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Feature

Multiple deadlocks in the development of nonprofit drugs

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The current Coronavirus 2019 (COVID-19) pandemic has shown us that the pharmaceutical research community can organize and administer large nonprofit clinical trials (RECOVERY and SOLIDARITY) and achieve the swift development of common, unpatentable drugs for a new indication: in this case an old, inexpensive drug, dexamethasone, for COVID-19. Why is it that such nonprofit efforts are so rare and are not organized as a systemic, routine part of drug development in the public interest? Based on my own experience with repurposing the alcohol-abuse drug disulfiram (Antabuse) for cancer, I identify at least four serious deadlocks to development of nonprofit drugs. All of these obstacles should be addressed to leverage the potential of the COVID-19 pandemic for better future healthcare systems in all countries around the world.

Keywords: Nonprofit drugs; Dexamethasone; COVID-19; Disulfiram; Biomedicine; Clinical trials

A need for cheap and effective medicines

Healthcare worldwide faces two fundamental problems. First, we need new medicines, especially for diseases that many people die from (metastatic cancer, Alzheimer's disease, infectious diseases, etc.). Second, we also need affordable medicines. Even though the unavailability of medicines because of their cost is particularly noticeable in poor countries (according to the WHO, almost 2 billion people do not have access to basic medicines[1]), the financial sustainability of health systems in rich countries, such as the members of The Organization for Economic Co-operation and Development, is also becoming a serious issue.[2] This is why the European Union has set out, as part of its pharmaceutical strategy, 'to ensure that patients have access to affordable medicines and that health systems remain financially sustainable.'[3]

There is a general consensus expressed, for example, by former National Institutes of Health (NIH) Director Francis Collins, that one way to speed up and make drug discovery and development cheaper and more efficient is to find new indications for medicines already in the clinic.[4] One such example is the commonly used and inexpensive drug dexamethasone, which was shown rapidly to be effective in treating the critical course of COVID-19.[5] As Martin Landray, an epidemiologist at the University of Oxford, stated: 'For less than £50 (US$63), you can treat eight patients and save one life.'[6] The availability of medicines used by several generations of patients (i.e., that are safe) and, therefore, that are very cheap, for the treatment of diseases that still await a cure would be a major breakthrough for the quality and sustainability of healthcare worldwide.

Despite strong public interest, there is no systemic approach to the development of such medicines for new indications anywhere in the world. In this report, my aim is not to discuss drug repurposing in the

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broad sense of the word, but, as the title suggests, focus instead on obstacles that prevent unpatentable, common drugs being approved for new indications in a nonprofit way (i.e., nonprofit drugs).

First deadlock: preclinical data

As is generally known, the situation in biomedical research is poor. According to the 10-year efforts of scientists at Amgen, 89% of the studies they examined in the field of hematology and oncology could not be reproduced.[7] The causes of this are related to serious questions of the sociology of science and the ability of biomedicine to solve its long-known systemic problems.[8,9]

Research in drug repurposing, even in the case of unpatentable drugs, produces a vast amount of data often with no clear significance for translation to the clinic. The situation has gone so far that, for example, the anti-alcoholism medication disulfiram has been proposed in preclinical studies as a drug for various cancers,[10] Alzheimer's disease,[11] TB,[12] Lyme borreliosis,[13] sepsis,[14] and COVID-19,[15] among others, but has not progressed any further. Is it possible that this drug is almost a panacea? Such a situation undermines the credibility of the data to be used as a stimulus for further clinical evaluation.

In preclinical research, the quality of data should be assessed not only by their reproducibility, but also by realistic evidence of the mechanism of action of the drug. By 'realistic evidence', I mean identification of the active compound in animals (in the case of disulfiram, this is the major problem)[16] and *in vitro* experiments based on physiologically meaningful concentrations of the compound. Most importantly, the mechanism of action of the active compound in cells must be the same as in animals.

Second deadlock: organization and administration of clinical trials

In terms of clinical trials, the ongoing COVID-19 pandemic has taught us a significant lesson. Commonly used drugs were inserted directly into the second phase of clinical trials in the hope that their effectiveness against COVID-19 would be verified quickly. However, this has resulted in thousands of clinical trials that have been poorly performed and that only increase chaos and mistrust in research results.[17] We have witnessed the promotion of unverified treatments by not only a previous President of the USA,[18] but also by many doctors, which has led to confusion among the media, public, and patients and their relatives.[19,20] Therefore, the search for quality criteria of scientific studies must be approached not only from a purely scientific point of view, but also with the involvement of patient organizations, governments, and other public life institutions to make the public understand clearly why given data must be of good quality and why public opinion should rely on it and to what extent.

However, the COVID-19 pandemic has also shown us that large, trustworthy, and well-executed clinical trials of various drugs in the public interest are possible. The RECOVERY (UK) and SOLIDARITY (WHO) clinical trials even assessed the effectiveness of some off-patent drugs, one of which (the afore-mentioned dexamethasone) was shown to be a truly effective drug in the treatment of the serious course of the disease.[21,22] However, before the pandemic, such large-scale, nonprofit-funded clinical trials were a rarity. Perhaps the only example was a successful clinical trial of the antibiotic paromomycin against black fever, paid for by Bill and Melinda Gates Foundation, World Bank, WHO, and others.[23]

The idea of nonprofit development of unpatentable drugs in the public interest (i.e., so-called nonprofit drugs) had already been proposed, with disulfiram as a pilot case.[24] Even though it is certainly a matter of public interest, it is not clear who should not only fund the clinical trials for these drugs, organize and administer such studies, but also process and present the results of these studies to regulatory authorities, such as the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) (Table 1).

