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Review | Обзор

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Aetiopathogenetic Architecture for Pharmaceutical Development (Using Gout as a Case Study)

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ABSTRACT

INTRODUCTION. A holistic understanding of the physiological and biochemical pathways involved in pathogenesis is needed both for doctors diagnosing and treating patients and for drug developers. The accumulated knowledge in medicine and related fields, combined with the rapid development of digital tools, enables simulating the response systems of the body under normal and pathological conditions at a qualitatively new level. Being able to perform such simulations will lead to creating a digital architecture of body conditions, with interconnected links in the chain of pathogenesis being the focal points for researchers advancing medicines from early development to clinical trials.

AIM. This study aimed to review existing approaches that could form a foundation for constructing an aetiopathogenetic architecture of pathological conditions and diseases that would serve as a framework for targeted drug development.

DISCUSSION. Using gout as a case study, the authors demonstrated the necessity and possibility of developing a three-dimensional aetiopathogenetic architecture of pathological conditions and diseases that would be based on the hierarchical relationships of pathological processes at different biological organisation levels. The study identified key applications for the aetiopathogenetic architecture. In medicine, the aetiopathogenetic architecture could be used in data-driven individual diagnostics and personalised pharmacotherapy. In pharmaceutics, the aetiopathogenetic architecture could provide a platform for investigating pharmacodynamics, from screening candidate compounds to applying targeted and multitargeted approaches in pharmaceutical development. The authors used the aetiopathogenetic architecture of gout as a case study to discuss the logic behind designing studies of medicines.

CONCLUSIONS. The article proposes a methodology for constructing an aetiopathogenetic architecture reflecting cause-and-effect relationships of different significance to the development of pathological conditions and diseases. The aetiopathogenetic approach should become an integrative framework for all stages of the development and use of novel medicines, as well as a basis for expanding the indications for existing medicines. New opportunities are arising for the development of aetiopathogenetic models of varying complexity that can be used in projects ranging from drug design at the molecular level to pathophysiological modelling at the organism level.

Keywords: pathogenesis; sanogenesis; aetiopathogenetic clusters; diagnosis of conditions; experimental models of aetiopathogenesis; pharmaceutical development; gout; aetiopathogenesis

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Этиопатогенетическая архитектура разработки лекарственных средств (на примере этиопатогенеза подагры)

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РЕЗЮМЕ

ВВЕДЕНИЕ. Системное понимание патофизиологических и патобиохимических путей заболеваний и патологических состояний является насущной потребностью как для врачей при постановке диагноза и лечении конкретного пациента, так и для разработчиков лекарственных средств (ЛС). Накопленные знания в медицинской и в смежных сферах, быстрое развитие цифровых инструментов делают возможным на качественно новом уровне смоделировать систему реактивности организма в норме и патологии. Это приведет к созданию цифровой архитектуры состояний организма с взаимосвязанными звеньями патогенеза, которые и будут находиться в фокусе внимания исследователей от дизайна ранней разработки ЛС до клинических исследований.

ЦЕЛЬ. Ревизия имеющихся подходов и построение на их основе этиопатогенетической архитектуры состояний и заболеваний как фундаментальной основы целенаправленной разработки лекарственных средств.

ОБСУЖДЕНИЕ. В исследовании были показаны необходимость и возможность (на примере подагры) построения объемной этиопатогенетической архитектуры состояний и заболеваний организма, основанной на иерархических связях патологических процессов на разных уровнях организации живого. Обоснованы основные векторы ее использования: для медицинских целей — основанная на данных диагностика состояний и заболеваний индивида, персонификация фармакотерапии; для фармацевтических целей — основа для исследования фармакодинамики ЛС начиная со скрининга веществ-кандидатов, использования методологических возможностей таргетных и мультитаргетных подходов в разработке ЛС. На примере архитектуры этиопатогенеза подагры обсуждена логика в разработке дизайна исследования ЛС.

