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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Tackling the COVID-19 “cytokine storm” with microRNA mimics directly targeting the 3’UTR of pro-inflammatory mRNAs

Jessica Gasparello a, Alessia Finotti a, Roberto Gambari a,b,*

a Department of Life Sciences and Biotechnology, University of Ferrara, Italy
b Center for Innovative Therapies in Cystic Fibrosis, University of Ferrara, Italy

A R T I C L E   I N F O

Keywords:
COVID-19
Cytokine storm
microRNAs
mRNA therapeutics

A B S T R A C T

COVID-19 is characterized by two major clinical phases [1]. The first is the SARS-CoV-2 infection of target cells and tissues, and a deep inflammatory state, known as “cytokine storm”, caused by activation of pro-inflammatory genes, such as NF-κB, STAT-3, IL-6, IL-8, IL-1β. Among possible anti-inflammatory agents, the “microRNA targeting” should be carefully considered, since it is well known that miRNAs are deeply involved in the expression of cytokines, chemokines and growth factors. The working general hypothesis is that targeting the microRNA network might be important for the development of therapeutic approaches to counteract the COVID-19 induction of inflammatory response. This hypothesis is based on several publications demonstrating the use of miRNA mimics for inhibitory effects on the production of proteins characterizing the COVID-19 “cytokine storm”.

Introduction

COVID-19 is characterized by two major clinical phases [1]. The first is the SARS-CoV-2 infection of target cells and tissues, leading to important clinical manifestations and complications, such as pulmonary failure [1]. The second phase is a deep inflammatory state, known as “cytokine storm”, caused by activation of pro-inflammatory genes, such as NF-κB, STAT-3, IL-6, IL-8, G-CSF [2–9]. In COVID-19 cytokine storm, this perturbation is initiated via attachment of the SARS-CoV-2 spike protein to ACE2 receptor, followed by the ACE/Ang II/AT1R axis activation leading to hyperactivation of NF-κB by IL-6/STATs axis [3]. Although SARS-CoV-2 itself activates NF-κB through pattern recognition receptors, it is the simultaneous activation of NF-κB and STAT-3 that enhances NF-κB activation machinery (the IL-6 amplifier) [4]. This hyper-activation of NF-κB via the IL-6 in the lung tissues induces a cytokine storm with subsequent ARDS (Acute Respiratory Distress Syndrome) that has been observed in severe COVID-19 patients [6,7]. In fact, several studies found a clear relationship between the hyper-inflammatory state and the severity of the disease [6–9]. The pharmacological approach for treating ARDS needs novel anti-inflammatory reagents as different COVID-19 patients might respond differently to these treatments [10–17].

Table 1 shows a partial list of studies outlining the induction of cytokines, chemokines and growth factors in COVID-19 [8,18–25]. As clearly evident, IL-1β, IL-6 and IL-8 are found up-regulated in most studies. Interestingly, upregulation of these proteins following SARS-CoV-2 infection is associated with poor outcome of the COVID-19 patients [7,8]. Finally, the therapeutic importance of these molecules is supported by the ongoing clinical trials based on their targeting, such as NCT04381052 (based on the IL-6 inhibitor Clazakizumab), NCT04247226 (based on the IL-8 neutralizing agent BMS-986253) and NCT04603742 (based on Anakinra, a recombinant IL-1 receptor antagonist, inhibiting both IL-1α and IL-1β).

Among possible anti-inflammatory strategies, the “microRNA targeting” should be carefully considered [26], since it is well known that microRNAs are deeply involved in the expression of cytokines, chemokines and growth factors [27].

MicroRNAs are from 19 to 25 nucleotides noncoding RNAs that regulate gene expression by targeting miRNAs, leading to translational repression or mRNA degradation [28,29]. Since their discovery, the number of microRNA sequences deposited in the miRBase databases is significantly growing [30]. The complex networks constituted by miRNAs and RNAs lead to the control of highly regulated biological functions, such as differentiation, cell cycle and apoptosis [31].

