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Original Article

Treatment with plasma antibodies against Coronavirus SARS-CoV-2, an appropriate hope in cure of disease COVID-19

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Abstract: Coronavirus activity at level lung alveolar cells depends on binding of S protein, from viral spicule, lied on cellular receptors, and the affinity of S protein at host cell proteases. The SARS-CoV-2 virus has been shown to use the ACE2 receptor in the alveoli of the lungs, for sub-alveolar entry or in blood vessels, sub-endothelial and an enzyme, serine protein TMPRSS2, for the activating of S protein. A clinically approved TMPRSS2 inhibitor could block the entry into the cells of the human body and can be a treatment option together with the administration of immune plasma containing antibodies anti-SARS-CoV-2 Coronavirus. Patients with SARS-CoV-2 in convalescents exhibit a neutralizing antibody response that can be detected even at 24 months after infection and is largely directed against protein S. Also, experimental SARS vaccines, including recombinant S protein and inactivated virus induce responses to neutralizing antibodies.

Keywords: SARS-CoV-2 virus, ACE2 receptor, serine protein TMPRSS2, S protein

Introduction

The SARS-CoV-2 Coronavirus, which is a virus with an RNA genome surrounded by a helically symmetric nucleocapsid, causes the current outbreak of COVID-19 respiratory disease with the severe acute respiratory syndrome, (SARS). Although much research is needed to establish the true extent and nature of this outbreak, it is clear that the spread of the virus in all world is an urgent global concern.

The persons with advanced ages and with pre-existing chronic diseases, like cardiovascular disease, HTA, obesity, chronic obstructive respiratory disease, (BPCO) or diabetes have a higher risk of severe COVID-19 disease. Men appear more vulnerable than women to SARS-CoV-2 Coronavirus.

Molecular mechanism of infection in cells: The cellular entry of coronaviruses depends on the binding of proteins with viral spicules (S) to the cellular receptors and the priming of the S protein by the host cell proteases. The SARS-CoV-2 virus uses the ACE2 receptor from the level of pulmonary alveoli, for entry and an enzyme, TMPRSS2 serine protein for initiating protein S. A TMPRSS2 inhibitor approved for clinical use blocked entry and could be a treatment option. Some results revealed communication between SARS-CoV-2 and SARS-CoV-2 (**Figure 1**) [1].

Main text

The patients with convalescent SARS-CoV-2 have a neutralizing antibodies response that can be detected in plasma even in 24 months after infection and are directed against the S protein. Besides, experimental SARS vaccines, including protein recombinant S and inactivated virus, induce the responses to neutralizing antibodies.

In last time, the researches results indicated that antibodies from human plasma, which appeared after some time, as a response to SARS-S virus, may provide some protection against SARS-CoV-2 infection [2].