ВЫВОДЫ. Предложена методология построения этиопатогенетической архитектуры как отражение причинно-следственных связей с разным уровнем значимости в формировании патологических состояний и заболеваний организма. Этиопатогенетический подход должен стать связующей основой между всеми этапами создания и применения новых ЛС, а также при исследовании возможности расширения показаний к применению уже использующихся ЛС. Появляются новые возможности и для разработки этиопатогенетических моделей разных уровней сложности: от drug-дизайна на молекулярном уровне до моделирования патофизиологических процессов на организменном уровне.

Ключевые слова: патогенез; саногенез; этиопатогенетические кластеры; диагностика состояний; экспериментальные модели этиопатогенеза; разработка лекарственных средств; подагра; этиопатогенез

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INTRODUCTION

Currently, the nosological approach dominates in the diagnosis and treatment of diseases, primary and secondary prevention, as well as rehabilitation. It uses disease symptoms confirmed by physical and laboratory findings, which is undoubtedly an effective basis for physicians to work on. The medical and pharmaceutical community is guided by ICD-10 and the transition to ICD-11. Clinical guidelines and medical care standards approved by the Russian government are a valuable basis for medical care standardisation (see Guidelines[1]). At the same time, medical scientists, biologists, and drug developers are looking for ways to reach a new level of understanding for this pathology and to move from disease treatment to patient treatment, namely affecting the body as an integrated system of interrelated processes.

The amount of empirical evidence, clinical observations, alongside with the emerging medical information systems and databases, IT applications using artificial intelligence (AI), and drug design platforms make it possible to fully switch to pathogenetically based pharmacocorrection, thus embodying the concept of 4P Medicine (prediction, prevention, personalisation, and participation) and 5P Medicine (+precision medicine) [1–4].

In our opinion, use of already known pathophysiological and pathobiochemical knowledge[2] is therefore required to build a system of body reactivity: from general pathologies through clusters of associated processes to more specific and localised body reactions, resulting in diagnosis, primary and secondary prevention, treatment, and rehabilitation[3]. This system of interrelated processes should have a multidimensional architecture, similar to the body volumetric system. To construct the system seems to be a complex combinatorial goal. Currently, transition to a new qualitative level of structuring medical knowledge and care is available (outcome prediction, personalised drug and non-drug treatment, decision support system for the doctors, lifestyle prescriptions, logistics, cost planning etc.). This dynamic architecture requires identifying etiopathogenetic relationship of processes and their clinical manifestations over time, with the corresponding extensive medical data (medical images, pathological anatomy, pathological biochemistry, immune homeostasis, genetic data etc.). This system should integrate several purposes: a fundamental understanding of cause-and-effect relationships, conditions of specific pathologies and their combinations, treatment personification, and drug development[4]. This will require new digital solutions, such as mathematical modeling data management, machine learning, and large computing capacities [5].

Currently, individual blocks are under active development (most of them in oncology and cardiology), including university teams (St. Petersburg State University, Sechenov Medical University, Pirogov Russian National Research Medical University, Samara State Medical University etc.) [6–9]. In our opinion, further joint efforts will make it possible to build an integrated architecture, dynamically complemented by new data on pathogenesis and effects of biologically active substances.

This study aimed to review the existing approaches and use them as a foundation for aetiopathogenetic architecture of conditions and diseases used for choosing drug development options.

The databases and library systems used to search for this review: PID; Reactome; BRENDA; KEGG; eLIBRARY.RU; Scopus; PubMed; PubChem; Cyberleninka, as well as materials from the official websites of the U.S. Food and Drug Administration (FDA), and European Medicines Agency (EMA).

The search in the above databases was carried out using the following search terms and/or their combinations: “aetiopathogenesis”, “drug

[1] Association of Rheumatologists of Russia. Gout. Clinical recommendations. 2018 (In Russ.).
Scientific and Clinical Center of Endourology. Urolithiasis. Clinical recommendations. 2020 (In Russ.).
[2] Zaichik ASh, Churilov LP. Pathological physiology. Vol. 2. Pathochemistry. St. Petersburg: ELBI-SPb; 2007 (In Russ.).
[3] Glybochko PV, Alyaev YuG, Grigoriev NA. Urology. From symptoms to diagnosis and treatment. Moscow: GEOTAR-Media; 2014 (In Russ.).
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development", "hierarchy of pathological conditions", etc. Relevant data were selected manually according to relevance and significance criteria. A total of 75 articles were selected as the most significant on the subject of the review. The keyword search depth is 15 years.