Fig. 1 shows microRNAs potentially regulating the expression of IL-1β, IL-6 and IL-8. Some miRNA-binding sites (which are boxed) are in
Table 1
Proteins involved in the COVID-19 “Cytokine Storm”

| Cytokines, chemokines and growth factors | Biological sample | Reference | Notes/comments |
|------------------------------------------|------------------|-----------|----------------|
| IL-2, IL-7, IL-10, M-CSF, G-CSF, MCP-1, MIP1-α, TNF-α | Serum | Costela-Ruiz et al., 2020 [18] | Up-regulated in serum of patients admitted to ICUs (Intensive Care Units). |
| IL-6 | Blood | Chen et al., 2020 [19] | Increased in 52% of admitted hospital patients with a diagnosis of COVID-19 pneumonia. |
| IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1-α, and TNF-α | Plasma | Huang et al., 2020 [20] | Up-regulated in the acute phase of the illness, in plasma samples of patients affected by COVID-19 infection. |
| IL-6 | Plasma | Wang et al., 2020 [21] | The level of IL-6 in peripheral blood is an early indicator of cytokine release syndrome in COVID-19-associated pneumonia. |
| IL-1α, IL-1β, IL-7, IL-8, IL-10, FGF, GM-CSF, IFNγ, G-CSF, IP10, MCP1, MIP1-α, PDGF, TNF-α, VEGF | Serum | Zhang et al., 2020 [22] | The listed ILs are increased in SARS-CoV-2 infection, among which IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1-α, TNF-α are higher in severe patients, while no major differences of serum IL-6 levels in ICU and non ICU patients were found. |
| IL-2R, IL-6, IL-10, TNF-α | Plasma | Chen et al., 2020 [23] | IL-2R, IL-6, IL-10, TNF-α were markedly higher in severe cases than in moderate cases. Of note, IL-6 levels were increased in both moderate and severe cases. |
| IL-1α, IL-6, IL-8, IL-10, sTNFR1 | Plasma | McElvaney et al., 2020 [24] | The listed ILs levels were detected in healthy volunteers, hospitalized but stable patients with COVID-19 (COVID stable patients), patients with COVID-19 requiring ICU admission (COVIDICU patients). IL-1α, IL-6, IL-8, and sTNFR1 were all increased in patients with COVID-19. COVIDICU patients could be clearly differentiated from COVID stable patients, and demonstrated higher levels of IL-1α, IL-6, and sTNFR1 but lower IL-10. |
| TNF-α, IL-6, IL-10 | Serum | Diao et al., 2020 [25] | Levels of TNF-α, IL-6, and IL-10 were significantly increased in infected patients, and their levels in ICU patients were significantly higher than in non-ICU patients. |
| IL-6, IL-8, TNF-α | Serum | Del Valle et al., 2020 [8] | High levels of IL-6, IL-8 and TNF-α at the time of hospitalization are strong predictors of patient survival. |

The hypothesis

The working general hypothesis is that targeting of the microRNA network might be important for the development of therapeutic approaches to counteract the COVID-19 induction of inflammatory response (Fig. 2). This hypothesis is based on several publications demonstrating the use of miRNA mimics for inhibitory effects on the production of proteins characterizing the COVID-19 “cytokine storm”. For instance, Fabbi et al. have demonstrated that miR-93-5p targets and inhibits the expression of IL-8 gene. Accordingly, transfections of several cell lines with pre-miRNA sequences lead to (a) increase of intracellular miR-93-5p content and activity and (b) sharp decrease of IL-8 mRNA content and IL-8 release [34].

Experimental evaluation of the hypotheses

Choice of the anti-miRNA molecule

This is a key step in designing a meaningful approach to negatively control the COVID-19 associated “cytokine storm”. In fact, several microRNA target sites are present in the 3’UTR of cytokine/chemokine mRNAs. An in silico analysis based on the analysis of molecular interactions between microRNAs and target sites present in the 3’UTR of pro-inflammatory mRNAs might be of great help for understanding the theoretical stability and possible importance of these interactions and for designing potential bioactive sequences. This is shown in Fig. 3 (boxed area). The sequence of the agomIR might be designed to display an even increased affinity to the target mRNA in respect to the original miRNA sequence. The miRNA mimicking approach (outlined in Fig. 2) might be verified in verifying which miRNA should be mimicked in order to decrease mRNA/protein expression.