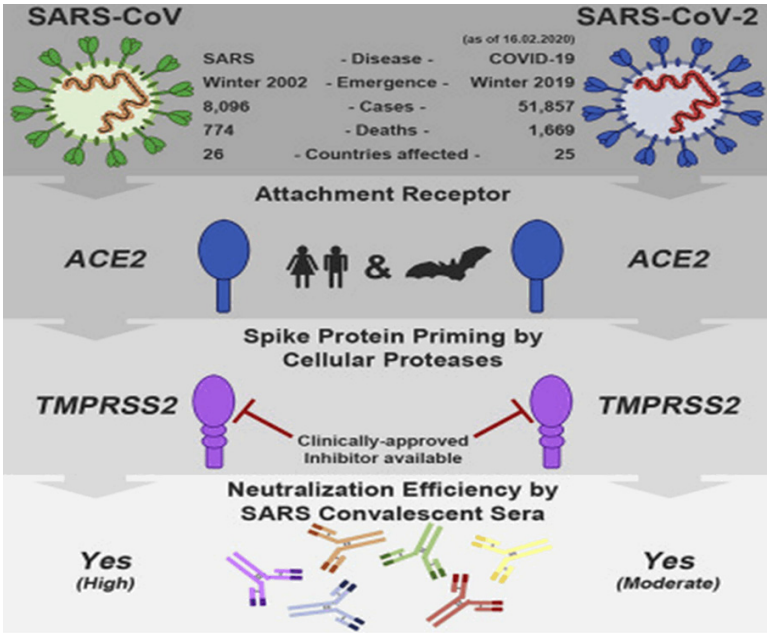


Figure 1. Communications between SARS-CoV-2 and SARS-CoV infection. Patients with SARS-CoV-2 in convalescents exhibit a neutralizing antibody response that can be detected even at 24 months after infection and is largely directed against protein S.

The blood plasma represents about 55-60% of the blood volume and contents 80% water, 1% inorganic substances, (mineral salts containing ions of which the most important are those of sodium, chlorine, potassium, magnesium, phosphorus, calcium, iron, other ions) and about 19% organic substances (proteins, carbohydrates, lipids, catabolism products, albumin, globulins.

The globulin γ fraction is represented by immune-globulins, (antibodies), that can be divided into Ig A, Ig D, Ig E and Ig G. γ-globulins that form in the lymph nodes a lymphoid organ, being synthesized by plasma cells from B lymphocytes, by their differentiation and proliferation. However, has been suggested that responses to elevated antibodies against SARS-CoV could least partially protect against SARS-CoV-2 infection (**Figure 2**) [3].

Some laboratories perform the tests in immunological windows and may be necessary to send the samples and to the reference laboratories for processing in time of antibodies development. In these cases, it may take a few days for results. The results of these tests could have important implications for understanding SARS-CoV-2 transmission and pathogenesis and reveal a target for rapid therapeutic intervention, (**Scheme 1**, Dynamics of anti-SARS-Cov-2 IgM and IgG antibodies among COVID-19 patients. J Infect 2020; 81: e55-e58) [4].

Methods used to detect SARS-CoV-2 infection

Rapid tests with antibodies or serological tests

There are two types of rapid tests, immunological test and direct antigen test.

The first type of test, Immunological test, (a drop of blood is taken from the finger, through the sting) and offers the results in 20-30 minutes. The antibody test produces positive results, in the case of infection, SARS-CoV-2, only after a few days if the antibodies have formed in the blood.

These tests are not suitable for the detection of active infections in the early phase of the disease.

This assay determines the presence of specific antibodies against the new subtype coronavirus (SARS-CoV-2), respectively IgM and IgG. It should be noted, however, that this Diagnostic testing for severe acute respiratory syndrome-related coronavirus 2: a narrative review onset of the disease. In other words, in the case of an asymptomatic person, who is more than 3-5 days after the onset of the disease, the test can be positive. If the test is negative for an asymptomatic person, it is recommended to repeat the test at 5 days, to show a seroconversion.

The second type of rapid test, Direct antigen test can be obtained from the nasopharyngeal exudate, gives results in 20-30 minutes and aims to identify the viral antigen and is similar to the rapid flu tests. These rapid tests are more effective than serological tests because they are useful for both early diagnosis and early diagnosis of new coronavirus infection. The tests for antigen detection for COVID-19