MAIN PART

Hierarchy of pathophysiology

Medical progress in physical examination, pathobiochemistry, and in generating and processing medical images allows for assessment of specific normal or pathological phenomena and processes in measurable quantities and aetiopathogenetic substantiation for diseases [10–13].

From the perspective of specialists studying process pharmacodynamics, the vertical architecture of process continuity and manifestations over time is of particular interest [14–15]. It is created by linking the processes at the molecular, cellular, tissue, organ, and organ system levels of biological organisation. This should be used to introduce importance weighting of pathophysiological processes in the development of pathology [16–20].

It is appropriate to represent the hierarchy of pathological processes by several levels *(Fig. 1)*, where each subsequent level of pathology localisation and manifestation is determined by processes of the underlying level.

Level 1. Defines the processes at the molecular, genetic and cellular levels - general pathological/typical processes / not tied to specific systems and organs, initiated by various aetiological causes and factors (level 0), as well as horizontal interactions of general pathological processes. These include metabolic disorders of proteins, fats, and carbohydrates; mineral metabolism; energy metabolism, reactivity disorders, inflammation, cancerogenesis and some other.

Level 2. Typical body reactions (common links of pathogenesis) manifested at the tissue level: a balance shift in the "prooxidant – antioxidant" system; changes in the lipid spectrum and cholesterol disorders; disorders of thermoregulation, water-electrolyte balance, acid-base balance, immune homeostasis, adaptation mechanisms; hypoxia, shock, stress etc.

Level 3. Pathological processes localised at the level of functional systems and organs that form intersecting cascades of various body reactions and create a landscape of nosological forms, including comorbid states at the organism level.

These include various manifestations associated with disorders of higher regulatory systems – neurohumoral and hormonal (overactivity of the sympathetic nervous system, cytokine storm); metabolic processes (atherosclerosis, osteoporosis, metabolic syndrome); immunodeficiency states and autoimmune processes. The interdependent processes form a vast pathogenetic network of entire clusters of conditions and further associated diseases.

Level 4. The nosological units, as well as their complexes – disease clusters formed by common and interrelated links at different organisation levels. The severity confirmed by medical data is the basis for medical (and other) decisions in diagnosing patients' conditions, preventive measures, and medical treatment.

Clusters of pathological processes: conditions and diseases

In terms of structuring causal relationships of pathological processes, the concept of aetiopathogenetic clusters and algorithmic matrices proposed by Z. Kovač deserves special mention. Aetiopathogenetic clusters represent interrelations, intersections, and integration points of natural pathophysiological development over time [21]. At present, 91 identified clusters tend to construct a network and intercluster connections at various hierarchical levels of reactivity of the human body.