Experimental strategy to verify potential anti-inflammatory activity of miRNAs targeting the 3’UTR regions of COVID-19 associated pro-inflammatory mRNAs

In order to validate the hypothesis cytokines/chemokines/growth factors should be analysed using well known biochemical approaches (for instance those based on ELISA and Bio-plex assays). One example has been reported in several studies and it is based on the use of a 27-plex analyzing, among others, most of the COVID-19 associated cyto/chemokines, such as IL-6, IL-8, IP-10, G-CSF and TNF-α. The experimental approach that might be employed is described in Fig. 3 and it is based on the induction of pro-inflammatory mRNAs following exposure of in vitro growing cell lines to the SARS-CoV-2 Spike protein. This treatment leads to a fast and reproducible increase of the expression of pro-inflammatory mRNA, as published by Wang et al. [37] who reported an upregulation of IL-6 and TNF-α induced by SARS-coronavirus spike protein in murine macrophages via NF-kB pathway.

The key steps of the experimental strategy are summarized in Fig. 3. Among the cell lines that have been demonstrated to respond to SARS-CoV-2 Spike exposure are human airway epithelial Calu-3 cells, CFBE410o- and the IB3-1 human cystic fibrosis (CF) bronchial epithelial
cells, and the mouse RAW 264.7 macrophage-like cells [37–40]. The experimental plan should verify (a) response to different concentrations of SARS-CoV-2 Spike protein for different length of time; (b) co-treatment with different concentrations of pre-miRNAs targeting pro-inflammatory mRNAs that have been found over-expressed on COVID-19; (c) isolation of RNA and quantitation of pro-inflammatory mRNAs by RT-qPCR; (d) analysis of the secretome profile. Recombinant SARS spike glycoprotein is commercially available. In addition, several plasmids for recombinant SARS-CoV-2 Spike production might be obtained from different sources; for instance, a SARS-CoV-2 (2019-nCoV) Spike RBD Gene ORF cDNA clone expression plasmid, C-His tag (Codon Optimized) is available from Sino Biological.

Final experimental validation

The final experimental validation of the tested approaches should be based on infection of target cells with viable SARS-CoV-2 viral particles and testing the activity on pro-inflammatory mRNAs and secretome profile. In addition, suitable delivery systems should be considered and tested, in order to develop treating strategies for COVID-19 patients carrying other pathologies. This should be considered a primary goal for the development of treatments of COVID-19 patients affected by associated pulmonary diseases, such as cystic fibrosis, COPD and asthma. In this context, aerosolic delivery might be considered, as well as the use of novel delivery reagents, such argininocalix[4]arene macrocycles as reported by our research group for miRNA delivery [41].

Consequences of the hypothesis and discussion

The expected outcomes of the approach described in this paper are the following.

- Development of a protocol based on the exposure of target cells to the SARS-CoV-2 spike protein, in order to induce high expression levels of genes involved in the COVID-19 “cytokine storm”.
- Protocols for the alteration of the inflammasome using miRNA targeting and/or mimicking.

Conclusions

The proposed approaches might lead to the development of protocols for the reduction of the expression of key components of the COVID-19 “cytokine storm” [1–5]. This is a major issue in the management of COVID-19 patients [6–17]. As far other DNA- and RNA-based therapeutic interventions [42] suitable delivery systems should be considered for optimizing the proposed treatment.

