The long and winding road to Covid-19 treatments and vaccines

Part 1: drug repurposing

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Note: highlighted in italic are information for non-biologists

Introduction

In the past few months, we have been witness of the most rapid and unprecedented growth of scientific and clinical information regarding one specific field of investigation. SARS-CoV-2 (CoV-2) and Covid-19 pandemic have represented a unique opportunity to create the strongest synergies among scientists and clinicians belonging to different expertise: from epidemiology, to virology, molecular and structural biology and bioinformatics, to immunology, pneumology, cardiovascular and social sciences. This great effort, besides pandemic containment and the collection of a huge amount of knowledge about CoV-2 biology, still aims at finding efficient solutions in terms of therapies and vaccines, to definitively eradicate this coronavirus and its related pathology. Currently, we know that Covid-19, in its severe clinical manifestation, is

Figure 1

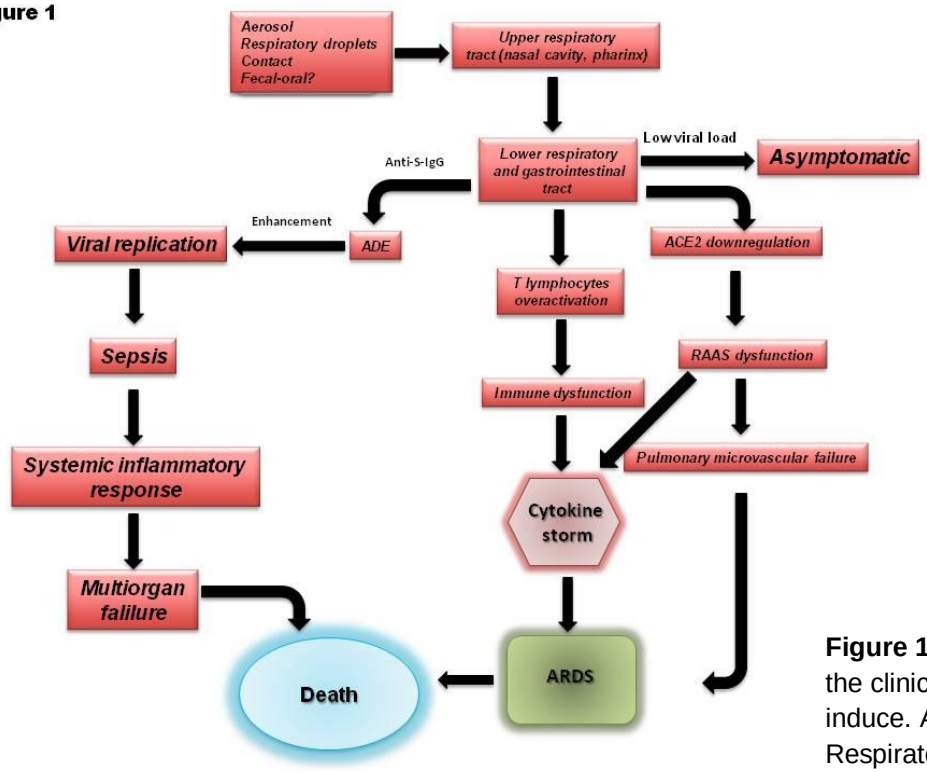


Figure 1. Graphical representation of the clinical manifestations CoV-2 may induce. Abbreviations: ARDS= Acute Respiratory Distress Syndrome

a hyperinflammatory, multiorgan and potentially lethal pathology (figure 1). We may also define severe Covid-19 as a “multifactorial” disease, as a dismal prognosis depends on a variety of factors, including viral load, pre-and co-existing pathologies, age, gender[1], Angiotensin Converting Enzyme 2 (ACE2) and Human Leukocyte Antigen (HLA) polymorphism[2,3], ethnicity[4]. Therefore, Covid-19 has to be approached by multimodal therapeutic protocols.

To date, many therapeutic routes have been explored - synthetic peptides, small molecules, monoclonal antibodies and convalescent plasma, cell therapy - and many clinical trials are ongoing (table 1). Furthermore, we have a number of top runners vaccines which will be presumably ready for massive production in the forthcoming autumn.

Table 1

Treatment	Number of trials
Remdesivir	16
Lopinavir/ritonavir	35
Ribavirin	3
Tenofovir	2
Galidesivir	1
Darunavir	2
Camostat	6
Favipiravir	21
Ivermectin	26
Hydroxychloroquine	186
Umifenovir	4
Tocilizumab	36
Steroids	12
Interferon	20
Convalescent plasma	104
Stem cells	47
Vaccines	130

Drug repurposing

One strategy to unveil novel therapeutic routes is drug repurposing, *that is the use of already known and approved drugs, successfully employed for the treatment of other pathologies.* Indeed, the first line of treatment to counteract and alleviate Covid-19 symptoms was represented by a combination of antivirals and corticosteroids. The recent proteomic analysis of 26 (out of 27) CoV-2 proteins and the identification of high-confidence host interactors have indicated targets for repurposing strategies[5]. CoV-2 proteins interact with mediators of pivotal host cell functions. 40% of CoV-2 proteins interact with endomembrane and vesicular trafficking pathway, which may explain the massive re-shaping of endoplasmic reticulum (ER)/Golgi apparatus trafficking during viral infection. Some proteins interact with epigenetic regulators - such as Histone Deacetylase 2

(HDAC2) and bromodomain and extra-terminal domain (BET) readers - as well as with proteins of innate immune pathway, ubiquitin pathway and host translational machinery[5]. This kind of analyses have identified a number of already approved, preclinical and investigational new drugs[5]. Among them, protein biogenesis inhibitors and ligands of Sigma 1 and 2 receptors – two transmembrane receptors expressed in the brain and immune system[6,7], reduced CoV-2 infectivity[5].

