamic interactions of drugs is essential in contemporary healthcare. This work is of direct clinical relevance, as it helps to guide the dosage regimens and medication administration in patients. Special concern in patients who are most susceptible, such as elderly patients and patients with liver and kidney dysfunction, helps to provide individualized care to patients in a safer pharmacotherapy manner. (Rajput, n.d.)

Pharmacodynamic interactions, involving molecular, cellular, and organismic mechanisms, affect the response to pharmacologically active agents as interactions at the molecular level, involving the relationship of the compound with the receptor, as well as at the cellular and organismic level, are responsible for the additive effects of the therapeutic or harmful actions of the pharmacologically active agents. On the whole, the further research of drug-drug interactions is an improver of basic knowledge on the pharmaco- variance of drugs and is an essential element in the provision of safe, effective, and rational drug usage.(Rajput, n.d.)

Drug-Drug interactions (DDIs) are a serious problem in contemporary healthcare, as they literally influence the efficacy of therapies and the safety of patients. The measurement and understanding of DDIs are of paramount importance, as DDIs lead to a change in the efficacy of drugs, to adverse drug reaction, or to the need to change the dosage and formulation of a drug. The number of publications in the Biomedical Literature and the complexity of Clinical Text contribute to the difficulties of understanding DDIs. (Aparasu et al., 2007)

DDIs are commonly expressed in the form of highly complex sentences with more emphasis on the medical and pharmacological contexts where the terms associated with drug interaction are presumably at varying placement positions. This is especially because of the complexities involved in the expressions of such contexts that may eventually raise issues of incomplete or incorrect identification of such drug interactions.

Aside from the identification of interaction occurrence, the evaluation of the severity of these interactions is of great clinical interest. The identification of the severity of an interaction as mild, moderate, or severe can help health practitioners in distinguishing interactions which are favorable to the user, those to be treated with caution, and those of high severity. (Aparasu et al., 2007)

Severity-level classification of DDIs improves clinical decision support systems by focusing them, first and foremost, on high-priority DDIs. Using severity levels in the classification of DDIs leads directly to enhanced prescribing, lower occurrences of ADREs, as well as more effective resource allocation in healthcare. The integration of both DDI detection and severity in clinical and pharmaceutical expert systems enables more favorable outcomes for patients when taking medications.(Salman et al., 2022)

Drug-drug interactions (DDIs) are considered a significant problem in contemporary healthcare practice because these drug interactions can be causally linked to medication-induced morbidity and mortality observed in outpatient healthcare settings. According to nationally representative data, there is a measurable number of outpatient office visits where two or more medication pieces were prescribed that had a potential DDI on a scale significant enough to pose a substantial public health problem despite the relatively low percentage rate of these office visits.

Important DDIs in a clinical setting assume greater relevance in the context of patients taking two or more medications together. The risk of exposure to drug combinations that might interact increases substantially as the count of medications escalates, that is, by more than twice as the count goes beyond two medications. This assumes prominence in establishing polypharmacy as a contributory factor for DDIs in the outpatient setting today. (Aparasu et al., 2007)

Age is another important determinant of clinically relevant DDI outcomes in a hospital setting. The incidence of co-administration significantly increases after the age of 44yrs, and patients aged over 74yrs are at its peak. The results suggest that older people are more susceptible to DDI than

others either due to natural physiological degradation with age or due to increased use of more medications because of chronic ailments associated with increased age. Patients enrolled under Medicare also tend to be at a higher risk of a potential interaction between different prescription drugs after adjusting the variables for age and other factors associated with patients.

Anticoagulants, especially warfarin, are responsible for most of the clinically important DDIs encountered in outpatient practice. The majority of warfarin-related interactions involve nonsteroidal anti-inflammatory drugs, thyroid hormones, and fibric acid derivatives. Such interactions are clinically significant and may enhance bleeding with a need for individualized dose adjustment, close monitoring, and patient education. Although such risks are surmountable through appropriate prescribing and follow-up care, patients on interacting medications remain at risk when their medications are changed or doses altered. (Aparasu et al., 2007)

The clinical significance of DDIs has implications that transcend prescribing issues. The drug-related problems that result from DDIs are some of the contributors of the burden of care in health facilities. The significance of Medication Therapy Management (MTM) initiatives among older persons and those with polypharmacy cannot be overemphasized in mitigating the potential dangers of DDIs. The pharmacist has significant potential in detecting DDIs that are of clinical significance and providing constant surveillance and teaching of the involved patients.

