DRUG REPOSITIONING: LESSONS FROM THE COVID-19 PANDEMIC

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We overview the possibilities and limitations of drug repositioning in the context of the COVID-19 pandemic and ways to reduce the new biogenic threats in the future. Drug repositioning — identifying new indications for approved drugs — is a natural prompt response to SARS-CoV-2 / COVID-19 viral infection. The current state of the research and development of drugs for the therapy of COVID-19 using *in silico* and *in vitro* methods is considered. In conclusion, it is noted that nowadays, the creation of innovative medicines, despite the success of translational science, takes a lot of time. Therefore, in order to select the most promising pharmaceutical agents, it is essential to integrate and analyze entire available information obtained using *in silico*, *in vitro* and *in vivo* methods.

Key words: SARS-CoV-2, COVID-19, pharmacological targets, drug repositioning, virtual screening, molecular modeling, machine learning, *in vitro* studies

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РЕПОЗИЦИОНИРОВАНИЕ ЛЕКАРСТВ: УРОКИ ПАНДЕМИИ COVID-19

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В статье обсуждаются возможности и ограничения репозиционирования лекарств в условиях пандемии COVID-19 и пути для снижения опасности новых биогенных угроз в будущем. Репозиционирование лекарств — выявление новых показаний у разрешенных к медицинскому применению лекарственных препаратов — является естественным оперативным ответом на вирусную инфекцию SARS-CoV-2/COVID-19. Рассмотрено современное состояние поиска и разработки лекарственных препаратов для терапии COVID-19 с применением *in silico* и *in vitro* методов. В заключение отмечается, что в современных условиях создание инновационных лекарственных средств, несмотря на успехи трансляционной медицины, занимает достаточно много времени. В силу этого для отбора наиболее перспективных препаратов крайне необходима интеграция и анализ всей доступной информации, полученной с применением всех выше обозначенных методов.

Ключевые слова: SARS-CoV-2, COVID-19, фармакологические мишени, репозиционирование лекарств, виртуальный скрининг, молекулярное моделирование, машинное обучение, исследования *in vitro*

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Drug repositioning is the identification of the new indications for drugs approved for medical use. The availability of information on the pharmacological and toxicological characteristics of a known drug enables its swift adoption in a new nosology [1]. The need for a rapid response to the COVID-19 pandemic has given the impetus to a large-scale research into the associated opportunities. A Google search for “COVID-19 AND drug repurposing” returns over six million results. Remdesivir, Favipiravir and Umifenovir (Arbidol) were originally designed for other indications and later repositioned to treat the SARS-CoV-2 infection. Same is true about Triazavirin, Nobasit, Nafamostat and a few other drugs that currently are subjects of clinical trials involving COVID-19 patients.

The search for the new pharmacological effects that known drugs may have involves *in silico* and *in vitro* studies. Computer-aided investigations rely on models of interaction of the analyzed compounds with molecular targets, identification of analogs based on the structural similarity, analysis of the “structure-activity” relationships using machine learning, and establishing associations by the network pharmacology [2]. The *in silico* approach can be applied to virtual (not yet synthesized) molecules providing the initial set of “hits”. Next, the predictions delivered by such computer-aided investigations are validated in the *in vitro* experiments. The *in vitro* determination of anticoronavirus potency relies on biochemical and cellular assays [3, 4]. Preliminary selection (virtual screening) of the potentially active compounds that is based on the data obtained through *in silico* investigations significantly increases the chances of success [5].

A number of large-scale experimental studies aimed to screen *in vitro* 1,400 to 12,000 drugs against one or several targets; the efforts yielded shortlists of candidates for repositioning. In many cases, different test systems gave different results for the same drug [3,4,6]. The reasons behind this inconsistence are lack of generally accepted reference drugs and absence of unifying standards for assays, which are developed independently by different researchers.

As noted by the authors of a recent analytical review published in the Chemical Society Reviews that looked into the computational approaches employed for COVID-19 drug

discovery: «… truly impactful computational tools must deliver actionable, experimentally testable hypotheses enabling the discovery of novel drugs and drug combinations, and that open science and rapid sharing of research results are critical to accelerate the development of novel, much needed therapeutics for COVID-19» [2].

In conclusion, it should be noted that current conditions make drug repositioning especially relevant. The reason behind this relevancy is the significant time required to develop innovative drugs in a pandemic, regardless of the advancements of translational medicine. At the same time, to select the most promising drugs for further experimental validation of their effects in the context of repositioning for SARS-CoV-2/COVID-19 (based on the analysis of the available data), it is necessary to integrate and analyze all the available information obtained *in silico*, *in vitro* and *in vivo* studies.

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