Of course, large Phase III clinical trials have high financial costs and require significant effort in terms of organizing and administering such studies. Therefore, it is vital that the selection of drugs for this purpose minimizes the risks of failure (in terms of both strong scientific and clinical records and the expected benefit to patients). Finally, emphasis should be placed on ensuring that such studies are carried out in a high-quality manner. However, both the RECOVERY and SOLIDARITY studies showed that the risk of a negative result is high. Therefore, it is necessary right from the beginning to pay attention to the risk and work with it from an educational, ethical, political, and economic point of view. It is important to understand that even negative results can be useful in terms of the progression of knowledge in medicine, and science in general.

Third deadlock: mining from academic clinical trails

As the cases of disulfiram and other common drugs[25] show, it is often possible to find second phases of academic clinical trials (the first phase of clinical trials is not necessary in the case of commonly used medicines) of nonprofit drugs. These tests are paid for, organized by, and administered within academic institutions. For example, the metabolite of disulfiram, dithiocarb, or disulfiram itself were successfully tested in combination with chemotherapy using randomized, placebo-controlled Phase II studies in patients with high-risk breast cancer and metastatic lung cancer, the first of which was published as early as 1993.[26,27] Since then, there has been no progress in clinical research into the efficacy of disulfiram in

TABLE 1

Development of commercial vs. nonprofit drugs.[a]

Role	Drug type	
	Commercial drug	Nonprofit drug
Funding late-stage trials	Pharmaceutical company	No designated entity
Organizing late-stage trials	Pharmaceutical company	No designated entity
Legal responsibility	Pharmaceutical company	No designated entity
Submitting data to regulators	Pharmaceutical company	No designated entity
Postapproval responsibility	Pharmaceutical company	No designated entity

[a] Pharmaceutical companies are entities that fund, organize, and administer late-stage clinical trials of for-profit drugs. They are also in charge of submitting data for approvals or have a postapproval responsibility. In the case of non-profit drugs, there is no such entity for any of these stages.

breast cancer (let alone in lung cancer). There is a lack of awareness in the public space of the importance of this agenda, public institutions, including government bodies, regulators, insurance companies, patient organizations, are not prepared for such a situation. Although academic institutions are still producing new data in the field of repurposing of unpatentable drugs, especially at the laboratory level, their practical application is rare and there are certainly no systemic tools to use these data to develop low-cost and, at the same time, more effective drugs in the public interest.

Small academic studies might be enough to justify the compassionate use of drugs[28] or accelerated drug approval,[29] although even this does not happen with unpatentable drugs. In the latter case, it is not clear from a legal and professional point of view who should process the data obtained by academic studies and submit them to regulatory agencies for assessment. What is certain is that academic institutions are not prepared for such a task. It might be that data published during the early 1990s or earlier have not been used yet for the possible treatment of terminally ill patients and, under the current drug development system, there is no prospect that they will ever be used. We are witnessing a situation instead in which, through the accelerated authorization of medicines, patients often receive very expensive medications, which help them very little or not at all.[30]

Fourth deadlock: neglected potential of pharmaceutical companies

Pharmaceutical companies should also have a significant role in efforts to develop nonprofit drugs. For pharmaceutical companies that produce generic drugs, the motivation to join the endeavor is understandable. The bigger the possibility of using such drugs in a clinic, for example in new indications, the wider application their products will have in the global market. Significant interest can be expected even in the case of the innovative pharmaceutical industry. The gap between laboratory results and clinical reality can be bridged by examining the positive side effects of common drugs used for decades in the clinic.[31] In this way, new, unexpected mechanisms of action can be discovered that will allow the next generation of commercial drugs to be formulated. The accidental discovery of an unexpected mechanism of action (serendipity) is often the basis of a breakthrough in modern medicine. One such example is bortezomib, used under the name Velcade for the treatment of multiple myeloma, and the further generation of drugs with a mechanism of action inspired by the accidental discovery of bortezomib.[32,33] Similarly, the mechanism of action of disulfiram against cancer represents a completely new, unexpected discovery[16] and, if disulfiram proves to be effective against some metastatic cancers, it could lead to the development of commercial drugs with a similar mechanism of action. Thus, nonprofit efforts could help innovative pharmaceutical companies to identify new mechanisms of action in a real clinical environment, which is an invaluable way forward, especially in the current crisis of reproducibility of laboratory data.

Concluding remarks

New inexpensive medications for deadly diseases should be among the highest priorities of governments and societies around the world. Nevertheless, we have very few unpatentable drugs repurposed for new indications in a nonprofit manner; paromomycin for visceral leishmaniosis and dexamethasone for COVID-19 are the exceptions. Although the COVID-19 pandemic has shown us that rapid, high-quality, and nonprofit repurposing of unpatentable drugs is possible, multiple deadlocks to the development of nonprofit drugs remain. Here, I have presented four main deadlocks to the development of nonprofit drugs. First, the crisis of reproducibility and realistic identification of mechanism of action in preclinical and clinical research, which prevents identification of most promising candidates and undermines the credibility of medical science; second, the organization and administration of late-stage nonprofit clinical trials still lack a systemic solution; third, the lack of application of available data from academic clinical studies for compassionate use or accelerated approval of nonprofit drugs; and fourth, pharmaceutical companies are not engaged in, and/or incentivized for, the process of nonprofit drug repurposing. I do not propose any simple solution; instead, my intention is to call the public attention to this topic and to open discussion about how to break these, and other, deadlocks.

Conflicts of interest

The author has no conflict of interest to declare.

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