Effective identification and management of clinically significant DDIs are crucial in ensuring the safety of pharmacotherapy in contemporary medical practice. This can be made possible through proper prescribing, monitoring, patient education, and the implementation of computerized alert tools. Nonetheless, advances are needed in the development of Clinical Decision Support Systems to improve the identification of clinically significant interactions and suppress non-relevant alerts. There is also a need for ongoing research and endeavors in the identification of the outcomes of DDIs, particularly those affecting the economic and humanistic aspects of patient care.(Aparasu et al., 2007)

Pharmacokinetics of drug – drug interactions

The pharmacokinetic interactions of drugs with other drugs are a key determinant in the evaluation of the safety and efficacy of anticancer medications since a large number of antineoplastic agents used in pharmacotherapy have a narrow therapeutic margin. Such interactions take place in altered ways of drug absorption, metabolism, and excretion of drugs in amounts of significance for pharmacological activity in organisms. Within oncology, even small changes in drug concentrations in the plasma lead to severe toxicity and failure of treatment efficacy. (McLeod, 1998)

Some anticancer drugs are extensively metabolized by the liver via cytochrome P450 enzyme complexes, such as CYP3A, while others are mainly eliminated renally. The simultaneous use of other drugs that inhibit and induce these metabolic routes can cause significant differences in drug clearance rates. For instance, the inhibition of xanthine oxidase activity by allopurinol has been shown to cause a marked increase in the bioavailability of 6-mercaptopurine due to increased plasma levels of which potentially toxic consequences are observed. On the other hand, enzyme-eliciting anticonvulsives such as phenytoin and phenobarbitone have been observed to enhance the elimination of etoposide and teniposide.

Changes in the rate of drug excretion are another significant pharmacokinetic interaction. The kidney-secreted methotrexate will present delayed elimination and enhanced systemic concentrations due to concurrent administration with other drugs such as probenecid that share a mechanism in the kidneys. This interaction has been implicated in increased half-life and blood toxicity. Other interactions occur when nephrotoxins cause a reduction in kidney functions and therefore affect the mechanisms by which the body eliminates methotrexate. (McLeod, 1998)

Pharmacokinetic interactions may also happen through regulation of metabolic enzymes dealing with drug breakdown. In other words, inhibition of dihydropyrimidine dehydrogenase, which plays a pivotal role in metabolizing 5-fluorouracil, may culminate in massive drug accumulation and toxicity. Clinical data have confirmed that reduced activity of this metabolic pathway can elevate patient plasma concentrations of 5-fluorouracil to a significant extent, which clearly indicates the unexplored relevance of metabolic capability.(McLeod, 1998)

Personalised medicines

Personalized medicine can be described as a healthcare approach which attempts to customize medical treatment according to the unique qualities presented by every patient instead of adopting standardized treatment practices. As mentioned in a discussion by Harvey et al., personalized medicine basically represents a unification of biological, genetic, clinical, and environmental factors in a bid to enhance disease prediction and prevention as well as its treatment and diagnosis. The key role played by advances in genomic technology in achieving personalized medicine lies in its capacity to allow researchers to identify unique genetic differences of patients which contribute to disease susceptibility as well as drug responsiveness. The article here makes it clear that personalized medicine seeks to shift healthcare from a traditional reactive approach towards a more predictive and preventive approach in which treatment options depend on unique risk categories of patients. The article also makes a critical point by stating that personalized medicine is more than genomics and seeks to bring together several other technology platforms as well as healthcare systems in a bid to enhance well-informed healthcare decision-making.(Harvey et al., 2012)