Table 2

| miRNA | miRNA binding sites |
|-------|---------------------|
| IL-1β | miR-21-5p, miR-204-5p, miR-376c-3p, miR-155-5p, miR-181c-3p, miR-587, miR-101-3p, miR-10b-5p, miR-126-3p, miR-128-3p, miR-129-2-3p, miR-203a-3p, miR-34a-5p, miR-34c-5p, miR-375, miR-429, miR-449a, miR-7-5p |
| IL-6  | miR-155-5p, miR-125a-3p, miR-149-5p, miR-192-5p, miR-590-3p, miR-100-5p, miR-671-5p, let-7b-5p, miR-16-5p, miR-376a-5p, miR-335-5p, miR-98-5p, miR-124-3p, miR-1-3p, miR-34a-5p, miR-98-5p, miR-99a-5p, miR-191-5p, miR-128-3p, miR-138-5p, miR-182-5p, miR-195-5p, miR-203a-3p, miR-205-5p, miR-21-3p, miR-21-5p, miR-221-3p, miR-27a-3p, miR-27a-5p, miR-330-3p, miR-34b-5p, miR-375, miR-429, miR-7-5p, miR-373-3p, miR-372-3p, miR-302a-3p, miR-148b-3p, miR-133a-5p, miR-122-5p |
| IL-8  | miR-195-5p, miR-20a-5p, miR-106a-5p, miR-17-5p, miR-30c-1-3p, miR-93-5p, miR-373-3p, miR-520c-3p, miR-10a-3p, miR-1225-5p, miR-22a-3p, miR-23b-3p, miR-206-3p, miR-302c-5p, miR-302d-5p, miR-450a-5p, miR-493-5p, miR-499a-3p, miR-519d-3p, miR-520a-3p, miR-526b-3p, miR-5582-3p, miR-587, miR-664a-3p, miR-1-3p, miR-429, miR-34a-5p, miR-155-5p, let-7b-5p, miR-124-3p, miR-126-3p, miR-16-5p, miR-27a-3p, miR-335-5p, miR-1291, miR-138-5p, miR-101-3p, miR-107, miR-129-2-3p, miR-130a-3p, miR-146a-5p, miR-147a, miR-194-5p, miR-203a-3p, miR-21-3p, miR-21-5p, miR-210-3p, miR-212-3p, miR-214-3p, miR-221-3p, miR-29a-5p, miR-29a-3p, miR-30d-3p, miR-376a-5p, miR-671-5p, miR-7-5p, miR-941, miR-99b-5p, miR-520f-3p, miR-372-3p, miR-148b-3p, miR-133a-3p, miR-9-5p, miR-30a-5p |

![Fig. 1. Venn diagram showing (a) the number of miRNA binding sites present in the 3′UTR of IL-1β mRNA (18 miRNA binding sites), IL-6 (40 miRNA binding sites) and IL-8 mRNA (64 miRNA binding sites) and (b) the miRNA binding sites found in common (which are enlisted in the boxes).](image-url)
Fig. 2. Possible use of “miRNA therapeutics” for downregulation of SARS-CoV-2 induced IL-8 gene expression. The upregulation of the IL-8 gene, occurring through the NF-kB/STAT-3 axis [3] might be strongly inhibited by transfection of pre-miRNA (agomiRNA) targeting the 3′UTR of IL-8 mRNA. This might lead to IL-8 mRNA degradation or inhibition of IL-8 translation and consequent release. Evidences supporting (a) SARS-CoV-2 mediated IL-8 transcription and (b) post-transcriptional, miRNA dependent regulation of IL-8 production have been reported in several studies [3,4,34–36].

Fig. 3. Evaluation of the hypothesis. Induction of IL-8 upregulation can be obtained by exposing cultured in vitro cell lines to the SARS-CoV-2 Spike protein (S-protein). Possible inhibition of IL-8 gene expression can be obtained by transfection of the cells with agomiR molecules (in the example agomiR-93-5p) able to interact with the 3′UTR sequence of IL-8 mRNA (as depicted in the boxed area). Effects on mRNA content and translation (see also Fig. 2 for a scheme of the agomiR-mediated effects) can be analyzed by RT-qPCR and ELISA (or Bio-plex approaches).
Declaration of Competing Interest

The authors declare that they have no competing interests.