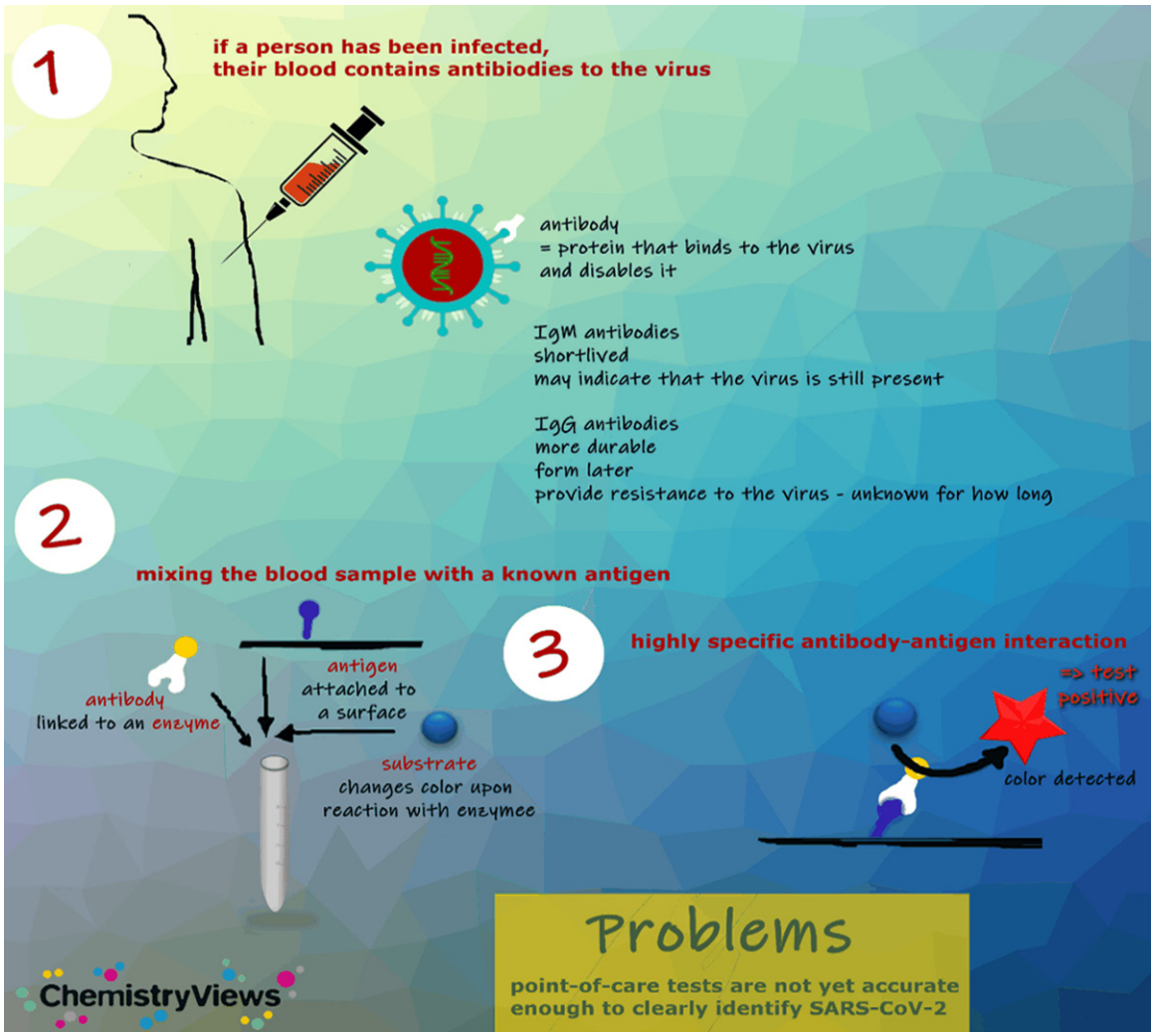


Figure 2. Rapid antibody test is effective only after a few days if antibodies have formed in the blood. This assay determines the presence of specific antibodies against the new subtype coronavirus (SARS-CoV-2), respectively IgM and IgG, (Koester K. COVID-19 Specific Testing. Chem Views Magazine, 2020, www.chemis-tryviews.org) [3].

