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Treatments for COVID-19: emerging drugs against the coronavirus - reply

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To the Editor,

I would like to express my gratitude to Sara Khademolhosseini and colleagues for the kind appreciation of our review (1).

In their comment, they point to further extend the spectrum of pharmacological targets against SARS-CoV-2 infection. In particular, they suggest considering strategies aimed at preventing viral particle shedding, in addition to those described by us. Approaches targeting virion exocytosis seem being overshadowed by those aimed at inhibiting viral entry and replication. This apparent discrepancy could be explained by the molecules involved in these last two processes (i.e., Spike protein, TMPRSS2, M^{pro}, etc.), which can offer more specific drug targets, compared to the intracellular machinery involved in the exocytosis. In fact, the vesicular traffic exploited by the virus could be active also in uninfected cells, and its dampening would lead to unpredictable off-target effects.

The specific mechanisms underlying SARS-CoV-2 exocytosis are not known yet. The process may develop through cellular pathways that are common to other coronavirus infections (2), involving the secretory pathway associated with the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). On the basis of the high similarity in sequence identity between SARS-CoV-2 and SARS-CoV-1, it has been hypothesized that the two viruses could share the same exocytosis pathway, which depends on the Golgi coatomer complex and the coatomer protein complex subunit beta2 (COPB2), in particular. There is evidence that if COBP2 is defective, SARS-CoV-1 assembly and release are impaired. Wide compound screening campaigns identified reserpine as an effective agent in counteracting COBP2 functionality (3–5). Further in vitro studies showed that reserpine may revert the transcriptional signature induced by SARS-CoV-2 in a human alveolar cell line (4). Therefore, Sara Khademolhosseini and colleagues wanted to suggest reserpine as a potential agent to be repurposed for treating COVID-19. However, caution must be applied since two out of three of the previous studies are preliminary reports that have not been peer-reviewed yet.

As a pharmacologist, I would like to express some concerns about the possible use of reserpine in this context. Reserpine is an old, well known anti-hypertensive drug, with a peculiar ability to counteract the sympathetic nervous system at both central and peripheral levels. Mechanistically, it inhibits the vesicular monoamine transporter 2 (VMAT2), preventing the accumulation of catecholamines and serotonin into the synaptic vesicles of the adrenergic neurons. Its use has been largely supplanted by other treatments that have shown equal or superior efficacy together with greater tolerability (6,7). Reserpine shows a peculiar, dose-dependent toxicity profile, characterized by sedation, nasal stuffiness, severe depression, even long-lasting after stopping treatment, gastrointestinal disorders, hyperprolactinemia, bradycardia and other cardiac arrhythmias, parkinsonism (8). The putative antiviral activity of reserpine has not been tested in vivo and no indication about effective doses exists. By impairing the sympathetic control, a dose range similar to that used in antihypertensive therapy may be harmful in

critically ill patients with COVID-19. Multiple drug interactions may also occur, such as with adrenaline or other sympathomimetic amines, antiarrhythmic drugs, and sedative drugs like dexmedetomidine, clonidine, which are increasingly used in intensive care units.

For these reasons, we have not included reserpine and other drugs with similar potential in our review. However, we agree that further research is needed to deepen the knowledge of the SARS-CoV-2 exocytosis pathways and may represent a chance of finding new weapons against this global threat.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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