There is growing interest in personalised medicine because this type of approach targets patients individually according to their own characteristics and aims to ensure patients receive the right treatment at the right time and dose. According to Maughan, personalised medicine is easier to apply for patients suffering from single genetic mutations where dramatic results were seen with imatinib therapy in chronic myeloid leukaemia (CML). For most chronic

ailments such as cancers and non-cancerous diseases, results are more complex due to multiple genetic and environmental factors, which is more difficult to apply when personalised medicine is considered. The applications of personalised medicine are not limited to treatments but also cover prevention and diagnosis where differential diagnosis according to molecular characteristics is used depending on patients' progress and response to treatment according to certain markers or profiles according to Maughan. There is also the aspect of having a balanced perspective according to Maughan because there is potential prejudice in personalised medicine when overly enthusiastic hopes are prioritised in patients and research personnel. Thus, personalised medicine needs to integrate scientific objectivity in genomic and molecular analysis with an appreciation of an individual not solely definable by his/her genetic particulars.(Maughan, 2017)

Relevance to personalised medicine and individualized therapy

Personalized medicine is increasingly indicative of the human desire for a futuristic approach to medicine that embraces both individualization and holistic system regulation, rather than merely regarding them as distinct strategies. A functional personalized medical system must both factor in individual variation and embrace an integrated and holistic perspective of the human body as a whole. Macro-level state descriptions give personalized medicine a critical advantage with regard to regulating and controlling diseased systems.(Yuan, 2022)

Although precision medicine is pressing forward with targeted therapies according to specific biological states, the reductionist approach makes it challenging to realize a holistic fusion within comprehensive disease treatment. On the other hand, traditional Chinese medicine (TCM) embraces individualized treatment as well as a natural fusion within a more comprehensive regime of holistic state regulation. The incorporation of precision medicine's personalized treatment strategy within a comprehensive regime is inevitably supported by a model that is greatly attuned to the therapeutic aims of personalized medicine. Building on the prolonged validation within practical clinical applications, it is apparent that traditional Chinese medicine offers a proven model for state description and regulation that does not need reconstruction on first principles. Indeed, it is a fact that Western medicine has capitalized on Chinese medicinal knowledge. This is evident in the development of artemisinin drugs using Artemisia annua plants or acupressure's transformation into trigger-point dry needling. The integration of Western models such as cybernetic systems for state regulation within the treatment systemsization of traditional Chinese medicine may possibly provide a platform for the development of personalized frameworks within a therapeutic regime that is more comprehensive while scientific.(Yuan, 2022)

Under present-day conditions, patients are generally administered doses of drugs, but the dosages are then optimized by the clinician depending on the clinical response or, when possible, on blood levels, such as the INR. However, these procedures could lead to suboptimal dosing, empirical therapy, and taking a considerably longer time for optimal dosing, resulting in elevated costs as well as morbidity and mortality. One of the most important aims of pharmacogenetic studies, hence, is the discovery of the genetic component that determines why some individuals or groups do or do not respond in similar ways to medications, making possible the individualized dosing of medications right from the time of administration in order to minimize the risk of ADREs.The issue of designing dosage regimens based on the genotype for various medications, for instance, antidepressive medications, 6-mercaptopurine, and others, is an important improvement in personalized medicine. However, the evaluation of patient benefit in clinical studies and, as a final goal, more efficient pharmacotherapy and fewer side effects are, in fact, very important..(Oscarson, 2003)

Network Pharmacology: A Systems-Level Framework

Principles of network pharmacology

Network pharmacology is an approach based on a systems-level perspective that considers diseases, including cancer, to be a result of complex derangements in interconnected molecular networks. By modulating multiple targets within biological networks rather than targeting one specific target with a single drug, network pharmacology aims to produce better therapeutic results.

Network pharmacology's core principle is that biological systems can be represented in the form of networks. In these networks, the nodes represent genes, proteins, and/or metabolites (as well as any other biological entity), while the edges represent the functional relationships between nodes - i.e., protein-protein, signalling and regulatory relationships. By viewing disease states as dysregulation of a system-level network, rather than just a number of individual molecular defects, we gain a greater understanding of how diseases work. (J. Tang & Aittokallio, 2014).This model is based on a network-based strategy for determining which targets to prioritize. Traditional methods used to rank targets based on their stand-alone value have been used since the beginning of drug development. However, network pharmacology will determine how the target fits in the entire context of the disease network and how well it interacts or connects with other potential targets. Oftentimes, the more centrally located or bottlenecked a target is, the greater its utility as an intervention point, since modifying the target will have a much greater impact on multiple downstream pathways.