- **Antivirals**
  - **Interferons**

    CoV-2 may suppress primary immune responses also impairing interferon production and signaling[8,9]. Furthermore, in earlier reports, interferons seem to be detrimental instead of beneficial, as they enhance ACE2 expression, potentially increasing CoV-2 infection ability[9]. Furthermore, as receptors for type I and II interferons are ubiquitously expressed, an interferon-based therapy has to face with dangerous side effects. However, type III interferon λ has been suggested as a potential therapeutic agent, as impairs prevent viral dissemination from nasal epithelial cells to the upper respiratory tract[10] and is a protective molecule rather than pro-inflammatory[11]. Very recently, interferon λ has been proven to be effective in inhibiting viral replication in airway epithelial cells and to have prophylactic and therapeutic activity in the only mouse model currently available recapitulating CoV-2 infection (figure 2)[12].

Figure 2

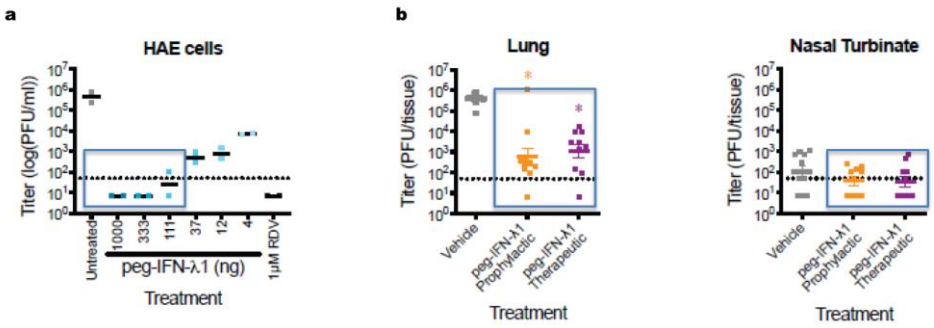


Figure 2. Effect of IFN λ on the viral load "in vitro" and "in vivo". a) Human airway epithelial cells. b) Mouse lung (left) and nasal turbinate (right). Highlighted. a blu rectangle, data obtained by by IFN λ administration
Abbreviations: HAE=human airway epithelial cells. *peg=pegylated interferon **pegylation is the process of conjugating molecules with polyethilenglycole (PEG) to enhance their delivery in tissues and cells.* (Adapted from: *Dinnon et al., bioRxiv. 2020 May 7:2020.05.06.081497. doi: 10.1101/2020.05.06.081497).*

- **Inhibitors of RNA polymerase (RNAP)**

  a. Remdesivir. Many clinical trials (table 1) are currently testing the efficacy of this drug in counteracting CoV-2 infection. Remdesivir is a prodrug nucleoside analog, which is converted within the cell into an adenosine triphosphate analog, inhibiting the viral RNA polymerase. It has been already use to treat Ebola[13] virus infection and it has been demonstrated to possess antiviral activity against SARS-CoV and MERS-CoV[14] in non clinical models, and against CoV-2 "in vitro"[15]. The structural basis of remdesivir action has been recently clarified by the CryoEM structure of CoV-2 RNA-dependent RNA Polymerase (RdRp), at 2.5 Å resolution, complexed with: i) non structural proteins (nsp) 7 and 8, which enhance RdRp binding to RNA templates and processivity; ii) a 50 base pair RNA template primer; iii) remdesivir (figure 3)[16]. Remdesivir, in its monophosphate form (RMP), lies into the catalytic RdRp region, at the 3' site of the RNA primer and is incorporated in the replicated strand at the first base pair, leading to chain termination, once converted into its triphosphate form (RTP)[16]. This kind of mechanism has been proposed for other antiviral drugs, such as favipiravir, galidesivir, ribavirin, with the same inhibitory action on RdRp[17].

Figure 3

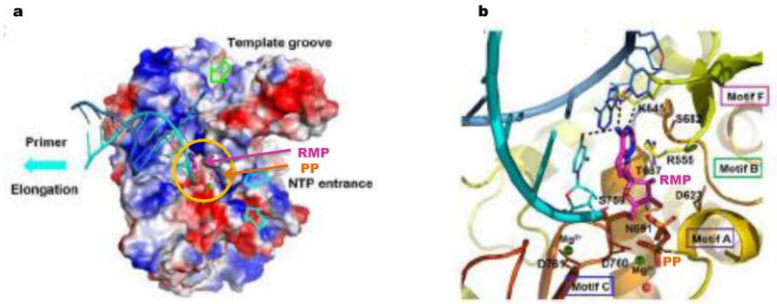


Figure 3. a) Structure of RdRp catalytic domain, with its electrostatic potential from negative (red) to positive (blue), bound to the RNA template (cyan). The enzyme active site is highlighted by a yellow circle. Remdesivir, in its monophosphate form (RMP) is shown in purple and pyrophosphate (PP), required for the conversion of remdesivir from mono-to triphosphate form trifosfato (RTP), in orange. b) Magnification of RdRp active site. Beside RMP and PP, magnesium ions (Mg^{2+}), also required for remdesivir conversion, are shown in green. Abbreviations: RMP=remdesivir monophosphate; PP=pirophosphate; NTP=nucleotide triphosphate. (Adapted from: *Yin et al, Science, 2020*).

In a first report, related to the compassionate use of remdesivir, in 36 out of 53 severe Covid-19 patients (30 receiving mechanical ventilation and 4 receiving extracorporeal membrane oxygenation), a clinical improvement was observed (figure 4a and b)[18]. The first randomized, double blind, placebo controlled clinical trial using remdesivir (with the addition of lopinavir/ritonavir and corticosteroids) on 237 severe patients reported no statistically significant clinical benefits (ClinicalTrials.gov identifier: NCT04257656) (figure 4c). However, early remdesivir-treated individuals experienced faster clinical improvement than the placebo group, suggesting more promising results in a larger cohort of patients when treated at the onset of the disease (figure 4d)[19].

