Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Repurposing of host-based therapeutic agents for the treatment of coronavirus disease 2019 (COVID-19): a link between antiviral and anticancer mechanisms?

Sir,

Drug repurposing, also called repositioning or rediscovering, refers to the process of developing a known drug for a novel use that is different from its original clinical indication. This concept has focused great attention on the search for viable treatments in the context of the current coronavirus disease 2019 (COVID-19) pandemic. The recently published article by Serafin et al. in the *International Journal of Antimicrobial Agents* [1] presented a selection of repurposing drug candidates for potential use in the management of COVID-19. The authors conducted a systematic search of PubMed, Scopus and Web of Science databases and identified recent studies investigating drugs from different pharmaceutical classes with antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and SARS-CoV. Remarkably, at least four drugs reported by Serafin et al. with promising early results in COVID-19 [1], including hydroxychloroquine, chloroquine, nitazoxanide and metformin, have also been previously explored as anticancer agents. The antimalarials hydroxychloroquine and chloroquine are known to inhibit autophagic pathways in aggressive metastatic cells and potentiate the efficacy of chemotherapy in various types of cancer. Autophagy is considered a cytoprotective mechanism that confers drug resistance, representing a key obstacle to effective cancer treatment [2]. Likewise, the antiparasitic drug nitazoxanide induces cancer cell cytotoxicity under hypoxic conditions and could be an excellent candidate to target dormant cancer cells in hypoxic regions of tumours in combination with chemotherapeutic agents [3]. Metformin, an effective medication used in type 2 diabetes mellitus, is able to modulate tumour cell signalling and metabolism. Although the underlying mechanisms have not been completely characterised, metformin reduces tumour cell growth, inhibits the expression of microRNAs associated with tumorigenesis, and limits energy availability by affecting mitochondrial metabolism [4]. Moreover, cell starvation caused by metformin triggers the release of cytokines such as interleukins IL-6 and IL-8, and promotes recruitment of immune cells in the tumour microenvironment [5].

We would like to add some comments regarding the importance of drug repurposing as an emerging approach for the development of host-based antiviral agents, highlighting similarities between antiviral and antitumour mechanisms, when considering other drugs such as lovastatin and ivermectin. Development of host-based antiviral strategies is emerging as an attractive approach to complement the treatment of patients with severe COVID-19 at risk for acute respiratory disease syndrome (ARDS). Clinically approved drugs could be used to target viral entry or viral replication as well as to modulate the innate immune responses [6]. Mechanisms essential for viral infection, such as host cell proteolytic processing, endocytosis, nuclear transport and intracellular signal transduction, among others, have been indicated as better targets to identify broad-spectrum antiviral agents, with some advantages over direct-acting antivirals targeting viral components. For instance, host-based therapeutics could overcome limitations associated with drug resistance or viral mutations.

Well-tolerated compounds with documented antitumour properties are attractive as potential host-based drug candidates for the management of critically ill COVID-19 patients. Lovastatin, a fungal antibiotic used in the treatment of hypercholesterolaemia since the mid-1980s, has been demonstrated to produce potent antitumour effects in experimental mouse models at non-cytotoxic concentrations [7]. In particular, lovastatin holds promise for the clinical management of triple-negative breast cancer [8]. The compound reduces membrane localisation of Rho proteins, thus affecting signalling molecules involved in regulation of the actin cytoskeleton during tumour cell migration and metastatic colonisation [9]. Interestingly, it is known that RhoA signalling is also associated with cellular functions that are relevant to the pathogenesis of several viral infections, including actin organisation and the production of proinflammatory cytokines [10]. It appears that cholesterol depletion by lovastatin causes the shutdown of host cell signals required for viral pathogenesis, similar to the effects on tumour cell signalling.

Lovastatin and other lipophilic statins such as simvastatin and atorvastatin also have profound effects on endothelial cell biology, and it is known that the angiostatic action plays a key role in statin-induced antitumour activity [11]. Likewise, by targeting the host response to infection, statins act on endothelial dysfunction and may contribute to the return to homeostasis in patients with severe COVID-19 [12]. Statins, as well as angiotensin receptor blockers, are able to upregulate angiotensin-converting enzyme 2 (ACE2) [13,14], which is the viral entry receptor for SARS-CoV-2 [15]. However, there is presently no evidence indicating that these medications enhance viral entry into host cells. In fact, once COVID-19 infection has progressed, ACE2 mediates protective effects against lung injury [16], and elevated levels of ACE2 are associated with a reduced severity of ARDS [17]. Hence, treatment strategies that modulate the host response by manipulating the renin–angiotensin system might attenuate the destructive lung disease associated with COVID-19 [12,16].

The well-known antiparasitic drug ivermectin has been reported to possess antiviral activity against a wide range of viruses as well as to display promising antitumour effects in different preclinical models of aggressive cancers [18]. Ivermectin appears to produce pleiotropic actions in virus-infected host cells and malignant tumour cells, but the precise mechanisms are not completely understood. Among other actions, ivermectin affects tumour cell

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Table 1
Selected repurposed drugs with antitumour effects and potential antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Drug	Original indication	Potential antitumour/antiviral mechanisms of action	References
Lovastatin [a]	Cholesterol-lowering drug	Inhibits Rho signalling associated with tumour spread and viral pathogenesis. Counteracts tumour angiogenesis and endothelial dysfunction in ARDS	[9,12]
Ivermectin	Antiparasitic agent	Inhibits nuclear import mechanisms of oncoproteins and viral proteins. Induces immunogenic cell death	[19,21]
Metformin	Hypoglycaemic drug	Among various effects, triggers cytokine release and recruits immune cells	[1,5]
Nitazoxanide	Antiparasitic agent	Not clearly defined. Induces cell cytotoxicity under hypoxic conditions	[1,3]

ARDS, acute respiratory disease syndrome.
[a] Other lipophilic statins such as simvastatin and atorvastatin share similar antitumour and/or antiviral effects.

growth, induces caspase-dependent apoptosis, and causes immunogenic cell death [19]. A few years ago, ivermectin was reported to affect the interaction between the integrase protein of human immunodeficiency virus 1 (HIV-1) and the importin heterodimer $\alpha/\beta 1$. The drug was later confirmed to behave as a potent inhibitor of the nuclear import mechanisms of viral proteins in host cells, including SV40 simian virus large tumour antigen and dengue virus non-structural proteins [20]. Very recently, it was proposed as a mechanism for inhibiting the entry and replication of SARS-CoV-2 [21]. Interestingly, this mechanism of inhibition of nuclear protein trafficking had been suggested as a potential universal target against RNA viruses [22] and could also explain part of the antitumour properties of ivermectin [23]. In this regard, nuclear transport plays a central role in cancer by moving key mediators of carcinogenesis across the nuclear pore [24].

Altogether these evidences stress the importance of host-based strategies in the rapid identification of therapies for COVID-19 patients and, in particular, underscore the potential of certain repurposed drugs with known antitumour activity. Drug repurposing permits reduced development time and cost and implies lesser safety concerns as data on long-term pharmacovigilance for adverse effects are already available. Table 1 presents a summary of selected repurposed drugs, their original medical indications, and potential mechanisms of action. Drugs such as lovastatin, ivermectin, metformin and nitazoxanide constitute promising therapeutic approaches that deserve clinical testing in COVID-19, either alone or as components of antiviral therapy regimens.

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