Another principle of computational model/data integration is that network pharmacology brings together multiple distinct types of datasets (genomics, transcriptomics, proteomics, as well as chemical–protein interaction data) to design and assess disease/target networks related to drugs. The computational model allows for the ability to predict how a drug will behave medically, find which drugs complement each other, and analyse certain types of treatment strategies before any type of validation of those strategies through experimentation.(J. Tang & Aittokallio, 2014)

Network pharmacology is a systems-level discipline that investigates the action of drugs by integrating molecular targets, biological pathways, and disease phenotypes into interconnected networks. The drug-target-pathway-disease

network is the basis of this discipline since it has provided an organized view of how drugs act on complex biological systems. Network pharmacology treats diseases as disruptions at a network level instead of focusing on molecular-level malfunctions. It uses target-drug-pathway-disease networks to model complex relationships: Drugs are associated with their corresponding molecular targets and mapped to paths such as metabolic pathways to link paths to disease. This allows for a macro-level understanding of drug regulation at both a cellular and organismic level. (Li et al., 2021)

These types of networks aid in the identification of regulatory nodes with high importance, along with functional modules, involved in critical pathways of progressive events of various diseases. Upon topological analysis, it is made possible to understand the paths through which the effect of the modulator affects the pathways with respect to the processes involved in various diseases. This validates the efficacy of the treatment based on the pathways regulated by the modulator.

Notably, the drug-target-pathway-disease networks form the theoretical basis of bringing together experimental data, predictions, and observations. Within the context of network pharmacology, the drug-target-pathway-disease networks are commonly used in the study of the mechanisms of diseases, the explanation of therapeutic mechanisms, and the comprehensive assessment of therapeutic approaches from a perspective of personalized medicine. (Li et al., 2021)

Predictive Modeling of Drug–Drug Interactions

Computational and network-based approaches have emerged as powerful tools for the in silico prediction of drug-drug interactions by leveraging largescale biological and pharmacological data. These methods basically emanate from representing drugs, targets, and biological processes in the form of interconnected networks where nodes denote entities such as drugs or proteins, and edges represent interactions or functional associations. This allows integration of drug-target interaction networks, protein-protein interaction networks, and disease-associated pathways to empower network-based models to conduct a systematic analysis of how multiple drugs might interactively influence biological systems.

The topological properties of the network, such as shared targets, network proximity, and signaling pathways, are utilized jointly by the network inference algorithms for the prediction of DDIs. The computational methodologies such as similarity-based prediction, random walk-based prediction, matrix factorization, and graphical models have been utilized extensively for the prediction of hidden interactions in large-scale networks. The methodologies have the capability of predicting DDIs even in the absence of direct experimental validation.

Significantly, network-based computational approaches focus not only on one drug-target interaction but, more importantly, can harvest information related to the system-wide effects of combinations of drugs. Indeed, a holistic approach, such as that provided by network-based models, is most useful for gaining insight into possible instances of synergy or antagonism due to convergent or divergent pathway modification. Thus, scalable, data-driven predictive approaches for DDI, provided by network-based computation, offer an important step forward for safer drug development, combination therapy, or personalized medicine.(Wu et al., 2018)

2. Conclusion

The growing complexity of therapeutic regimens under modern health practices has further accentuated the importance of drug interactions (DDIs), especially with the advent of personalized medicine where treatment practices are designed according to individual patients' profiles. DDIs act as crucial factors determining the efficacy and safety of medications and their outcomes on patients, and the prediction thereof holds utmost importance in rational pharmacotherapy practices. Traditional methodologies, although effective and helpful, have limitations with respect to understanding the complex phenomenon of drug interactions. Network pharmacology has recently emerged as a systems-level platform with predictive capabilities in the DDIs modeling process by considering the interaction of drug-target, biological pathways, disease, and multi-omics data. Computer and network models are also being used to reveal the latent, unobserved, or unknown DDIs. These models can provide a complete understanding of the mechanisms of the drug, which can demonstrate a beneficial or adverse interaction among the drugs. Looking ahead, the future of DDI prediction will involve the increased integration of network pharmacology, pharmacogenomics, real-world clinical data, and artificial intelligence learning approaches. The integration of patient-specific genetic differences, time-dependent disease states, and long-term clinical data will allow the personalization of DDI risk prediction. Moreover, the incorporation of standard, interpretable, and validated network models will play an essential part in their integration into the framework of clinical decision support tools. In the continued advancement of data quality, processing power, and frameworks, the use of predictive network pharmacology will assume an essential part in the advancement of personal health, aimed at enhancing the safety, effectiveness, and sustainability of therapy.