b. Other RNAP inhibitors. By molecular docking experiments, other nucleoside analogs have been reported to potentially inhibits RdRp activity and viral replication. Ribavirin and sofosbuvir (already tested for limiting HCV infection[20]), tenofovir (employed for HIV prevention)[21] and galidesivir (considered as potential treatment against Ebola and hemorrhagic fever virus)[22] have been shown a binding energy for CoV-2 RdRp similar to that of physiological nucleotides (figure 5a). Intriguingly, another nucleoside analog, IDX184, currently in clinical trial for HCV[23], showed an even better binding energy and therefore stronger affinity for CoV-2 RdRp (figure 5a). This difference in RdRp affinity, relies on the number of hydrogen bonds, hydrophobic, halogen and π–cation interactions (*that is, a non-covalent binding between the face of a chemical compound with a cyclic (namely, aromatic) structure, provided with resonance bonds, which confers a high stability, and a cation*) (figure 5b)[24]. Moreover, favipiravir, a purine nucleotide RNAP inhibitor, has been proven to be effective in ameliorating the clinical conditions of Covid-19 patients[25].

c. β-d-N4-hydroxycytidine (NHC) ribonucloside analogs. These analogs have been already shown a braod antiviral activity. Very recently, it has been demonstrated that they also possess antiviral activity against MERC-CoV and CoV-2 in primary human airway epithelial cells (figure 5c)[17]. More importantly, EIDD-2801, an orally bioavailable prodrug of β-d-N4-

Figure 4

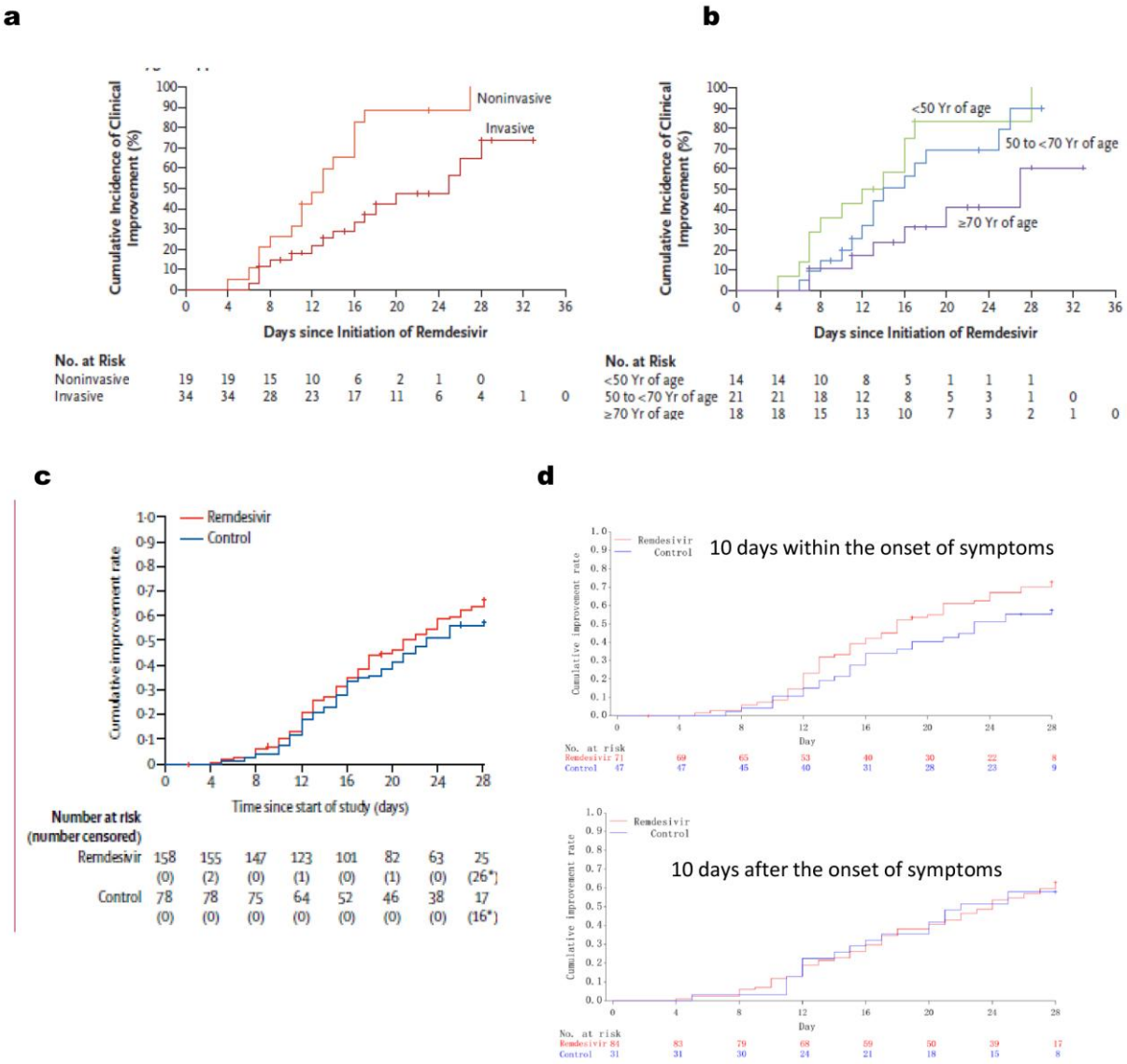


Figure 4. Effect of compassionate use of remdesivir on patients stratified for ventilation procedure (invasive vs non invasive) (a) and age (b). c) Effect of remdesivir on 158 patients (with respect to the control group, 79 patients) with pneumonia and sPO_2 of 94% or low. Treatment was initiated 10 days after the onset of symptoms. d) Effect of remdesivir when administrated 10 days within the onset of symptoms (upper panel) or after (lower panel). (Adapted from: *Grein et al., NEJM, 2020; Wang et al., Lancet, 2020*).

