A review on COVID-19 effective pharmaceutics considering their molecular targets and Single nucleotide polymorphisms effects

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Abstract

COVID-19 is a highly contagious viral disorder which declared a global pandemic and results in more than 6 million mortalities worldwide since the late December 2019. Considering it continues to be a major health problem, finding the best medicines to concur with the effects of COVID-19 is essential and various drugs are suggested and used in clinical trials against covid-19. This review article provided an overview of the potential therapeutics in the management of COVID-19 based on the current disseminated scientific documents. After categorizing pharmaceutics in to the anti-interleukin drugs, Antiviral factors, Monoclonal antibodies, Corticosteroids and Anticoagulant drugs we presented a comprehensive description of their molecular mechanisms and clearly demonstrated the function on the target cells in COVID-19 virus infection. Moreover, we reviewed the single nucleotide polymorphisms located at direct target of these drugs and may be interfered with their functions. Our intention in this review attempted to supply beneficial therapeutic drugs to treat COVID-19 patients. We hope that this Review shed light on the field of current COVID-19 research, raise awareness and help researchers to select the best treatment protocols against COVID-19.

Keywords: COVID-19, treatment, anti-interleukin, Antiviral, drugs, SNP

Introduction

The Coronavirus disorder 2019 (COVID-19), is investigated as a superlative tension global pandemic that is derived from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1). Coronaviruses are an assortment of RNA viruses that contaminate humans, and even also animals (2). based on their morphology as round virions with a core-shell and surface layouts that resemble a solar corona, they were denominated coronaviruses (Latin: corona = crown) (3). They are classified in to four subfamilies, including alpha-, beta-, gamma-, and delta-coronaviruses. Pneumonia, asymptomatic infections and gastrointestinal manifestations were identified as primary clinical signs of COVID-19 disease (4). SARS-CoV-2 targets lung alveolar epithelial cells by receptor-mediated endocytosis utilizing the angiotensin-converting enzyme II (ACE2) as an entrance receptor (5). Common symptoms of this disease include cough, fever, dyspnea, musculoskeletal symptoms, gastrointestinal symptoms, and anosmia/dysgeusia (6).

The World Health Organization (WHO) states there is currently no specific treatment for coronavirus. furthermore, considering standard care, treatment of covid 19, just be carried out in approved, randomized, controlled trials (7). Threatening agents for patients infected with COVID-19 is underlying diseases such as cardiovascular disease, chronic lung disease, diabetes, and older age and obesity (8, 9). Management of COVID-19 relies on severity of the condition (8). mild COVID-19 typically cause common cold symptoms. cough with or without hyposmia and sputum are it's the most typical symptoms (8, 10). Homecare, rest and consumption of enough water and adequate calorie, usually ameliorate Patients with mild symptoms (11). However moderate or severe form of the disease needs intensive care and sometimes hospitalization(8). probably antiviral medications like remdesivir and antibody-based treatments are most impressive when prescribed early (12). anti-inflammatory medications, immunomodulators, and anticoagulants are the other effective medications (8, 13).

Single nucleotide polymorphisms (SNPs) are the most common variations in genome (14). They can be used to anticipate how an individual might react to specific medications, their vulnerability to environmental hazards like toxins, and their likelihood of developing certain illnesses(14).

Therefore, single nucleotide variations in the drugs target genes could affect their impression and maybe it would be important to take them in to consideration in the treatment process of COVID-19. In this review, we summarize effective pharmacological treatments for COVID-19 considering their molecular targets and effective single nucleotide polymorphisms.

1. anti-interleukin drugs:

cytokines are some mini proteins that are playing a major role in cell signaling pathways (15). chemokines, interferons, interleukins, lymphokines, and tumor necrosis factors, are included in the cytokine family that is produced by a wide range of cells, involving immune cells such as macrophages, T lymphocytes, B lymphocytes, and mast cells as well as fibroblasts, endothelial cells, and various stromal cells (16, 17). Cytokine storm is associated with the expansion of unrestrained systemic inflammation and further hyperproduction of cytokines (18). Regulation of immune responses caused by cytokine release is disrupted and causes epithelial cell apoptosis and endothelial and vascular leakage, and reduction of the T cell responses which results in inefficiency and hyperactivity of virus-infected macrophages and disturbance of tissue homeostasis followed by pathogenesis and severity of macrophage activation storm (MAS) resulting in MODS (multiple organ dysfunction syndromes) and ARDS(Acute respiratory distress syndrome) (19).