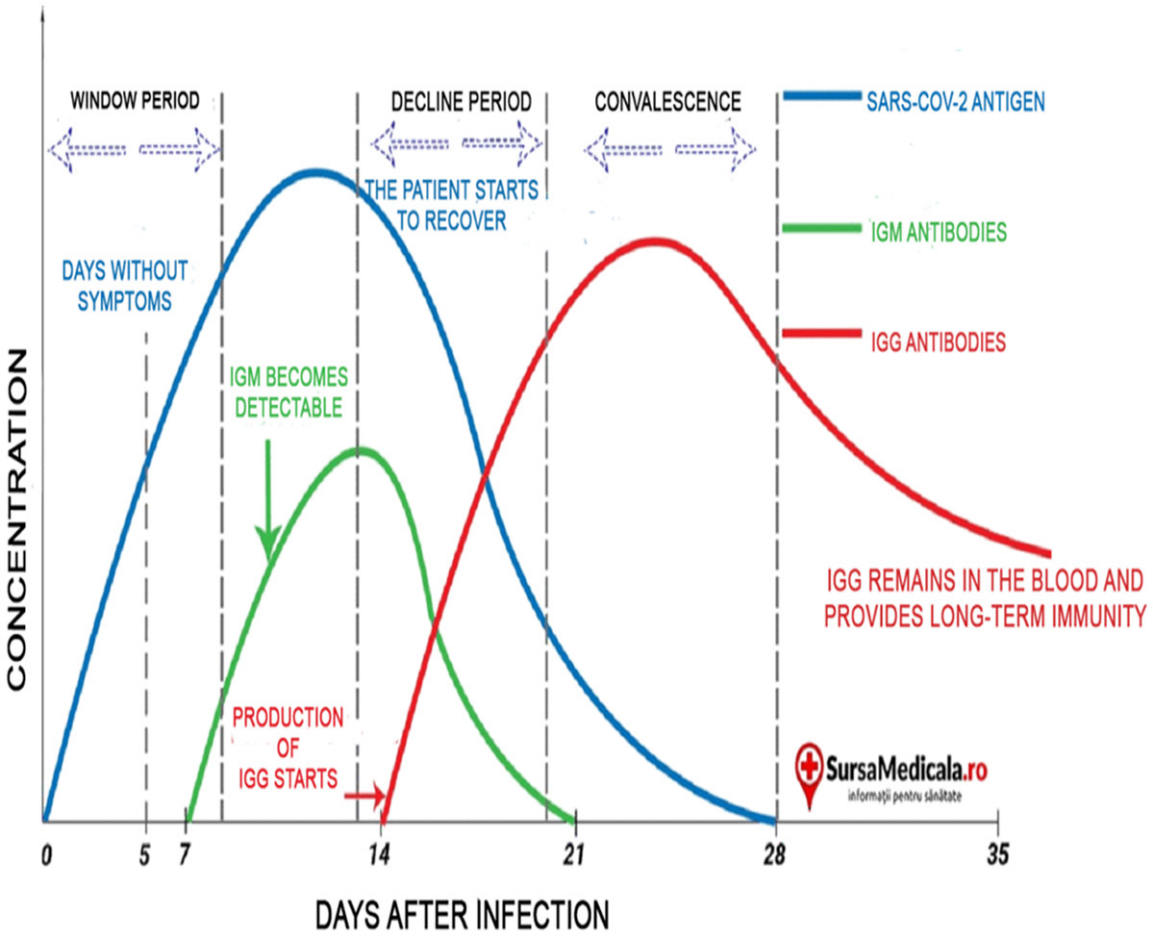
need to be evaluated and is not currently recommended for clinical diagnosis pending more evidence on test performance and operational utility (**Figure 2**) [5].

No, any testing rapid method is perfect. Any test leads to a proportion of false-positive results (the one tested is healthy, but the test considers it bad) and false-negative (the tested one is ill, but the test considers it healthy).

Evidence for Coronavirus SARS-CoV-2 by ELISA method

Through the Enzyme-linked immune-adsorbent assay, (ELISA), the IgM or IgG antibody binds SARS-CoV-2 virus with high affinity. The human antibodies IgG1, IgG3, isotype and IgM are available to discover antibody responses observed in COVID-19 disease. The ELISA method is an essential technique for discovering seroconversion in more severe, and hypotoxic cases [6].