Figure 5

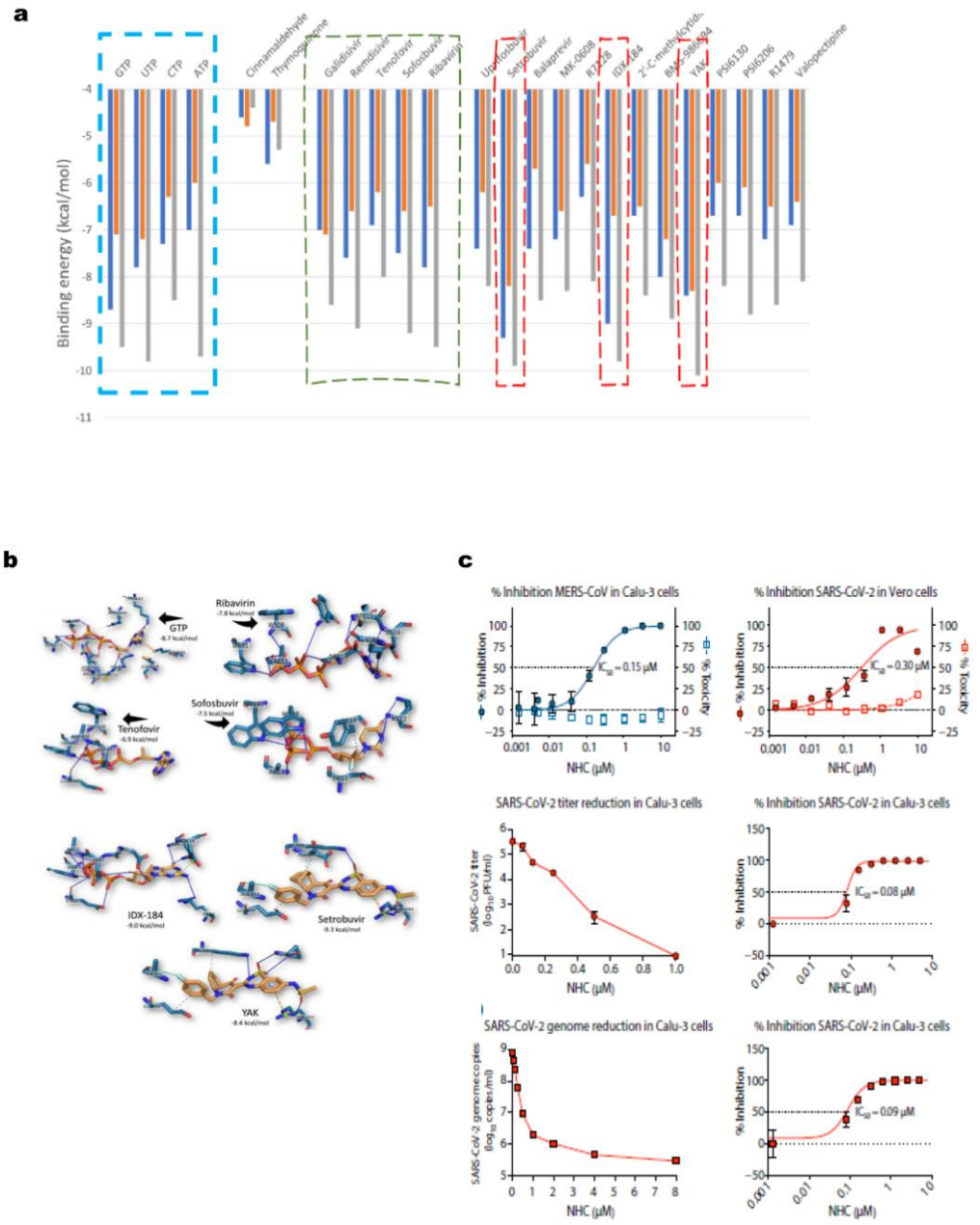


Figure 5. a) Binding energy of different RNAP inhibitors, compared with that of phyisiological nucleotides (dashed blue line). b) Binding between the different inhibitors shown in a) and RNAP. c) Effect of β-d-N4-hydroxycytidine on viral infectivity of MERS-CoV and SARS-CoV-2. (Adapted from: *Elfiky AA, Life Sci, 2020; Shean et al., Sci Transl Med, 2020*).

hydroxycytidine -5'- isopropyl ester, has been proven not only to reduce SARS-CoV and MERS-CoV replication and pathogenesis, but also to possess prophylactic properties in mice. These effects are driven by an increase in the mutation frequency in the viral genome[17]. However, no similar "in vivo" data currently exist for CoV-2, although a recent animal model of SARS-CoV-2 infectimmodel has been recently generated[12].

d. G-quadruplexes inhibitors. G-quaruplexes (G4s) are tetrahelical structures formed by guanine-rich regions of both DNA and RNA (figure 6)[26]. Interestingly, RNA G4s are more stable than DNA G4s. Putative G4s (PG4s) have been found in a wide variety of human genomic loci and, recently, also in about 7000 viral genomes[27]. Moreover, two macrodomains in SARS-CoV have been identified to bind G4s, involved in viral replication and transcription[28]. By a Quadruplex forming G-Rich Sequences web server database search, about 25 PG4s have been detected in Wuhan CoV-2 genome (NCBI reference sequence: NC_045512.2)[29]. However, G4s ligands are poorly employed in clinical trials, as they lack specificity and drug-like properties. An alternative strategy, may be targeting CoV-2 helicase, which unwind the 3' end of the nascent RNA and allows the transfer to the 5' end of the complimentary leader sequence. Helicases also unwind G4s. To date, helicase inhibitors (such as bananin[30]) and aptamers (*oligonucleotides that may interfere with viral replication*)[31] have not been translated to the clinical practice. However, a search for already approved FDA drugs in the DrugBank database, indicated 20 potentially active molecules against helicases[29] which may be repurposed for Covid-19 treatment.