SARSCoV-2 infection motivates hyperinflammation of the innate and adaptive immune systems, which results in a cytokine storm. hypercytokinemia, or "Cytokine Storm (CS)" identified via a severe hyperinflammatory immune response is the principal symptom of covid-19. It is initiated by activation of macrophages, T-cells, and discharge of other cytokines leading to activation and recruitment of other cells involved in the immune system. The increase in the serum levels of pro-inflammatory cytokines and chemokines mainly IL-6, IL-1, IL-12, IL-17, TNF-α, IFN-γ is characteristic of the cytokine storm (20). As well as cytokines raised serum levels of C-reactive protein, lactate dehydrogenase, procalcitonin, creatinine, d-dimer, ferritin, and White Blood Cell count are serious parameters for the prediction of respiratory failure in COVID-19 patients (21). In the following paragraphs we will explain more about Interleukin 1, Interleukin 6, Interleukin 17 and Interleukin 23 proteins.

a) Interleukin 1:

Increased levels of IL-1 that is released in viral diseases cause inflammation of the lung tissue, fibrosis and fever (19). Excessive expression of interleukin 1 by activating some factors such as nuclear and transcription factors, activator protein 1, and activating factor 2 develops viral disease (22). It stimulates pro-interleukin-1 and the regulative cells in the innate and adaptive immune systems producing certain immune responses (19). As a result, interleukin 1B is produced and leads to lung damage and respiratory complications in the host infected with the virus

(19). IL-1a and IL-1b are mediators of inflammatory responses to tissue damage. They are secreted from damaged epithelial and endothelial cells and permeate to macrophages, neutrophils, and monocytes (23). IL-1 receptor antagonist is the basic innate regulatory mechanism that prevents inordinate Inflammation caused by IL-1(24).

A recombinant, intravenous drug, named Anakinra is a non-glycosylated form of the human interleukin-1 receptor antagonist which is expressed in Escherichia coli expression system (25). As the principal advantage, short half-life of this medicine permits quick disposal from circulation. Anakinra previously approved by the US Food and Drug Administration is available as a safe treatment to decrease adverse inflammation in patients suffering from COVID-19 (19). Anakinra as an interleukin IL-1 receptor antagonist inhibits activation of pro-inflammatory cytokines such as IL-1α and IL-1β and reduce hyperinflammation (19) (Figure 1). Studies have shown that early treatment with this drug attuned to the soluble plasminogen urokinase activator receptor (suPAR) reduces respiratory failure and amends the inflammatory balance (26).

b) Interleukin 6:

IL-6 is a crucial pro-inflammatory cytokine and is involved in activating Janus kinase (JAK) signal by binding the transmembrane (cis-signaling) or soluble form (trans-signaling) of the IL-6 receptor and linking with membrane-bound gp130 (21). it is involved in two signaling pathways called Classical-signaling and trans-signaling. In the classical signaling pathway with the production of C-reactive protein (CRP), it plays an essential role in the acute immune response against pathogens. while the trans-signaling pathway is involved in long-term inflammation (21). Excessive IL-6 signaling causes numerous effects that leads to organ damage, such as transforming naive T cells into efficacy T cells, inducing vascular endothelial growth factor (VEGF) expression in epithelial cells, expanding vessel permeability, and diminishing myocardial contractility (27).

After Coronavirus infection, a cytokine storm occurs that triggers the release of inflammatory cytokines such as IL-6, Tumor Necrosis Factor- α (TNF –α), and IL-12 (20) . most probably IL-6 has a major part in a cytokine storm, thus the drugs which their object is the IL-6 receptor suggested for severe disease COVID-19 patients (28). Tocilizumab is a recombinant humanized monoclonal anti-IL-6R antibody. It is prescribed intravenously and attaches to both soluble and membrane-bound IL-6 receptors to suppress IL-6 cis-signaling and trans-signaling (27) (Figure 2). Infection reduction, diminish of fever and a subtracted

demand for supportive oxygen is appeared a few days after receiving tocilizumab (27).