References

[1] Aparasu, R., Baer, R., & Aparasu, A. (2007). Clinically important potential drug-drug interactions in outpatient settings. *Research in Social and Administrative Pharmacy*, *3*(4), 426–437. https://doi.org/10.1016/j.sapharm.2006.12.002

[2] Ec, L. (2018). Tim Wilsdon, Anthony Barron, Guy Edwards, Ryan Lawlor Charles River Associates. *Final Report*.

[3] Harvey, A., Brand, A., Holgate, S. T., Kristiansen, L. V., Lehrach, H., Palotie, A., & Prainsack, B. (2012). The future of technologies for personalised medicine. *New Biotechnology*, *29*(6), 625–633. https://doi.org/10.1016/j.nbt.2012.03.009

[4] Maughan, T. (2017). The Promise and the Hype of 'Personalised Medicine.' *The New Bioethics*, *23*(1),

13–20. https://doi.org/10.1080/20502877.2017.1314886

[5] McLeod, H. L. (1998). Clinically relevant drug–drug interactions in oncology. *British Journal of Clinical Pharmacology*, *45*(6), 539–544. https://doi.org/10.1046/j.1365-2125.1998.00719.x

[6] Oscarson, M. (2003). Pharmacogenetics of Drug Metabolising Enzymes: Importance for Personalised Medicine. *Clinical Chemistry and Laboratory Medicine*, *41*(4). https://doi.org/10.1515/CCLM.2003.087

[7] Rajput, A. (n.d.). *Investigation of Mechanisms and Clinical Implications of Drug Interactions: A Review*. *6*(1).

[8] Salman, M., Munawar, H. S., Latif, K., Akram, M. W., Khan, S. I., & Ullah, F. (2022). *Big Data Management in Drug–Drug Interaction: A Modern Deep Learning Approach for Smart Healthcare*.

[9] Tang, C., Lin, J. H., & Lu, A. Y. H. (2005). METABOLISM-BASED DRUG-DRUG INTERACTIONS: WHAT DETERMINES INDIVIDUAL VARIABILITY IN CYTOCHROME P450 INDUCTION? *Drug Metabolism and Disposition*, *33*(5), 603–613. https://doi.org/10.1124/dmd.104.003236

[10] Tang, J., & Aittokallio, T. (2014). Network Pharmacology Strategies Toward Multi-Target Anticancer Therapies: From Computational Models to Experimental Design Principles. *Current Pharmaceutical Design*, *20*(1), 23–36. https://doi.org/10.2174/1381612813199990470

[11] Vicente, A. M., Ballensiefen, W., & Jönsson, J.-I. (2020). How personalised medicine will transform healthcare by 2030: The ICPerMed vision. *Journal of Translational Medicine*, *18*(1), 180. https://doi.org/10.1186/s12967-020-02316-w

[12] Wu, Z., Li, W., Liu, G., & Tang, Y. (2018). Network-Based Methods for Prediction of Drug-Target Interactions. *Frontiers in Pharmacology*, *9*, 1134. https://doi.org/10.3389/fphar.2018.01134

[13] Yang, K. (2020). What Do We Know About Remdesivir Drug Interactions? *Clinical and Translational Science*, *13*(5), 842–844. https://doi.org/10.1111/cts.12815

[14] Yuan, B. (2022). What Personalized Medicine Humans Need and Way to It- Also on the Practical Significance and Scientific Limitations of Precision Medicine. *Pharmacogenomics and Personalized Medicine*, *Volume 15*, 927–942. https://doi.org/10.2147/PGPM.S380767

[15] Li, S., Ding, Q., & Wang, X. (2021). *"Network target" theory and network pharmacology*. In S. Li (Ed.), **Network pharmacology**. Springer, Singapore. https://doi.org/10.1007/978-981-16-0753-0_1