This assay determines the presence of specific antibodies against the new subtype coronavirus (SARS-CoV-2), respectively IgM and IgG. It should be noted, however, that this type of rapid test does not provide an early diagnosis, as it is positive 3-5 days after the clinical onset of the disease. In other words, in the case of an asymptomatic person, who is more than 3-5 days after the onset of the disease, the test can be positive. The test helps you when it comes out positive because it has high speci-



Scheme 1. Dynamics of specific antibody formation against SARS-CoV-2. In first 5-6 days from onset the PCR Test can be negative. In the case of an asymptomatic person, who is more than 5-6 days after the onset of the disease, the test can be positive. If the test is negative for a symptomatic person, it is recommended to repeat the test at 5 days, in order to show a seroconversion, ie from the absence of antibodies to the presence of antibodies specific to the new type of coronavirus.

ficity. If the test is negative for the asymptomatic person, it is recommended to repeat the test at 5 days, to show a seroconversion, ie from the absence of antibodies to the presence of antibodies specific to the new type of coronavirus.

Sequential gene nucleotide (SGN) using SmartXGene®NGS analyzer

The SmartXGene®SGN module is based on the IDNS (Integrated Database Network System). The genetic analysis method can be chosen by the user to detect a variety of microbial menus. Previously, the intelligent analysis analyzer was used to accurately characterize a variety of bacteria but, as far as we know, the utility of the software package has also been reported for SARS-Covig-2 virus.

SmartXGene intends to introduce automated sequencing analysis software into the future and impact of copy variants on a single 16S rRNA genome. To minimize the proportion of negative results, it is recommended to further test the samples collected from the respiratory apparatus in very suspicious cases and to check the sample quality when testing PCR [7].

Reverse transcription-polymerase chain reaction assay (RT-PCR)

Currently, for the detection SARS-CoV-2, is used reverse transcriptase-polymerase chain reaction, (RT-PCR) assays, identifying the genetic fingerprint of viral genome RNA. There are several PCR platforms and the sample can be taken from respiratory secretions, nasopharyngeal exudate or bronchoalveolar lavage, in the

intubated oro-tracheal patient, in whom we have no diagnosis and in which the exudate test was negative. The waiting time varies, depending on the platform used, from 45 minutes to 6 hours [8].

Researchers from the University of Oxford, UK and Oxford Suzhou Center for Advanced Research (OSCAR), Suzhou, China, have developed improved SARS-CoV-2 coronavirus testing technology, which causes the current outbreak of COVID-19. The assay is three times faster than the currently used and more sensitive viral RNA assays. The new method is based on viral detection that can specifically recognize SARS-CoV-2 RNA and RNA fragments. The test has built-in controls to prevent false positive or negative resistances. Rapid detection sets were used on eight positive and eight negative samples, and the results were confirmed by conventional reverse-reaction reverse transcription (RT-PCR) methods. The new test takes only half an hour, compared with 1.5-2 hours for the previous methods. Its high sensitivity may allow detection of COVID-19 in earlier stages.

RT-PCR is a laboratory method used to make a very large number of copies of the short sections of DNA in a very small sample of DNA so that it can be detected. This process is called "amplification" of DNA. However, because SARS CoV-2 is an RNA virus, and RNA is a single-stranded nucleic acid molecule, it must be transformed into DNA before it can be amplified. During the assay, an enzyme called Reverse Transcriptase binds to the single-stranded RNA of the virus and makes a DNA copy that can now be amplified by the usual PCR process. If a sufficient amount of viral RNA is present in a sample, it will be amplified and detected, and the test will be positive. If no viral RNA is present, the test will be negative. Most COVID-19 assays are based on RT-PCR (reverse transcriptase-polymerase chain reaction) testing to detect virus RNA in a patient's tract respiratory sample [9].