c) Interleukin 17 and Interleukin 23:

Interleukin 17 is one of the members of cytokine storm produced by Th17, Tc17, and other lymphoid cells (29). Interleukin 17 is mainly secreted from T helper 17 cells in response to any viral respiratory infection such as COVID-19 in the lungs (30). The first function of interleukin 17 is the initiation of neutrophil penetration into infected tissues and the tissue response prompt to extracellular pathogens, and the second function is indirect, such as the induction of chemokines (31). Interleukin-17 stimulates the production of cytokines, chemokines, other inflammatory mediators, matrix metalloproteinases, and growth factors (30). Interleukin 17 can directly activate fibroblasts and indirectly increase viral mediators in the inflammatory process. In addition, it can stimulate fibrogenesis by activating pro-coagulation pathways. So its inhibitors can be used for acute stages of COVID-19 and are also useful to prevent long-term fibrotic consequences (31). There are three ways to reduce the effects of interleukin 17, including blocking interleukin 17, its receptor and its pathway (32). (Figure 3).

Netakimab, is a monoclonal antibody against interleukin 17-A that is used in diseases such as moderate-to-severe plaque psoriasis, ankylosing spondylitis, and psoriatic arthritis (29). Moreover, it can be a possible target for COVID-19 therapy, and reduction of the inflammatory response (29, 33). Secukinumab may suppress T-helper 17 cytokine storm (33) and Brodalumab hinders IL-17R (29). (Figure 3).

similar to interleukin 17, interleukin 23 is a major cytokine in the maintenance of helper T cells, which mediates defense mechanisms against pathogens. Interleukin 23 inhibitors may play an important role in attenuating important cytokines through their effect on T helper 17 (34). Risankizumab, a humanized IgG monoclonal antibody binds with high affinity to the p19 and inhibits IL-23 (34) (Figure 3).

2. Janus kinase inhibitor

The Janus kinase (JAK) family plays a critical role in the immune system's response to viral infections such as COVID-19 (35). Upon viral infection, the host immune system activates cytokines and other signaling molecules to initiate an immune response (35). The JAK family of proteins is involved in the downstream signaling of these cytokines, transmitting signals from the cell surface to the nucleus, where they activate transcription factors such as STAT (Signal Transducers and Activators of Transcription) proteins (36). Thus, the Janus

kinase family, specifically JAK1 and JAK2, have emerged as potential therapeutic targets for COVID-19, and JAK inhibitors have shown promising results in reducing inflammation and improving outcomes in COVID-19 patients.

a) Baricitinib

Baricitinib is a small molecule inhibitor that selectively targets the Janus kinase family, with specificity towards JAK1 and JAK2 (37, 38). The inhibition of Janus kinases by Baricitinib results in the prevention of downstream phosphorylation and activation of Signal Transducers and Activators of Transcription (STAT) proteins (39). Consequently, JAK inhibitors such as Baricitinib can modify the signaling pathways of various interleukins, interferons, and growth factors (36). In addition to its anti-inflammatory profile, Baricitinib exhibits antiviral effects by blocking the entry of SARS-CoV-2 into lung cells by reducing the endocytosis of SARS-CoV-2 through the inhibition of AP2-associated protein kinase 1 and cyclin G associated kinase (39, 40) (41) (Figure 4). The recommended dosage of Baricitinib is 4 mg once daily for up to 14 days. Baricitinib has been suggested as a potential therapeutic option for COVID-19 due to its significant immunosuppressive and antiviral properties (39).

b) Tofacitinib

Tofacitinib is a Janus kinase inhibitor, exhibiting partial selectivity towards Janus kinase 2, and possesses immunomodulatory and anti-inflammatory properties (42). Tofacitinib functions by binding to Janus kinases, which inhibits the activation of the JAK-STAT signaling pathway, leading to a potential reduction in the production of pro-inflammatory cytokines (42) (Figure 5). Tofacitinib is administered orally at a dosage of 10 mg twice daily. Its effectiveness has been observed in Covid-19 patients admitted to hospitals (43) (44, 45).