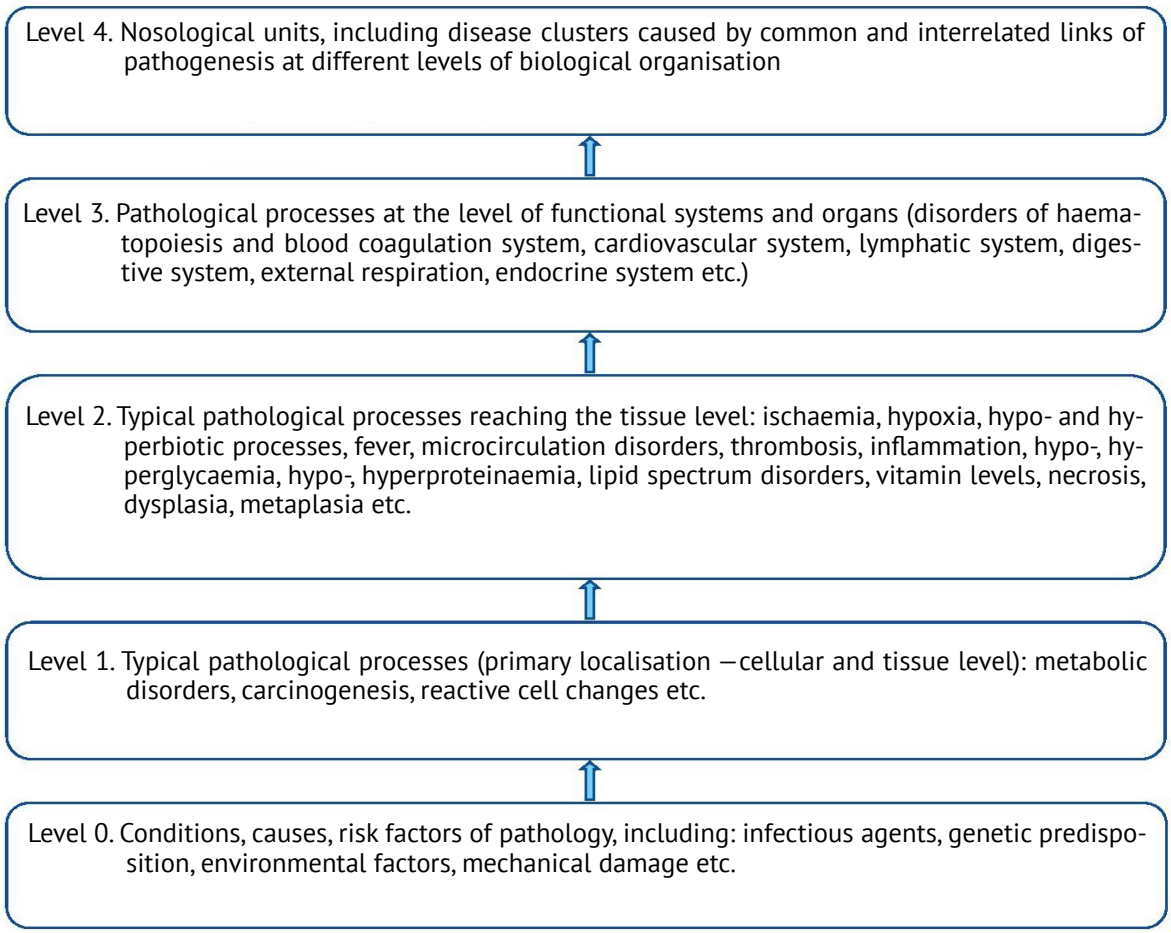
Based on this paradigm, the pathogenesis is described for almost one thousand diseases, which is valuable for the scientific community, practical healthcare professionals, and educational purposes.

In developing a systematic approach, the next step for the scientific community is to work with big data using artificial intelligence: determining the significance levels of medical data for assessing a patient's condition, data-

based diagnosis, outcome prediction and the emerging new pathologies. This will make it possible to create a multidimensional and dynamic digital architecture of the body states and their interrelation, at different levels of biological organisation, in a normal and pathological state.

