

# ON THE UNPREDICTABILITY OF OUTCOMES OF IMMUNOTHERAPY AND PREVENTIVE IMMUNIZATION AGAINST COVID-19

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This article analyzes the possibility of employing immunotherapy and preventive immunization to fight COVID-19. The authors think that treatment and prevention of the infection with anti-SARS-CoV-2 antibodies can have unpredictable outcomes. Although these antibodies can neutralize virus antigens (S-proteins), they also have the ability to enhance virus entry into the host cell. The article emphasizes the importance of solid evidence of efficacy and safety for candidate anti-COVID-19 therapies and protective measures.

**Keywords:** coronavirus, COVID-19, SARS-CoV-2, antibodies, preventive immunization, immunotherapy

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## О НЕПРЕДСКАЗУЕМОСТИ РЕЗУЛЬТАТОВ ИММУНОТЕРАПИИ И ИММУНОПРОФИЛАКТИКИ COVID-19

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В работе проведен анализ возможности использования иммунотерапии и иммунопрофилактики в борьбе с COVID-19. Результаты, к которым может привести профилактическое или терапевтическое применение препаратов, содержащих антитела против вируса SARS-CoV-2, на наш взгляд, неоднозначны, а взаимодействие антител с коронавирусными антигенами (S-протеинами) может повлечь за собой не только нейтрализацию вируса, но и усиление его способности проникать в клетку хозяина. В работе сделан акцент на необходимости научного доказательства эффективности и безопасности планируемых к применению методов терапии и профилактики COVID-19.

**Ключевые слова:** коронавирус, COVID-19, SARS-CoV-2, антитела, иммунопрофилактика, иммунотерапия

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Finding effective treatment and developing protective measures against the novel coronavirus infection COVID-19 is a critical challenge facing medical science. Today, many candidate approaches to managing this infection are under scrutiny. Obviously, the effective treatment is expected to directly block the virus and prevent it from replicating or entering the cell. Drugs designed to inhibit HIV (ritonavir, lopinavir) and Ebola virus (remdesivir) are now being evaluated for their potential to inhibit coronavirus replication [1, 2]. However, so far there is no solid evidence of their efficacy against COVID-12; this is true for both approved drugs and those still in clinical trials [3]. The possible anticoronaviral effect of quinolines and the unclear underlying mechanism of action need further investigation.

Immunotherapy and preventive immunization might hold promise for countering COVID-19. Indeed, vaccines and passive immunization have been successful in fighting various infections, including viral infections. However, because of the features demonstrated by the causative agent of COVID-1 SARS-CoV-2, extreme caution should be exercised when using active or passive immunization approaches.

This article is an attempt to point to the unpredictability of outcomes of using anti-SARS-CoV-2 antibodies for treating and preventing COVID-19.

### Interaction with viral S-proteins

Spike-glycoproteins (S-proteins) responsible for latching onto receptors of the host cell have long been identified as the primary

surface target for neutralizing antibodies. Using cell and animal models of severe acute respiratory syndrome (SARS-CoV) and Middle-East respiratory syndrome (MERS-CoV), researchers have demonstrated that antibodies can bind to and neutralize S-proteins [4, 5]. It is reported that anti-S-IgG for neutralizing MERS-CoV promote survival of viral clones that carry mutations in the S-protein encoding genes; as a result, the antibodies can no longer recognize the S-protein and neutralize the virus [6].

### Antibody-dependent enhancement of virus entry

Unfortunately, the emergence of clones unrecognizable to antibodies is not the only drawback of passive immunization/immunotherapy. Therapies with anticoronaviral antibodies can be devastating due to the phenomenon of antibody-dependent enhancement of virus entry. Briefly, some IgG variants can accelerate penetration of the virus into the cell because their Fab fragments can bind to the S protein of SARS-CoV, whereas other IgG domains, like Fc or unidentified sites, bind to a number of host cell receptors, including angiotensin-converting enzyme 2, dipeptidyl peptidase-4 and the Fcγ-receptor (see Figure). This phenomenon has been demonstrated in the models of some coronavirus-related infections, including SARS and MERS [7, 8]. Considering the similarity of pathogenesis between SARS, MERS and COVID-19, there is a high probability that SARS-CoV-2 will also provoke IgG-dependent enhancement of virus entry. Some authors believe that IgG-enhancement of virus entry is not limited to epithelial cells and can also occur

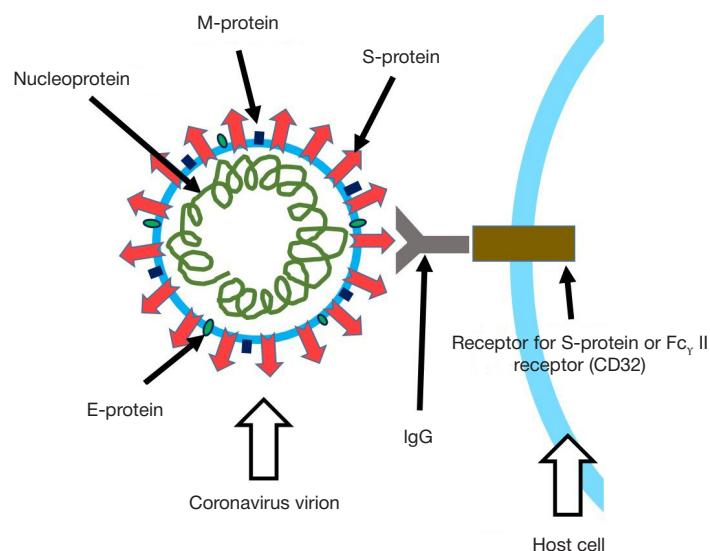


Fig. A schematic representation of antibody-dependent enhancement of virus entry

in immune cells via immunoglobulin FcγII receptors (CD32) [9]. IgG-dependent damage to immune cells might underlie the pathogenesis of uncontrolled immune system activation and cytokine storm in patients with SARS.

It is believed that antibodies do not always enhance virus entry, depending on the antibody binding site on the S protein, the IgG subclass, IgG concentrations and expression of cell receptors. This unpredictability means that convalescent serum and synthetic anti-S antibodies should not be used in COVID-19 patients without thorough thought. The same applies to preventive immunization against COVID-19. It cannot be ruled out that vaccination will stimulate production of polyclonal antibody variants responsible for antibody-dependent virus entry.

As COVID-19 is continuing its global rampage, a worrying trend is being born: scientists are engaged in a race to develop diagnostic, therapeutic and preventive tools for the novel infection at all costs. A similar situation unfolded in the USSR shortly after HIV was discovered. In an attempt to get ahead

of their foreign counterparts, some medical teams decided to treat AIDS patients with immunostimulants. The formal yet erroneous logic behind the decision dictated that a patient who developed immunodeficiency should be treated by stimulating the immune system. Dozens of patients fell victim to the ambitions of their doctors because immunostimulation provoked the irreversible progression of the disease. We hope that the story will not repeat itself with COVID-19 and that treatments for this infection will be evidence-based.

## CONCLUSIONS

1. On the one hand, antibodies against coronaviral S-proteins can neutralize the virion; on the other hand, they are also capable of enhancing virus entry into the host cell. 2. Although COVID-12 is an epidemiological emergency, its treatment and prevention should be based on solid evidence of safety and efficacy.

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