Furthermore, it suggests that high antibody responses against SARS-CoV could at least partially protect against SARS-CoV-2 infection. However, not all laboratories carry out this test and it may be necessary to send samples to the reference laboratories for processing. In these cases, it may take several days for results.

No testing method is perfect. Any test leads to a proportion of false-positive results (the one tested is healthy, but the test considers it bad) and false-negative (the tested one is ill, but the test considers it healthy). We still do not have enough data to know the percentage of these types of results in the case of COVID19. Considering the possibility of false-negative results, the World Health Organization (WHO) argues that a negative test result does not eliminate the possibility of COVID-19 infection and recommends multiple testing. Therefore, the statistics on the number of tests performed and those on the number of persons tested are similar, but not identical.

Ancillary tests

In the case of CoV-19 disease showed different values compared to the reference values in the case of hematologic analysis with Differential count, 5-Diff, (Lymphopenia Neutrophilia), number of Leukocytes, Thrombocytes, Reactive Protein C, Fibrinogen, VSH, Interleukin IL-6, Procalcitonin, Albumin, Glucose, Urea, Creatinine, Acid Uric, AST (TGO), ALT (TGP), LDH, FAL, Gama-GT, Bilirubin, Ferritin, Troponin I, Thromboplastin Time, (INR), APTT, Thrombin Time (TT) and D-Dimers with a predisposition to thrombosis. Extremely increased D-dimer in COVID-19 patients results from plasmin-associated hyperactive fibrinolysis [10].

Elevated fibrin degradation products (FDPs) and D-dimers are detected predominantly in patients with severe disease. Plasmin, a key player in fibrinolysis, enhances the virulence and pathogenicity of viruses as is the case with the SARS-CoV-2. Plasmin enhances the virulence and infectivity of SARS-CoV-2virus by cleaving its spike proteins Elevated plasminogen is a common feature in people with underlying medical conditions, including hypertension, diabetes cardiovascular disease, cerebrovascular disease, and chronic renal illness, who are susceptible to SARS-CoV-2 infection [11].

Patients with preexisting hypertension, diabetes, coronary heart disease, cerebrovascular disease, chronic pulmonary disease (COPD) and kidney dysfunction with the acute renal injury, (comorbidities) have worse clinical outcomes when infected with SARS-CoV-2. The mechanisms for high morbidity and mortality

of patients with comorbidities remain unknown until now. Many patients with COVID-19 develop multi-organ failure (MOF). The leading causes of deaths are septic shock with MOF, hemorrhage/coagulopathy, disseminated intravascular coagulopathy, (DIC), acute heart/liver/kidney injury, and secondary bacterial infections [12].

Was discovered that SARS-CoV-2 Coronavirus, which continues to spread on all continents, becoming an in the all world an urgency, develop the natural antibodies, (nAbs, which could be used as prophylactic and therapeutic agents to prevent, treat, and control the spread of infection.

Advanced studies on SARS-CoV Coronavirus and MERS-CoV VIRUS have shown that many fragments (S1-NTD, RBD, S2) of S proteins can be used as targets to develop natural antibodies, (nAbs). Also, were created specific antibodies anti-region RBD SARS-CoV Coronavirus which have greater potency to neutralize infection with divergent virus strains, suggesting that SARS-CoV-2 RBD may also serve as an important target for the development of strong and specific nAbs [13, 14].

Although there is no vaccine to this date, these antibodies are likely to be essential for protection. However, little is known about the response of the human antibody to SARS-CoV-21-5. An international report of 149 MERS-CoV convalescents showed that plasmas collected on average 39 days after the onset of disease symptoms had variable neutralization titers at half maximum, from undetectable in 33% to detection below 1:1000 in 79% of the analyzed cases [15].