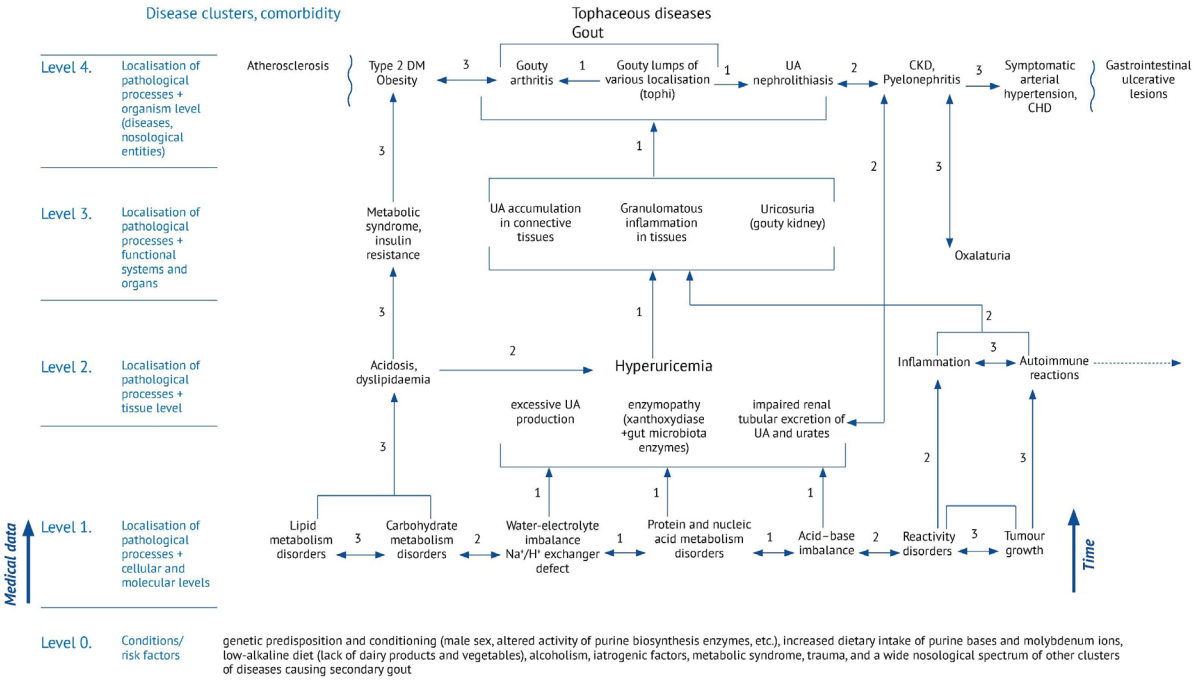
An example of an architecture fragment is a planar scheme we have compiled *(Fig. 2)*. It reflects purine and uric acid metabolism disorders that underly the pathogenesis of gout, urate nephrolithiasis and other associated diseases. The aetiopathogenesis is presented in accordance with the hierarchy of pathological processes *(Fig. 1)*; their interdependence is discussed in various publications and reviews [22–29]. The arrows indicate connections between conditions and body reactions at different levels of biological organisation; the numbers above the arrows indicate significance levels (weight) of the relationships and manifestation probability of conditions and diseases *(Fig. 2)*.

Based on aetiopathogenetic architecture of gout *(Fig. 2)*, it is practically significant to construct a diagram of a patient's conditions and diseases (level 4) based on the patient's medical data related to the relevant aetiopathogenetic links [22, 25, 28]. In fact, a cluster of patient diseases is based on the architecture/cluster of conditions. For ease of perception, volumetric architecture of patient's diseases is preferable as a diagram on a plane surface. Its purpose is to inform the doctor and the patient on the presence and severity of pathology(ies) in relation to time. During dynamic monitoring of the body's condition (for the data also reflected in subsequent similar diagrams), a prediction for diagnosed diseases and the risk of new diseases is assessed for



The figure is prepared by the authors

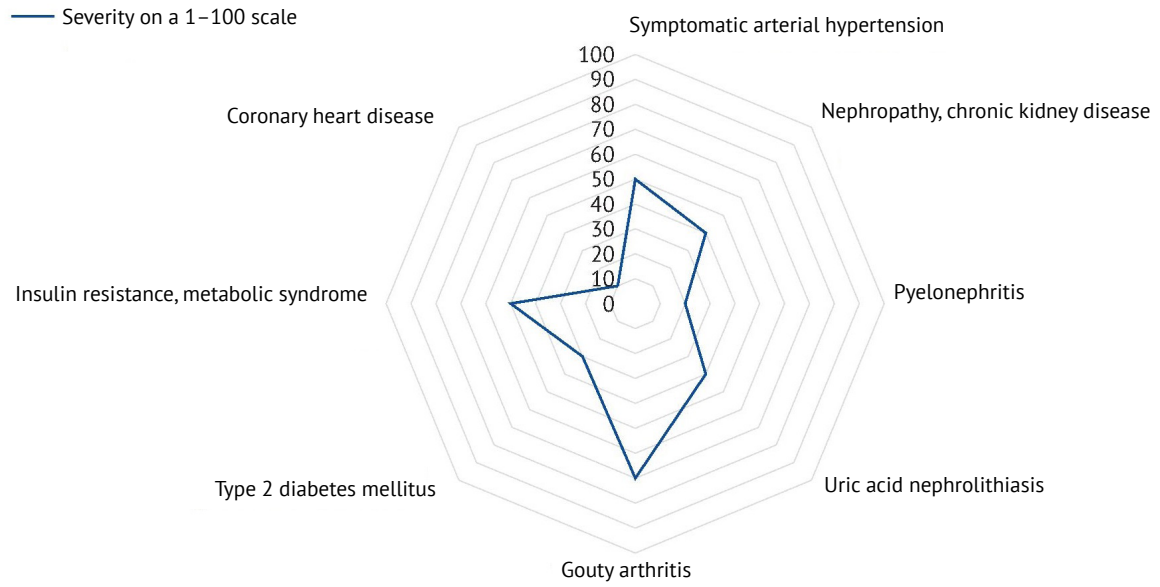
Fig. 1. *Schematic representation of the hierarchy of pathological processes*



