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EDITED AND REVIEWED BY
José L Medina-Franco,
National Autonomous University of Mexico, Mexico

*CORRESPONDENCE
Bruno O. Villoutreix,
bruno.villoutreix@inserm.fr

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Editorial: Development of COVID-19 therapies: Lessons learnt and ongoing efforts

Bruno O. Villoutreix[1]*, Claudio N. Cavasotto[2,3,4] and Juan Fernandez-Recio[5]

[1]INSERM Unit 1141, Hospital Robert Debré, University of Paris, Paris, France, [2]Computational Drug Design and Biomedical Informatics Laboratory, Instituto de Investigaciones en Medicina Traslacional (IIMT), Universidad Austral-CONICET, Pilar, Argentina, [3]Facultad de Ciencias Biomédicasand Facultad de Ingeniería, Universidad Austral, Pilar, Argentina, [4]Austral Institute for Applied Artificial Intelligence, Universidad Austral, Pilar, Argentina, [5]Institute of Vine and Wine Sciences, Spanish National Research Council (CSIC), Logroño, Spain

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Editorial on the Research Topic
Development of COVID-19 Therapies: Lessons learnt and ongoing efforts

The COVID-19 pandemic has led to a dramatic loss of human life worldwide, presented an unprecedented challenge to public health, and caused economic and social disruption at a global scale. The reviews and articles reported in this Research Topics are examples of studies dedicated to small chemical compounds, peptides, nanobodies, and vaccines that could interfere with COVID-19 while one review focuses more specifically on research strategies to that could help facing future health crises.

Research about molecular mechanisms at play and development of appropriate animal models got started soon after the pandemic began. Bastolla et al. investigate the importance of ACE2 in reversing inflammation and its functional role in COVID-19 infection. They propose that degradation of ACE2 by SARS-CoV-2 may cause failing the termination of the inflammatory process, which is ultimately related to both severe COVID-19 infection and its many post-infection manifestations, including the multi-inflammatory syndrome of children (MIS-C). This hypothesis brings potential therapeutic perspectives that might alleviate severe complications of COVID-19 by inhibiting the processes that prevent the reversion of the inflammatory state. Nickl et al. discuss the different SARS-CoV-2 animal models that were developed to assist COVID-19 research and facilitate drug discovery. They highlight the importance of such models during the pandemic, how some could help study long-COVID and comment about future directions. The challenges posed by new SARS-CoV-2 variants to existing vaccines, the partial protection and vaccine refusal, among others, are fueling the development of alternative anti-COVID therapies based on small molecules inhibitors (SMI) or small peptides. Puhl et al. analyzed 25 drugs which are either approved, in the

process of approval, or in the pipeline against COVID-19 for which both *in vitro* and *in vivo* data are available. They concluded that those drugs are structurally diverse, spanning a wide chemical space. Their characterization may help in identifying the fingerprints of a successful treatment for COVID-19, and provide insights about how to discover novel antivirals more efficiently in case of future pandemics. Ogbadoyi and Umar review the potential for development of therapeutics against COVID-19 based on different strategies, such as multicomponent and multi-target pan-viral therapies, multivalent or edible vaccines, and the use of natural products and phytopharming, as well as new methodologies like bioinformatics, computational biology and artificial intelligence methods, or nanomedicine. Villoutreix et al. report a mini review on furin, a critical host enzyme involved in several diseases that was shown to cleave and activate the SARS-CoV-2 spike protein. They extracted over 600 small compounds known to act on furin from open databases and analyzed these small molecules. Most of these compounds display structural alerts or have poor ADME-T properties and thus would need to be optimized in order to become drug candidates. Reboud-Ravaux and El Amri discuss the potential therapeutic power of induced degradations of viral proteins by PROTACs and of RNA by RIBOTACs for the treatment of COVID-19. They note that these approaches seem beneficial in the field of oncology or for autoimmune disorders and could definitively be valuable for infectious diseases. Buchwald review drug design strategies towards the identification of SMIs targeting protein-protein interactions (PPIs), such as the SARS-CoV-2 spike protein and the host ACE2, critical to virus attachment and entry into the cells. A summary of the progress in developing such PPI inhibitors is presented. Kahlenborn et al. report an observational study about the possible beneficial use of bismuth subsalicylate to Covid-19 patients suffering from gastric problems. They suggest that the preliminary positive results call for a detailed evaluation of this molecule as an adjunct treatment of Covid-19. Moroy and Tuffery discuss the rational design of peptides to assist the development of vaccines or as possible drugs, for instance to block protein-protein interactions or to act on enzyme active sites. Valenzuela-Nieto et al. review the use of nanobodies for the diagnosis and treatment of Covid-19 infection. Nanobodies are different from conventional monoclonal antibodies and their specific characteristics provide new possibilities for the generation of effective neutralizing antibodies. The authors discuss the current strategies for the production of nanobodies, and their application to help fighting SARS-CoV-2 infection, as well as other viral pathogens. Yan et al. note that vaccine efficacy has been greatly reduced by the advent of variants. This is of concern for the general population and even more so for vulnerable subjects. They comment about the benefits and risks of receiving booster vaccinations. Gold and Edwards present alternatives to traditional drug development models based, primarily, on patents. Having in mind the next pandemic, they state that open science partnerships (OSPs), combining the activity of the academic, philanthropic, and governmental sectors, and private incentives, will be instrumental to share knowledge and develop and evaluated SMIs. An example of this is the Viral Interruption Medicines Initiative, a not-for-profit Canadian OSP.

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