Rapid direct identification test of COVID antigen RNA-19, by CRISPR-Cas-13 technology. Recently, researchers from several countries are developing new technology for the direct administration of anti-Coronavirus antibodies SARS-Cov-2, targeting recipients with a passive immunity, with the hope of rapid cure of COVID-19 disease, The target fragments of ARN virus SARS-Cov-2, for specific antibodies, can be obtained by genetic molecular method CRISPR Technology Case 13 [16].

The CRISPR technology

Case 13a is a simpler and very versatile program based on a genetic panel that simultaneously analyzes RNA chain sequencing and has many advantages in the ability to analyze from one to thousands of samples simultaneously, the ability to check each sample for changes in multiple sequences in the RNA chain.

By researches experiments on line cells, were demonstrated ARN cleavage efficiency, tested in over 20 cell types including iPSCs, mESCs, N2A, CHO, A549, HCT116, HeLa, HEK 293, lymphocytes cell culture and several others.

The SARS-CoV-2 genome encodes the multiple structural and nonstructural proteins. The structural proteins encompass spike protein (S), an envelope protein (E), membrane protein (M), nucleocapsid protein, (N), and the nonstructural proteins which include open reading frame 1ab (ORF1ab 1-7 types).

Researchers at the University of Oxford, UK and the Oxford Suzhou Center for Advanced Research (OSCAR), Suzhou, China, have developed an improved testing technology for the SARS-CoV-2 coronavirus, which causes the current outbreak of COVID-19. The test is three times faster than the currently used and more sensitive viral RNA tests. The new method is based on a viral detection that can specifically recognize SARS-CoV-2 RNA virus and RNA fragments.

CRISPR-Cas-13 technology is a simple and very versatile program based on a genetic panel that simultaneously analyzes RNA and DNA chain sequencing, and has many advantages in the ability to analyze from one to thousands of samples simultaneously, the ability to verify each sample for multiple sequence changes in the RNA in the chain. Cas-13 targeted nucleases have given researchers the ability to manipulate virtually any genomic sequence, allowing easy creation of isogenic cell lines for the study of human disease and promoting exciting new possibilities for human gene therapy [17].

The new test have been developed by several laboratories, including an approved emergency authorization (EUA) analysis developed by the US Cen-ters for Disease Control and Prevention (CDC). However, the typical transformation time for the detection and diagnosis of patients with suspected SARS-CoV-2 was > 24 hours, given the need to send samples overnight to the reference laboratories.

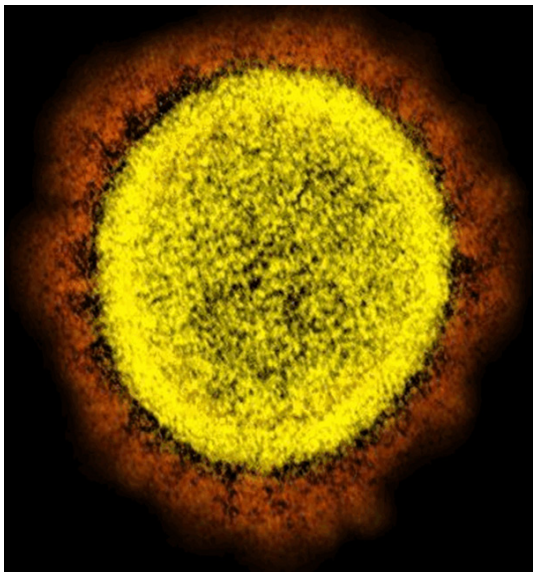


Figure 3. Transmission electronic; Transmission electron micrograph of the SARS-CoV-2 virus. (New CRISPR-based COVID-19 test kit can diagnose infection in less than an hour. UCSF Foundation, www.ucsf.edu, News Re-search; 2020) [20].