3. Antiviral factors (RNA-dependent RNA polymerase inhibitor)

a) Remdesivir:

In the class of RNA-dependent RNA polymerase inhibitor, Remdesivir is classified as a prodrug of a monophosphate nucleoside analog and it was developed for the treatment and antiviral function against some RNA viruses including coronaviruses (SARS-CoV, MERS-Co-V, SARS-CoV-2), filoviruses (Ebola viruses, Marburg virus), paramyxoviruses (parainfluenza type III virus, Nipah virus, Hendra virus, measles, and mumps virus), and Pneumovirus (respiratory syncytial virus) (46).

In theory, nucleoside analogs permeate through the cell wall barely. On their next entry into the host cell, they should undergo phosphorylation to produce nucleoside triphosphate (NTP), this is similar to adenosine triphosphate (ATP) and can be adopted in genome replication by the RNA-dependent RNA polymerase (RdRp) enzymes (46). After Remdesivir metabolization into the pharmacologic active analog adenosine triphosphate it participates in a competition with ATP and disrupts RNA synthesis (46) (Figure 6). Remdesivir constrains viral replication in human airway epithelial cell culture by interrupting the first stages of viral replication (47). World Health Organization(WHO), Food and Drug Administration(FDA) and the Infectious Disease Society of America(IDSA), approved and recommended this drug (47). However, like any other antiviral medicine, there are some concerns about the stability of mutant viruses (46).

Remdesivir is prescribed for patients with severe forms of the disease suffered from respiratory failure aged ≥ 12 years, with a body weight ≥ 40 kg (48) and can decrease time of hospitalization (46). The recommended treatment period is between 5-10 days (46), by Intravenous injection of 200 mg in the first day and 100 mg daily for 9 days (total 10 days of treatment) (48).

The metabolism of remdesivir is by cytochrome P450 (CYP450), thus possibly has drug-drug interaction (46). Remdesivir could disturb Cardiovascular, Pulmonary, Hematological, Endocrine, Gastrointestinal, Neurological, skin, Renal and Metabolic normal functions (46).

b) Favipiravir:

Favipiravir as an oral RNA-dependent RNA polymerase inhibitor is a purine nucleotide, or a guanine analog (47). It was used against RNA viral diseases like influenza and Ebola viruses, but it is now used for other RNA viruses like coronaviruses (47). Favipiravir is a purine base analog and intracellular phosphoribosylation converts it to its active form, ribofuranosyl-5B-triphosphate (favipiravir-RTP) (49). Favipiravir with high affinity to bind RNA-dependent RNA polymerase, inhibits RNA-dependent RNA polymerase (RdRp) of RNA viruses intently, which results in ending the chain and viral mutagenesis. favipiravir-RTP integrated with viral genome, along with mutagenesis leads to subtraction of RNA virus (49) (Figure 7).

Favipiravir is prescribed orally (47) in different dosages for patients with mild to moderate hepatic disorder(at the first day 1200 mg twice daily; Days 2-4: 800 mg twice a day) and patients suffering from severe hepatic disease at first day 800 mg twice daily; Days 2 to 3: 400 mg twice a day) (49). There is a possible

drug interaction between Favipiravir and drugs that inhibit aldehyde oxidase (49). The common side effects of it includes gastrointestinal troubling, increased uric acid, Neutropenia, Anemia, diarrhea, increase of aspartate aminotransferase (AST) and alanine transaminase (ALT), psychiatric symptom reactions, and excess triglycerides in the blood (49). It has contraindicated in pregnant women and lactating women (49).

c) Nirmatrelvir

Nirmatrelvir is a selective inhibitor of RNA-dependent RNA polymerase that specifically targets the 3C-like protease enzyme required for COVID-19 viral replication (50-52). This inhibition results in the prevention of virus replication. However, due to its short half-life, nirmatrelvir is co-administered with ritonavir, which is a potent inhibitor of cytochrome P450 (CYP) 3A4, leading to the inhibition of nirmatrelvir metabolism and an increase in its plasma concentration, thereby enhancing its pharmacokinetic profile (50, 53) (Figure 8). Ritonavir has no direct effect on SARS-CoV-2 (53). The recommended dosage for nirmatrelvir/ritonavir is two 150 mg tablets of nirmatrelvir and one 100 mg tablet of ritonavir taken together twice daily for five days (53). The FDA has granted emergency use authorization for nirmatrelvir/ritonavir for the treatment of COVID-19 patients (51).