Figure 6

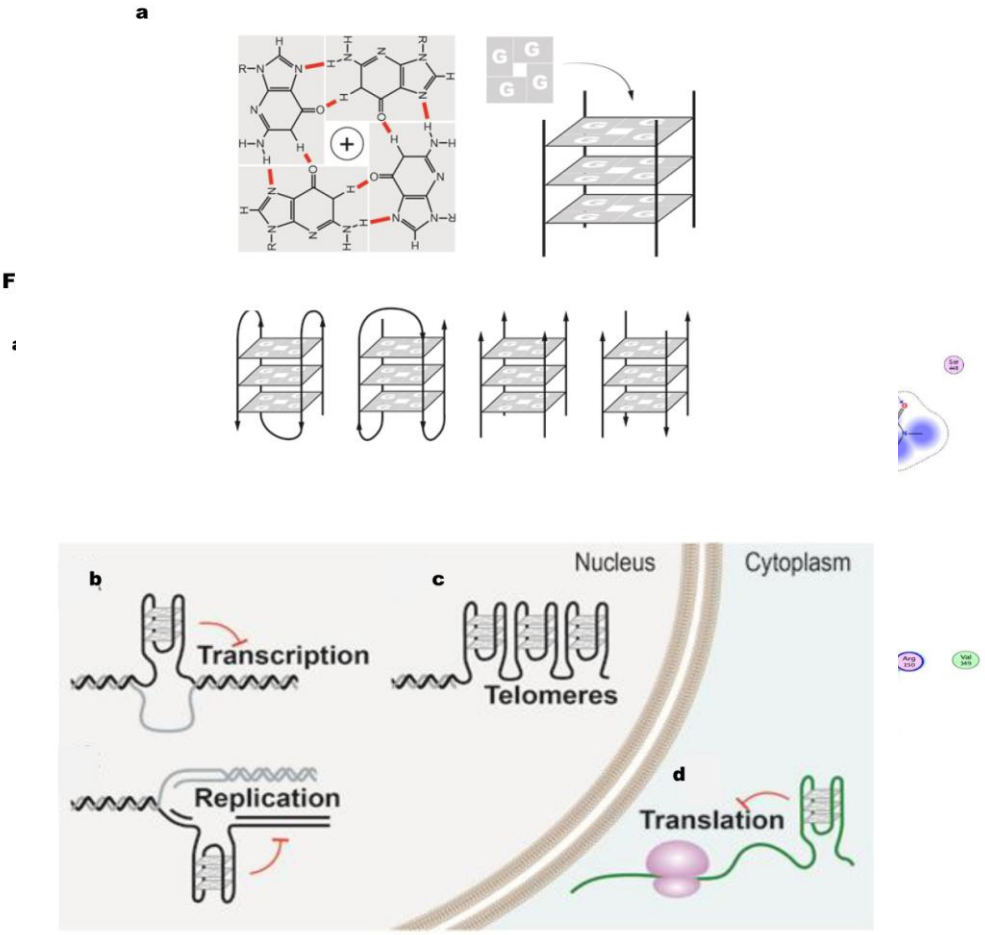


Figure 6. Structure of G-quadruplexes. a) G-quadruplexes arise from the association of four guanines into a cyclic arrangement stabilized by Hoogsten hydrogen bonding (N1–N6 and N2–N7). The planar G-quartets stack on top of one another, forming four-stranded helical structures. Monovalent cations (such as Na+ and K+) drive G-quadruplexes formation. b) G-quadruplexes can be sub-grouped into different families, for example parallel or antiparallel according to the orientation of the strands and can be inter- or intramolecular folded. The type of structure depends on the number of G-tracts in a strand. (Adapted from: *Rhodes & Lipps, Nucleic Acid Res, 2015*)

- **Protease inhibitors**

  a. Lopinavir/Ritonavir. Lopinavir and ritonavir, mostly administered in combinatorial treatment, and darunavir have been already used to treat HIV and MERS-CoV infection. Recent data from a clinical trial in Covid-19 severe patients have shown no clinical improvement nor a decrease in viral RNA load in the lopinavir/ritonavir group with respect to the standard care group

Figure 7

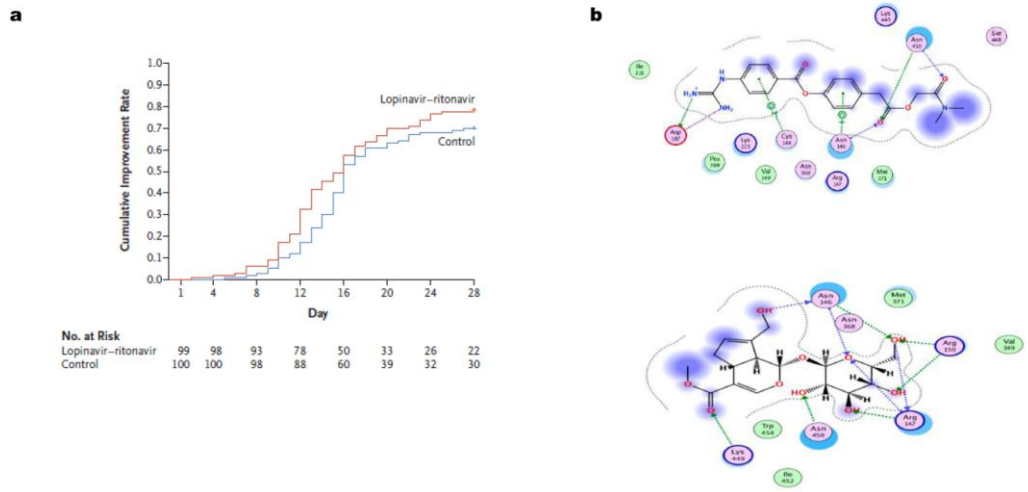


Figure 7. a) Effect of lopinavir / ritonavir treatment on 99 patients vs control group (100 patients). b) Number and type of bonds formed by Camostat (upper panel) and by compound NPC306344 (lower panel) with TMPRSS2. (Adapted from: *Cao et al., NEJM, 2020; Rahman et al., Molecules, 2020*).