UA, uric acid, sodium monourate; CKD, chronic kidney disease; DM, diabetes mellitus; CHD, coronary heart disease.

The figure is prepared by the authors.

Fig. 2. *Aetiopathogenetic architecture of gout (fragment)*



The figure is prepared by the authors

Fig. 3. *The disease manifestation diagram of patient "X"*

a particular patient. An example of a disease cluster for patient "X" is shown in *Fig. 3*.

The diagnoses indicated in the model diagram, in turn, are based on the dominant pathological processes [12, 13, 19], which should be represented in the corresponding architectures of their conditions (similar to *Fig. 2*). At the same time, a multidimensional individual architecture of conditions is formed (changing over time) in the dynamics of progressing/regressing diseases.

Thus, the outcome prediction of an existing pathology, the risks of developing diseases and early diagnosis of associated conditions

and diseases, as well as appropriate decision–making can increasingly use data (with metadata and meta-analysis as median values) and be reflected in the multidimensional digital architecture of body conditions. In addition, it can be a guideline for development and personalised use of medicines as a combined effect on several pathogenetic links, as well as on a specific target [30–35].

Aetiopathogenetic architecture as a methodological basis for experimental models and medicines

Both for fundamental understanding of various pathological conditions and for studying the effects of biologically active susbtances, aetiopathogenetic architecture can be implemented, starting from the screening of drug candidates and up to the post-marketing study of medicinal products.

Recently, there has been a paradigm shift of drug development from "classical" function-oriented approaches (biological effects of potential drugs assessed at the tissue or body level; "phenotype-directed" drug search; biomimetic approach etc.) with subsequent mechanistic studies to later target-based approaches; initial analysis usually includes evaluating drug interactions with certain (and often cloned recombinant) proteins *in silico* and *in vitro* (target–directed drug search), then *in vivo* models. In this regard, the hierarchical levels 0–2 turned out to be a priority for developers *(Fig. 1)* [36, 37].

As described, pathological processes at different levels of biological organisation are based on molecular changes, which are the study subject in a number of modern scientific directions. Various approaches are used to identify therapeutically significant targets and/or signaling pathways, such as identification of disease-causing genes [38], results of transcriptomic [39, 40], proteomic [41–45], metabolomic [46, 47], and multiomic studies, including those processed using machine learning algorithms [48–50]. The most comprehensive data sources on the processes occurring at the molecular and cellular levels are databases on signal transduction Pathway Interaction Database (PID) [51], Reactome, and BRENDA/KEGG databases on metabolic pathways.

At the same time, researchers note the reductive effect of the currently dominant target-oriented drug search and its insufficient effectiveness. Over time, this may cause a development crisis of low-molecular-weight drugs [52]. Some researchers suppose that the main theoretical drawback of target-oriented drug search is that it ignores the differences between complex and chain systems, simplifying the attitude towards structure and functions of biological processes [53, 54].