d) Molnupiravir

Molnupiravir is a prodrug that is a ribonucleoside small molecule derivative known as β-D-N4-hydroxy cytidine (NHC) (54, 55). It has been shown to possess antiviral activity against RNA viruses (54). NHC circulates in the body and undergoes intracellular phosphorylation to form NHC triphosphate (54). Subsequently, viral RNA polymerase combines with NHC triphosphate to misdirect the virus to bind to either guanosine or adenosine when replicating (54). This results in the accumulation of destructive mistakes in the viral genome, ultimately rendering the virus non-infectious and unable to replicate (54) (Figure 9). Molnupiravir is administered at doses of 600 and 800 mg twice daily for five days (54). The FDA has granted emergency use authorization for Molnupiravir in the treatment of COVID-19 (56).

4. Corticosteroids:

Corticosteroids have two subtypes called glucocorticoids and mineralocorticoids. Glucocorticoids have anti-inflammatory effects and mostly are involved in attenuating immune responses (57). Glucocorticoids based medicines are among the most widely used drugs and are used for various diseases such as autoimmune diseases and allergies. These drugs include betamethasone, dexamethasone,

hydrocortisone, triamcinolone, methylprednisolone, prednisone, clobetasol, beclomethasone, fludrocortisone, fluocinolone (57). Corticosteroids, mainly prednisolone or methylprednisolone, due to their immunosuppressive properties, have strong anti-inflammatory effects and are mainly used to reduce pneumonia, prevent the progression of respiratory failure and death, and are useful for patients with covid 19 (47, 58).

Corticosteroids alter the functions of dermal cells and leukocytes in inflammatory diseases. they can pass the cell membrane and react with receptor proteins in the cytoplasm to make a steroid-receptor complex. This complex needs to bind to DNA; thus, it moves into the nucleus. transcription of messenger RNA (mRNA) is changed following binding process. in conclusion, corticosteroids can stimulate or inhibit the synthesis of specific proteins (59) (Figure 10).

Corticosteroids should be used just in cases of chronic obstructive pulmonary disease exacerbation or septic shock, as recommended by the WHO and the Centers for Disease Control and Prevention (CDC) and Infectious Disease Society of America(IDSA) .(47) In addition the dosage should be low-to-moderate (≤0·5–1 mg/kg per day methylprednisolone or equivalent) and the duration should be short (≤7 days) (60). adverse effects such as e.g., hyperglycemia, neuropsychiatric symptoms, secondary infections (57). The current treatment with corticosteroid in COVID-19 is specialized to patients with fatal conditions that are correlated with cytokine storm such as ARDS, renal failure, and acute cardiac injury (57).

5. Monoclonal antibodies therapy:

In addition to anti interleukin Monoclonal antibodies that we described above several monoclonal antibodies have been developed to target the spike protein of SARS-CoV-2, including Bamlanivimab plus etesevimab, sotrovimab, and Casirivimab plus imdevimab. However, they are not approved for inpatient use and are prescribed intravenously or subcutaneously for individuals who are at least 12 years old and weigh at least 40 kg (61, 62) (Figure 11). Sotrovimab and Regdanvimab are recombinant human monoclonal antibodies that target the spike protein receptor-binding domain and receptor-binding domain (RBD) of the SARS-CoV-2 spike protein, respectively (63). Bebtelovimab binds to the viral spike protein to prevent it from attaching to the human ACE2 receptor (64). All three antibodies have received Emergency Use Authorization from the FDA for the treatment of mild-to-moderate COVID-19 (63). Sotrovimab is effective in treating mild-to-moderate COVID-19 based on clinical studies, with a recommended dosage of a single 500 mg intravenous infusion (65). Regdanvimab is administered as a single intravenous infusion at a dose of 40 mg/kg, while

Bebtelovimab is administered via IV injection at a recommended dosage of 175 mg over a minimum of 30 seconds (66, 67).