(figure 7a)[32].

b. <u>TMPRSS2 inhibitors</u>. One of the cellular protease involved in CoV-2 entry into host cells is the transmembrane serine protease 2 (TMPRSS2). Indeed, inhibiting TMPRS22 by Camostat treatment - already employed as a therapeutic agent for chronic pancreatitis and postoperative and reflux esophagitis - blocks SARS-CoV and CoV-2 entry into host cells[33]. Very recently, molecular docking and ligand-based pharmacophore approach were used to screen the natural compounds library Natural Product Activity and Species Source (NPASS), containing 30,927 compounds, against TMPRSS2. 12 drug-like compounds have been identified with one of them - NPC306344 - showing the highest affinity for TMPRSS2 (figure 7b)[34]. However, “in vitro” and “in vivo” validations are required to assess antiviral and pre-clinical efficacy of this compound.

c. <u>M^{pro} inhibitors</u>. The most studied CoV-2 protease is M^{pro} (named also 3C-protease), a dimeric chymotripsin-like protease, encoded by the nsp5 subgemomic RNA (sgRNA). A number of prediction studies have identified already small inhibitory molecules employed in other infectious disease. An example is represented by velpatasvir, ledipasvir and paritaprevir, used in

HCV infection treatment[35-37] and raltegravir, employed as a HIV inhibitor[38,39]. In addition to the repurposed drugs, newly identified or synthesized molecules have been also investigated to inhibit M^{pro}. Crystal structures of M^{pro}, complexed with both α–ketoamide inhibitors[40] and ebselen, an anti-oxidant drug, have been recently obtained[41,42]. Importantly, both ketoamide inhibitors and ebselen showed antiviral activity in vitro[40,42] (figure 8a and b) and the ketoamide inhibitor 13b also showed lung cellular tropism in CD1 mouse models[40]. Furthermore, a computational analysis of potential M^{pro} inhibitors have suggested darunavir, another HIV protease inhibitor, as a promising therapeutic agents[43]. 2 clinical trial employing darunavir are currently ongoing (table1).

d. Cathepsin-L (CatL) inhibitors. CatL, a cystein protease residing in endosomes, replaces TMPRSS2 activity once CoV-2 enter the cytoplasm and continues to cut the S1 subunit of Spike (S)[44]. This may explain why TMPRSS2 inhibitors and non-specific cathepsin inhibitors alone have limited efficacy in reducing CoV-2 infection of airway epithelial cells “in vitro”. Indeed, combined use of these inhibitors fully block CoV-2 infection “in vitro”[45]. Inhibiting CatL, however, raises several concerns, due to its ubiquitous expression. Nevertheless, a number of drugs have been approved by the FDA and may be re-deployed for Covid-19 treatement[46].

Figure 8

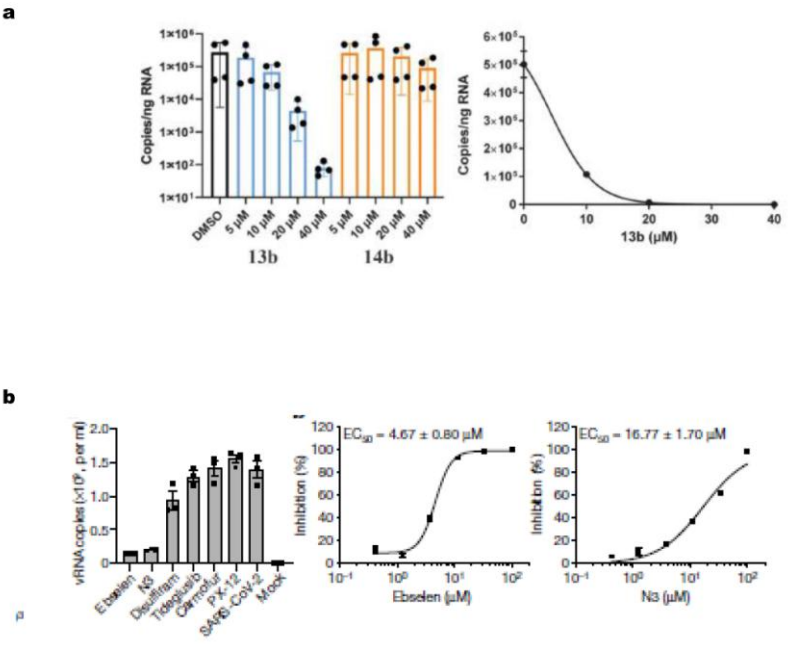


Figure 8. a) Effect of the ketoamidic inhibitor 13b on viral replication in human lung cells (left). On the right, a dose-response curve of the compound 13b *EC_{50} in inhibiting viral RNA replication. b) Quantification of the viral RNA molecules/ml of supernatant after 72 hours from the infection of Vero cells with CoV-2 (left) and treated with different compounds and vehicle (dimethylsulfoxide). Middle and right: dose-response curves show an* EC_{50} more efficient for ebselen than for compound N3, which shows, however, antiviral activity “in vitro” (left). Abbreviations: DMSO=dimethylsulfoxide.*EC_{50}= *in a dose response curve, the effective concentration which has “half” the efficacy between the basal and the maximal concentration (half maximal effective concentration)*. (Adapted from*: Zhang et al., Science 2020; Jin et al., Nature, 2020*).

- **2’-O- ribose methyltransferase inhibitors**.

  Another potential CoV-2 therapeutic target is the 2’-O-ribose methyltransferase, encoded by the nsp16 sgRNA. The activity of this enzyme is required for the methylation of capped sgmRNAs. In this way, viral sgmRNA are masked and protected from host cells defense mechanisms. A prediction study has recognized in bictegravir and dolutegravir (both HIV integrase strand transfer inhibitors) potential candidates for Covid-19 treatment[39].