References

[1] Paciarella G, Strumia A, Piliego C, Bruno F, Del Bueno R, Costa F, et al. COVID-19 diagnosis and management: a comprehensive review. J Intern Med. 2020;286:192-206.

[2] Mehta F, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.

[3] Mahmudpour M, Roohbakhsh J, Keshavari R, Farrokhzad S, Nabipour I. COVID-19 cytokine storm: The anger of inflammation. Cytokine 2020;133:155151.

[4] Murakami M, Hirano T. The Pathological and Physiological Roles of IL-6 Amplifier Activation. Int J Biol Sci. 2012;18:1267-80.

[5] Hirano T, Murakami M. COVID-19: A new virus, but a familiar receptor and cytokine release syndrome. Immunity 2020;52:731-3.

[6] Chi Y, Ge Y, Wu B, Zhang W, Wu T, Wen T, et al. Serum Cytokine and Chemokine profile in Relation to the Severity of Coronavirus disease 2019 (COVID-19) in China. J Infect Dis. 2020;222:746-54.

[7] Aggarwal A, Baker CS, Evans TW, Haslam PL. G-CSF and IL-8 but not GM-CSF correlate with severity of pulmonary neutrophilia in acute respiratory distress syndrome. Eur Respir J. 2006;15:895-901.

[8] Del Valle DM, Kim-Schulze S, Hsin-Hui H, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature helps predict COVID-19 severity and death. Nat Med. 2020;26:16:36-43.

[9] Chukwuma IF, Apeh VO, C OF. Mechanisms and potential therapeutic targets of hyperinflammatory responses in SARS-CoV2. Acta Virol. 2020. In press.

[10] Mehla P, Porter JC, Manson JJ, Isaacs JD, Gopenhaw PJJM, McInnes IB, et al. Therapeutic blockade of granulocyte macrophage colony-stimulating factor in COVID-19-associated hyperinflammation: challenges and opportunities. Lancet Resp Med. 2020;5:2213:3600:30267-8.

[11] Crisafiulli S, Iorgó V, La Corte L, Atzeni F, Trifirò M. Potential Role of Anti-interleukin (IL)-6 Drugs in the Treatment of COVID-19: Rationale. Clinical Evidence and Risks. BioDrugs 2020;34:1-8.

[12] Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol. 2020;29:2085-94.

[13] Rodrigues-Diez RR, Tejera-Munoz A, Marquez-Exposito I, Rayego-Mateos S, Sanchez LS, Marchant V, et al. Statins: Could an old friend help the fight against COVID-19? Br J Pharmacol. 2020;177:4873-86.

[14] Bosch-Barrera J, Martin-Castillo B, Buño M, Brunet J, Encinar JA, Menendez JA. Silibinin and SARS-CoV-2: Dual Targeting of Host Cytokine Storm and Virus Replication Machinery for Clinical Management of COVID-19 Patients. J Clin Med. 2020;9:6:e1776.

[15] Bahrami M, Kamalinjad M, Latifi SA, Seif F, Dadmehr M. Cytokine storm in COVID-19 and paroxysmal: preclinical evidence. Phytother Res. 2020. In press.

[16] Pelasa C, Tinello C, Vatrrella A, De Sarro G, Pelasa G. Lung under attack by COVID-19-induced cytokine storm: pathogenic mechanisms and therapeutic implications. Ther Adv Respir Dis. 2020;14.

[17] Amigues I, Pearlman AH, Patel A, Reid P, Robinson PC, Sinha R, et al. Coronavirus disease 2019: investigational therapies in the prevention and treatment of hyperinflammation. Expert Rev Clin Immunol 2020. In press.

[18] Costela-Ruiz VJ, Illecas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L. SARS-CoV-2 Infection: The role of cytokines in COVID-19 disease. Cytokine Growth Factor Rev. 2020;5:462-75.

[19] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.

[20] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.

[21] Wang W, Liu X, Wu S, Chen S, Li Y, Nong L, et al. Definition and Risks of Cytokine Release Syndrome in 11 Critically Ill COVID-19 Patients With Pneumonia: Analysis of Disease Characteristics. J Infect Dis. 2020;222:1444-51.