A recent systematic review of about 32,000 articles and patents published over the past 150 years demonstrated that a total of 9.4% of registered medicines were detected using a "target-oriented" search. In addition, biological effects unrelated to the main mechanism of action have been identified for these drugs [52]. At the same time, a target-oriented approach to drug search can be highly effective in some diseases caused by one or more proteins (for example, monogenic Mendelian disorders). The use of a target-oriented approach is an important asset for developing "next in class" drugs that helps to modify, describe structures and subsequently create best-in-class drugs [55].

According to a hypothesis, prioritising higher-level observations in the pathogenetic hierarchy for selection and optimisation of molecules can increase the search performance of first-in-class effective drugs. The success of this approach is confirmed by registration of Russia's first–in-class drug, a monoclonal antibody against the TRBV9 segment of the T-cell receptor [56].

The search for better results in clinical practice due to insufficient effectiveness of "one target, one molecule" paradigm led to the development of polypharmacology concept as a new therapeutic strategy. It involves combining various structural subunits in one framework, which allow for molecular recognition by more than one bioreceptor acting simultaneously on several targets connected by biochemical networks responsible for the disease pathophysiology [57].

Rationally developed multi-targeted drugs (also called multimodal or multifunctional drugs) have become an attractive choice for discovery of biologically active substances over the past 10–20 years as potential therapeutic solutions for diseases of complex aetiology and multidrug resistance [58-60]. Due to low-affinity binding (or partial agonism in some cases), multitarget drugs can avoid the frequent double trap of drug resistance and toxicity. At the same time, "non-selective non-selectivity" should be avoided for designed multi-targeted drugs, as this can lead to serious safety problems [61]. Various approaches are used for medical and chemical design of multi-targeted drugs, including those with non-overlapping, partially overlapping, and fully integrated "pharmacophores" [62].

An example of successful polypharmacology concepts are 86 multi-target drugs approved by the FDA among 462 new molecular compounds over 2000–2017 [63, 64]. Multi-target medicines approved for use in 2023–2024 are:

- aprocitentan (dual antagonist of endothelin receptors A and B) for the treatment of hypertension;
- birch triterpenes (trade name Filsuvez®, gel for external use) for the treatment of epidermolysis bullosa;
- repotrectinib (macrocyclic inhibitor of tyrosine kinases ROS1, TRK, and ALK);
- vamorolone (synthetic atypical glucocorticoid and antimineralocorticoid) for the treatment of Duchenne muscular distrophy;
- etrasimod (sphingosine-1-phosphate receptor modulator (S1PR), targeted at its subtypes 1, 4 and 5) for the treatment of ulcerative colitis;
- sparsentan (angiotensin type 1 and endothelin A receptor antagonist) used to reduce proteinuria in adult patients with primary immunoglobulin A (IgA) nephropathy.

Examples of multi-target drugs are plant-derived biologically active substances, most of them with a favorable toxicity profile [64–67].

Understanding diseases etiopathogenesis and comparability of pathological reactions in different conditions also makes it possible to extend the indications for authorised medicinal products (drug repurposing). Repurposing of a medicinal product available on the market allows for an immediate start of phase II research [68]. This reduces costs, since repurposing an existing drug costs about five (5) times less compared to registering a new drug [69].

Based on clinical observations or biologically relevant modeling, a pathogenesis concept of a particular disease and combined pathology (disease clusters) is formed and clarified from level 4 to level 0 *(Fig. 1)*. Understanding pathophysiology and quantifying the parameters is an experimental platform for screening and developing drugs or for expanding indications/contraindications for medicinal products that are already in use.

The authors of article [70] state that "cardioprotective properties of drugs with known anti–gouty effects and anti-inflammatory properties explained by inflammasome inhibition or blocking biological effect of its end products (interleukins) are a new milestone in cardiology." In other words, a specific molecular target is indicated – the NLRP3 inflammasome [71] at the level 1 *(Fig. 2)*, which should be one of the focuses in drug development and screening of biologically active substances, affecting the subsequent pathogenesis hierarchy to the organism level *(Fig. 3)*.