- **Antiparasitic agents**

  a. Ivermectin. Ivermectin is a veterinary drug which has been translated into human clinical practice. It has been demonstrated to impede HIV integrase nuclear import[47], inhibiting integrase/ importin $\alpha/\beta1$ interaction, and to limit infection of a wide number of viruses[48-51]. This braod spectrum of activity seems to rely on the requirement for RNA viruses on importin $\alpha/\beta1$ function. As SARS-CoV exploit importin $\alpha/\beta1$ for

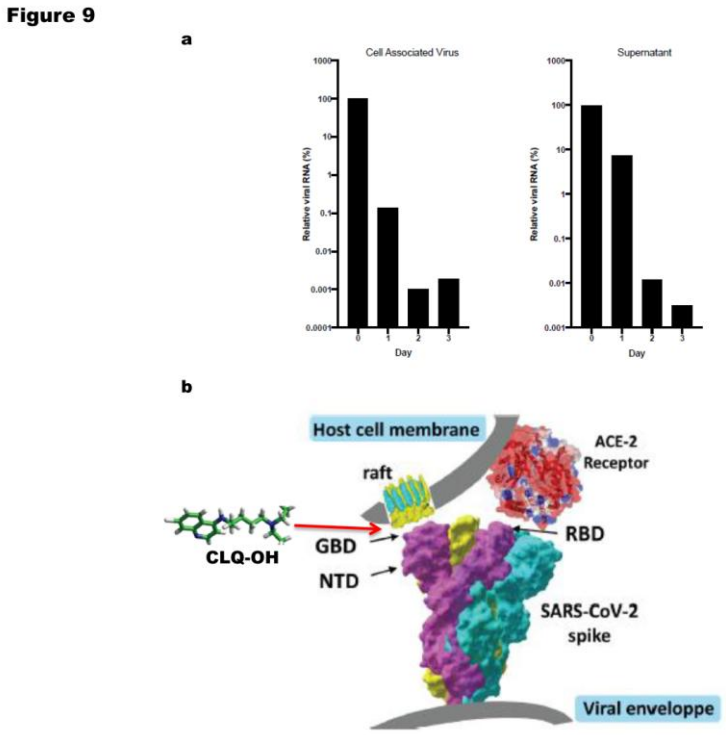


Figure 9. a) Effect ofIvermectin on viral RNA replication in Vero cells infected with CoV-2 and in related supernatant, at different days from infection. Ivermectin and vehicle (DMSO) have been added to the culture medium 2 hours after the infection procedure. b) Two-phase recognition model of the cell membrane by CoV-2 Spike. With its RBD, Spike binds ACE2 receptor, whereas recognizes gangliosides within membrane lipid raft, *that is regions of the membrane particularly rich in glicosphyngolipids and cholesterol,* with its N-terminal domain. CLQ-OH may intefere with this binding. (Adapted from: *Cali et al., Antiviral Res, 2020; Fantini et al., J Antimicrob Agents, 2020*).

the nucleo-cytoplasmic shuttling of the Nucleocapsid (N) protein[52] and inhibits STAT1 antiviral activity by sequestering importin $\alpha/\beta1$ into the ER/Golgi apparatus[53], it is conceivable that CoV-2 may use the same mechanisms and, therefore, ivermectin may be effective against CoV-2 infection. Indeed, Recent data showed that ivermectin administration reduced viral RNA both in the supernatant and within cells by 24 hours, reaching a 5000 fold reduction of these parameters in 48 hours (figure 9a)[54]. Indeed, currently, 27 clinical trials are ongoing using ivermectin for Covid-19 treatment (table 1).

b. Hydroxychloroquine/Azithromycin. Since the beginning of the pandemic hydroxychloroquine (CLQ-OH) received a great attention. CLQ-OH is the safer version of chloroquine, this latter synthesized in 1934 and used to treat malaria[55,56]. It exerts immunomodulatory effects in a wide range of pathologies, including AIDS and cancer[57,58]. In an early non-randomized, open label clinical trial, CLQ-OH, in combination with azithromycin (ATM), have been proven effective in reducing the viral load[59]. Very recently, one of the action mechanism of CLQ-OH has been predicted by molecular modeling[60]. Indeed, CLQ-OH has been demonstrated to possess high affinity for gangliosides, which are used, together with ACE2 receptor, by the Spike (S) protein, to enter host cells. *Gangliosides are membrane glycosphingolipids – constituted, in turn, by ceramide and oligosaccharides - containing one or more molecules of sialic acid bound to the sugar chain.* Indeed, a ganglioside binding domain has been identified at the tip of the N-terminal domain of CoV-2 S and a dual recognition model for S to mediate host cell entry has been proposed (figure 9b)[60]. CLQ-OH, bound to gangliosides, specifically to GM1 (*which is a ganglioside containing one molecule of sialic acid*) may interfere with S recognition of the host cell membrane, decreasing the strength of the interaction with ACE2. The same mechanism is likely to occur for ATM, which has a structure almost identical to a sugar moiety of the GM1 ganglioside[61].

- **Membrane fusion inhibitors**

a. Umifenovir. Umifenovir is an indole-derivative membrane fusion protein already employed for the treatment of influenza A and B. Limited results are currently available, while 4 clinical trials are ongoing (table 1). However, a

report on a study in 50 patients with mild/moderate disease, 16 treated with umifenovir alone and 34 with lopinavir/ritonavir, showed that umifenovir-treated patients recovered faster and became negative for viral RNA than patients in the lopinavir/ritonavir group[62].

b. Nelfinavir. Initially produced as an HIV protease inhibitor[63], nelfinavir has been observed to inhibit both SARS-CoV and CoV-2 S fusion with the host cell membrane, probably by binding to the N-terminus of S2 subunit of the trimer, and impairing the formation of the heptad repeat (HR) domain required for virus-host cell fusion (figure 10a)[64].