The new test is also extremely sensitive. It can detect the presence of 10 coronaviruses in a microliter of fluid taken from a patient - a volume hundreds of times smaller than an average drop of water. Although slightly less sensitive than existing PCR tests, which can detect only 3.2 copies of the virus per microliter in 15 minutes, the difference is unlikely to have a visible impact on diagnosis, as infected patients usual test (30-40 min) for the detection of SARS-CoV-2 in clinical trials. Visualization of the Cas12 detection reaction is performed using a FAM-biotin reporter molecule and side flows designed to capture labelled nucleic acids [18].

CRISPR-Cas13 Detector technology for the development of a rapid test to detect the virus in 4-6 hours.

The sherlock detector detection protocol for detecting COVID-19 virus involves three steps

Two nucleases, Cas12a and Cas13a, were particularly popular in the diagnosis of CRIS-PR. While Cas12a is specific for DNA, Cas13a works with RNA. Part of the mechanism is similar to that of Cas9 - a guide RNA that is complementary to the target sequence is required for specific binding and the Cas12a/Cas13a.

An interesting feature of Cas12 and Cas13 nucleases is that they have trans or collateral cleavage activity [19].

Amplification of synthetic viral RNA using recombinase polymerase amplification (RPA) technology, followed by in vitro transcription of amplified DNA back into RNA. RNA detection using Cas13 nucleases and crRNA provided targeting specific sequences. Visual color reading using a commercially available paper soap, which captures cleaved reporter RNA with the ends labelled on specific antibody bands [20].

Much big-ger. Saret-CoV-2 Detector adds to a rapidly growing suite of new COVID-19 diagnostic tests that researchers and clinicians hope will increase test capacity, including tests for specific antibodies in patients who have recovered from infection with COVID-19 (**Figure 3**) [21].

No test method is perfect. Any test leads to a proportion of false-positive results (the one tested is healthy, but the test considers it bad) and false-negative (the one tested is sick, but the test considers it healthy). We do not yet have enough data to know the percentage of these types of results in the case of COVID19. Given the possibility of false-negative results, the World Health Organization argues that a negative test result does not rule out the possibility of COVID-19 infection and recommends to be done and by another method.

For the vaccine development against SARS-CoV-2 from fraction proteins of Coronavirus and the evaluation of immunogenicity of vaccines in clinical trials, it is important to be used the epitopes of SARS-CoV-2 from the cellular membrane of infected cells and to be detected their immune responses in Covid-19 disease.

Patients with SARS-CoV-2 in convalescents exhibit a neutralizing antibody response that can be detected even at 24 months after infection and is largely directed against protein S. Also, experimental SARS vaccines, including recombinant S protein and inactivated virus induce responses to neutralizing antibodies. Although confirmation of the infectious virus is recent, our results indicate that neutralizing high antibody responses against SARS-S may provide some protection against SARS-CoV-2 *infection* [22].

Besides, experimental SARS vaccines, including recombinant S protein and inactivated virus induce responses to neutralizing antibodies. Although confirmation of the infectious virus is recent, our results indicate that neutralizing high antibody responses against SARS-S may provide some protection against SARS-CoV-2 infection [23].

The new genetic technology of molecular medicine CRISPR-Cas13a SHERLOCK was applied for the development of a rapid test (30-40 min), aiming to detect SARS-CoV-2 in clinical trials. The results of these methods have important implications for understanding SARS-CoV-2 transmission and pathogenesis and reveal a target for rapid therapeutic intervention [24, 25].

Conclusions

CRSPR-Cas-13 technology is a gold test in diagnosing COVID-19 and based on it, we can confirm cases much faster and we can tell when a patient has criteria for discharge from the hospital. The results of this method will have important implications for understanding SARS-CoV-2 transmission and pathogenesis and reveal a target for rapid therapeutic intervention.

Although are necessary and other experimental proofs to evaluate the immunogenicity of the peptides of SARS-Co-2 Coronavirus, used in the current studies of experimented RNA vaccines, the whole world has a hope inefficiency of this treatment with plasma antibodies for the cure of Disease COVID-19.

Disclosure of conflict of interest

None.

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