According to *Figure 2*, hyperuricaemia should be considered a proinflammatory trigger in tissues and organs (significance level 1), causing tophi, arthropathy, kidney and cardiovascular damage (level 3 and 4) [72]. However, in a vast majority of patients with prolonged hyperuricaemia, gout does not develop. Similarly, according to meta-analysis, hypercholesterolaemia, a proven atherogenetic factor, does not result in relevant clinical events in all patients [73]. These observations can be explained by pathological processes that lie deeper, such as universal inflammation at levels 1 and 2 of biological organisation *(Fig. 1 and 2)*. Their contribution to aetiopathogenesis is indicated by the second level of significance *(Fig. 2)*. Interleukin-1b, a product of NLRP3 inflammasome activation, is a multiprotein complex responsible for local inflammatory response in the synovial membrane and periarticular tissues involving macrophages and neutrophils

(incomplete phagocytosis), recognised as a key mediator of acute gout attacks.

At the cellular level, the NLRP3 inflammasome is activated by uric acid crystals and cholesterol only after activation by lipopolysaccharides, peroxidation products, and other damage factors associated with aging and comorbid conditions typical for gout and cardiovascular diseases [71–73]. Besides, activity of the NLRP3 inflammasome is genetically determined and defines frequency of these conditions (additionally, level 0). The discussed aetiopathogenetic mechanism explains why exposure to comorbidity-related factors (NLRP3 inflammasome) can reduce gout attacks along with cardiovascular outcomes.

At the integration level of disease clusters (level 4), clinically significant pleiotropic effects of statins and type 2 sodium-glucose transporter inhibitors have advantages over urate-reducing therapy in asymptomatic hyperuricaemia and are able to modify gout outcome. Their anti-inflammatory properties, cardio- and renoprotective effects, and advanced tolerability are being studied [70]. Blocking the inflammasome activity is a new universal/common therapeutic target for rheumatology and cardiology, especially in increased cardiovascular risk associated with hyperuricaemia [70–73].

There are two major test systems at the cellular level: inflammatory response and gout condition. *In vitro* cellular test systems are based on the primary human cell cultures, *a priori* known as cells involved in the pathogenesis. For example, to simulate hyperuricaemia conditions *in vivo*, a unique *in vitro* cellular test system was developed for stimulating blood cells of individual donors with uric acid [74]. Using the developed hyperuricaemic hemotest system in vitro, quantitative differences were found in the production of inflammatory cytokines produced by blood cells of potentially healthy donors and patients with hyperuricaemia and gouty arthritis. This hyperuricaemic haemotest system can serve as an *in vitro* cellular model for studying activation of signaling molecules of inflammasome inflammation in gouty arthritis. Moreover, it can be used for screening drug candidates.

The next stage is pathology modelling in animal experiments widely represented in both Russian and international practice of preclinical (experimental) research. However, in some cases, collecting sufficient and appropriate data at a higher level (3 and higher) may be inefficient, burdensome, and require a large number of animals. At the same time, data obtained at lower levels of the pathophysiological hierarchy (level 2 and below) can be based on knowledge of system biology, systemic pharmacology, and large-scale modelling [75]. Equally promising is a phenotypic approach to modelling the aetiopathogenesis considering significance levels for the disease manifestation. Measurability of the preset and determined parameters of pathology is also relevant, since it will provide structured data for digital platforms for assessing body conditions and developing drugs.

CONCLUSION

Analysis of published data in pathophysiology, pathobiochemistry, pathogenesis of diseases and conditions, and drug development has allowed the researchers to create a methodology for constructing a multidimensional architecture of body conditions based on medical data.

The architecture implements a well-known aetiopathogenetic approach, but with an emphasis on pathophysiological progression at different levels of biological organisation over time, with a prediction of probable disease manifestation based on the significance weights for emerging pathogenesis links.

The proposed architecture can be used in several ways. It is applicable in medical practice: from primary prevention to diagnosis and treatment of a particular patient. Regarding drug development, it can become an integrative framework for all stages of drug development, used to design a preclinical study, starting with the virtual screening of a drug candidate and subsequent selection of test systems of various complexity. The approach is applicable both for the development of new drugs and for expanding indications and expected effects for the authorised medicinal products.

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