Figure 10

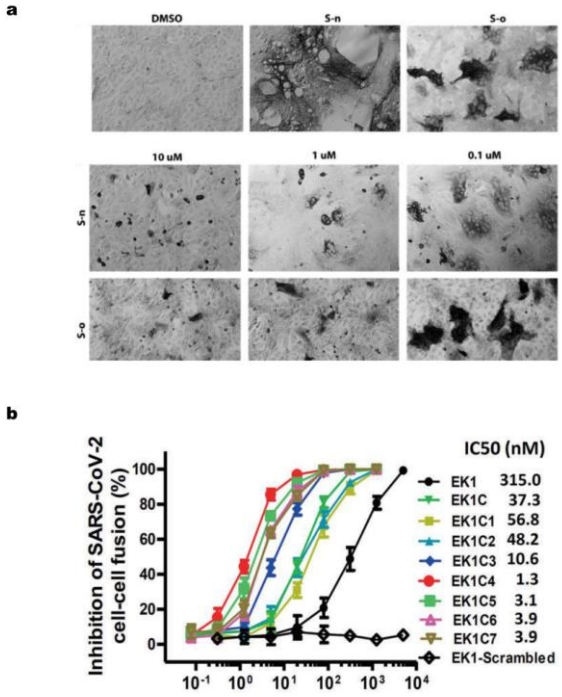


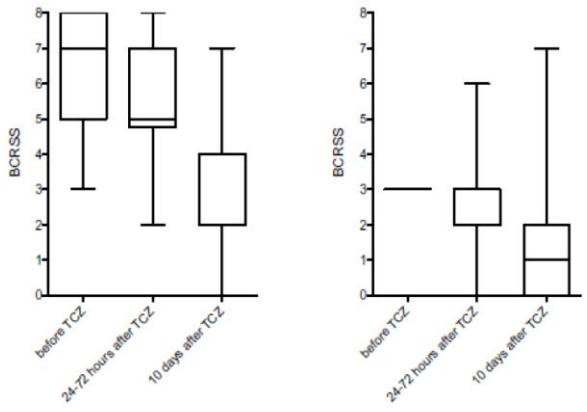
Figure 10. a) Membrane fusion in Vero cells infected with a plasmid encoding SARS CoV S (S-o) or CoV-2 S (S-n). Proteins have been visualized with specific antibodies, conjugated with HRP for the observation at the contrast-phase microscope. Lower panel. The same experiment performed in the presence of nelfinavir at different concentrations. b) Membrane fusion inhibition by compound EK1 and derivatives. Compound EK1C4, in red, shows a better efficacy. *IC_{50}= in a dose response curve, the concentration required to obtain half the maximal inhibition (half maximal inhibitory concentration).* Abbreviations: S-o=Spike-old (Spike of SARS-CoV); S-n=Spike-new (Spike ofSARS-COV-2. HRP=horse radish peroxidase. (Adapted from: *Musafar et al., J Med Virol, 2020; Xia et al., Cell Res, 2020*).

c. EK1 and related derivatives. A previously designed peptide inhibitor targeting coronavirus S HRs (EK1) has been already exploited to inhibit infection of SARSCoV, MERS-CoV, human CoVs (hCOVs) and SARS-related (SARSr) CoVs. It also showed prophylactic and therapeutic efficacy in infected mice[65]. As CoV-2 has a more potent membrane fusion capacity with respect to SARS-CoV, probably because of several mutated aminoacids in its S HR1, an advanced version of EK1 has been recently produced, by the addition of a cholesterol molecule. The new lipopetide, called EK1C4, showed a higher capacity to inhibit SARS-CoV-2 infection (figure 10b)[66].

- **Anti-inflammatory agents**

a. Anti-interleukin 6 (IL-6) receptor monocolonal antibody (Tocilizumab). One of the fixed and key points of Covid-19 pathogenesis is the so-called “cytokines storm” (see Episode 4 for details), whose IL-6 represents the harmful, end-point of the cascade. Therefore, interfering with IL-6 signalling was presumed to be effective in limiting Covid-19-related organ damage. Tocilizumab (TCZ) is a monoclonal antibody recognizing both membrane-bound and soluble IL-6 receptors and was first employed in treating rheumatoid arthritis[67]. Currently, 36 clinical trials on TCZ employment in Covid-19 patients are ongoing (table 1), one now recruiting patients in combination with remdesivir. To date, results on the efficacy of TCZ in severe Covid-19 are available for limited numbers of patients[68-70]. However, all the studies reported beneficial effects of TCZ in critically ill patients. In particular, 69 patients out of 100, treated with TCZ at Spedali Civili di Brescia, showed significant improvement of respiratory conditions (figure 11); 39,5% of patients requiring intensive care and undergoing mechanical ventilation were extubated[70].

Figure 11



Figue 11. Effect of Tocilizumab on the respiratory conditions of patients requiring ICU (left) or in the general ward (right). Abbreviations: BRCCS=Brescia Covid-19 Respiratory Scale[70]. ICU= intensive care unit. (Adapted from: *Toniati et al., Autoimmun Rev, 2020).*

b. Steroids. Contradictory results are reported on the use of corticosteroids in treating Covid-19 patients. A meta-analysis of available studies on the use of corticosteroids in SARS-CoV, MERS-CoV and CoV-2 infection, reported that no clinical benefits were observed. On the contrary, adverse events occurred[71]. However, inhaled corticosteroids have been demonstrated to limit CoVs infection in vitro[72], and in a retrospective study on 46 patients, 15 receiving early and low dose methylprednisolone, a recovery of the pulmonary clinical conditions was observed, both in terms of a faster

improvement in SpO_2 and chest CT scans[73]. Very recently, dexamethasone, a cheap and largely available steroid drug, have been proven to reduce Covid-19 mortality about 20%. The results of the clinical trial, performed in UK and enrolling 2100 patients treated with dexamthasone compared with 4300 individuals receiving standard Covid-19 cares, have still to be published, but in a press release it was stated that dexamethasone was efficient in recovering critically ill patients, especially those requiring mechanical ventilation. Patients undergoing oxygen therapy also showed an improvement, while non effect were observed for patients with mild symptoms. Dexamethasone was administered at a low dose (6mg/day) and for a limited period of time (10 days), underlying the caution attitude required when using systemic steroid therapy[74].

Conclusions

Drug repurposing represents a powerful tool to face Covid-19. Indeed, repurposed drugs are already tested for their safety in human clinical application and, in some cases, available in large quantities and inexpensive. In the absence of novel and efficient therapies, this represents the only feasible strategy for the early treatment of patients, to avoid life threatening outcomes, and to recover not only moderately but also severely affected-individuals.

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