[22] Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clin Immunol. 2020;214:108393.

[23] Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130:2620-9.

[24] McElvaney OJ, McEvoy NI, McElvaney OF, Carroll TP, Murphy MP, Dunlea DE, et al. Characterization of the Inflammatory Response to Severe COVID-19 Illness. Am J Respir Crit Care Med. 2020;202:812-21.

[25] Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning I, et al. Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19). Front Immunol. 2020;11:827.

[26] Hansa J, Hossain GS, Kocerha J. The Potential for microRNA therapies and Clinical Research. Front Genet. 2019;10:478.

[27] Palanisamy V, Jakyimiv A, Van Tubergen EA, D’Silva NJ, Kirkwood KL. Control of Cytokine mRNA Expression by RNA-binding Proteins and microRNAs. J Dent Res. 2012;91:651-8.

[28] Alvarez-Garcia I, Miska EA. MicroRNAs functions in animal development and human disease. Development 2005;132:653-62.

[29] He L, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. Nat. Rev. Genet. 2004;5:52:32.

[30] Griffiths-Jones S-Jones The microRNA Registry. Nucleic Acids Res. 2004;32:D109-111.

[31] Lim LP, Lau NC, Garrett-Engele P, Grimson A, Schelter JM, Castle J, et al. Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. Nature 2005;433:769-73.

[32] Zhou CH, Shrestha S, Yang CD, Chang NW, Lin YL, Liao KW, et al. miR-17TargetBase 2018: a resource for experimentally validated microRNA-target interactions. Nucleic Acids Res. 2017;46:D296-302.

[33] Huang HY, Lin YC, Li J, Huang KY, Shrestha S, Hong HC, et al. miR17TargetBase 2020: updates to the experimentally validated microRNA-target interaction database. Nucleic Acids Res. 2020;48:D146-54.

[34] Fabbri F, Borgetti M, Montagner G, Bianchi N, Finotti A, Lamponti I, et al. Expression of microRNA-93 and Interleukin-8 during Pseudomonas aeruginosa-mediated induction of proinflammatory responses. Am J Respir Cell Mol Biol. 2014;50:1144-55.

[35] Oglesby IR, Venckcn S, Agrawal R, Gaughan K, Molley K, Higgins G, et al. miR-17 overexpression in cystic fibrosis airway epithelial cells decreases interleukin-8 production. Eur Respir J. 2015;46:150:60.

[36] Hong L, Sharp T, Khorand B, Fischer C, Ilisson S, Salem A, et al. MicroRNA-200c Represses IL-6, IL-8, and CCL-5 Expression and Enhances Osteogenic Differentiation. PLoS ONE 2016;11:e0169015.

[37] Wang W, Ye L, Ye L, Li B, Gao B, Ye Z, et al. Up-regulation of IL-6 and TNF-alpha induced by SARS-coronavirus spike protein in murine macrophages via NF-kappaB pathway. Virus Res. 2007;128:1-8.

[38] Tseng CT, Tseng J, Perrone L, Worthy M, Popov V, Peters CJ. Apical Entry and Release of Severe Acute Respiratory Syndrome-Associated Coronavirus in Polarized Calu-3 Lung Epithelial Cells. J Virol. 2005;79:9470-9.

[39] Dittmar M, Seung Lee JS, Whig K, Segrest I, Li M, Jurado K, et al. Drug repurposing screens reveal FDA approved drugs active against SARS-Cov-2. In press.

[40] Poschet JF, Perkett EA, Timmins GS, Deretic V. Azithromycin and ciprofloxacin screens reveal FDA approved drugs active against SARS-Cov-2. In press.

[41] Poschet JF, Perkett EA, Timmins GS, Deretic V. Azithromycin and ciprofloxacin screens reveal FDA approved drugs active against SARS-Cov-2. In press.

[42] Fiyush B, Rajantri K, Chartjee A, Khan R, Ray S. Nuclear acid-based therapy for coronavirus disease 2019. Helioyn. 2020;5:9:e05007.