6. Anticoagulant drugs:

Many patients with COVID-19 develop clinical coagulation identified with the following signs: Thrombocytopenia, Prolonged prothrombin time (PT), and partial thromboplastin time (aPTT), Increased serum D-dimer and fibrinogen, etc. and are at hazard for major vascular thrombosis (68), therefor anticoagulants are recommended for the prevention and treatment of thrombosis (69, 70). There are many anticoagulant drugs that are classified into wide categories as well as Heparin or enoxaparin, dalteparin, and rivaroxaban (70, 71). Heparin as the first anticoagulant encompasses unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) (70).

Heparin can reduce inflammation through impeding neutrophil infiltration and inhibiting the production of inflammatory factors, such as IL-8, IL-6, and TNF-α and (68). It can also attach to the spike protein of SARS-CoV-2 and serve as a competitive suppressor for virus entry, thus reduce infectivity(69). Moreover, both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) can bind to antithrombin III which inhibits the activation of FX. Unfractionated heparin (UFH) also can blocks thrombin by consisting heparin-antithrombin-thrombin complex and leading anticoagulation (70).

So as mentioned above, heparin has notable features such as anti-inflammatory, antiviral, and anticoagulant properties (69-71) (Figure 12). Bleeding and thrombocytopenia are major disadvantages of heparin, as well as alopecia, and hyperkalemia (69, 70).

Single nucleotide polymorphisms (SNPs) located at direct targets of anti-COVID-19 drugs and may interact with their functions:

As we discussed above inflammatory elements such as IL-1R, IL-6R, IL17A, IL17RA, JAK1, JAK2 could be possible targets for anti-COVID-19 medicines. But all of these genes have some SNPs which may impact on gene expression, associated with other inflammatory diseases and interferes with drug function. We provide the complete information about SNPs of these genes based on snpedia and dbsnp, in table1. Although there are limited studies about interactions between their SNPs and drugs, several studies demonstrated association of interleukin 6 two SNPS, rs12083537 and rs2228145 with tocilizumab function.

the rs2228145 SNP (single nucleotide polymorphism), which has been associated with variation in the response to tocilizumab treatment in patients with rheumatoid arthritis (RA), results in a change from guanine (G) to adenine

(A) at position -174 in the promoter region of the IL-6R gene. The A allele has been associated with increased IL-6R production and activity, whereas the G allele is associated with reduced IL-6R production and activity. One study found that patients carrying the AA genotype had a slower and less pronounced response to tocilizumab compared to those carrying the GG or GA genotypes (72). Another study found that patients with the AA genotype had higher levels of IL-6R and C-reactive protein (CRP) at baseline, and were less likely to achieve remission after tocilizumab treatment (73).Moreover, another study demonstrated better response of IL-6R rs12083537 AA compared to GA and GG (74). However, in this investigation no association was found between rs4329505 and tocilizumab therapy, AAC haplotype of three polymorphisms (rs2228145 A allele, rs12083537A and rs4329505 C allele) was associated with poor response to tocilizumab treatment (73). And GAT-haplotype was related with good response (73).

Conclusion

COVID-19 is known as an inflammatory disorder. With due attention to its high rate of mortality finding a best treatment protocol and appropriate therapeutics is imperative. In this mini-Review we described various efficient drugs prescribed in patients suffering from COVID-19 with mild to severe symptoms. We tried to collect and classify drugs and express their molecular target briefly. However, this review didn't conclude all medicine used for COVID-19 treatment and we mentioned just the medicines involving prominent evidences of high efficiency and performance.in addition we provided SNPs related to drugs prescribed against covid-19. Inconclusion this review presents beneficial information about covid19 appropriate therapeutics according to the molecular targets.

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Author Contributions

Zahra Saadatian and Saba Seyedi designed the study.

Saba Seyedi, Ziba Nariman-Saleh-Fam and Shadan Navid, Samira Ezi and Lida Nariman-Saleh-Fam carried out the search.

Zahra Saadatian and Saba Seyedi wrote the manuscript with support from Samira Ezi and Shadan Navid.

Mohammadreza Gerami drew the Figures.

Zahra Saadatian, Lida Nariman-Saleh-Fam and Ziba Nariman-Saleh-Fam revised the first draft.

All authors commented on the manuscript.

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Competing Interests

All authors declare no financial or non-financial competing interests.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

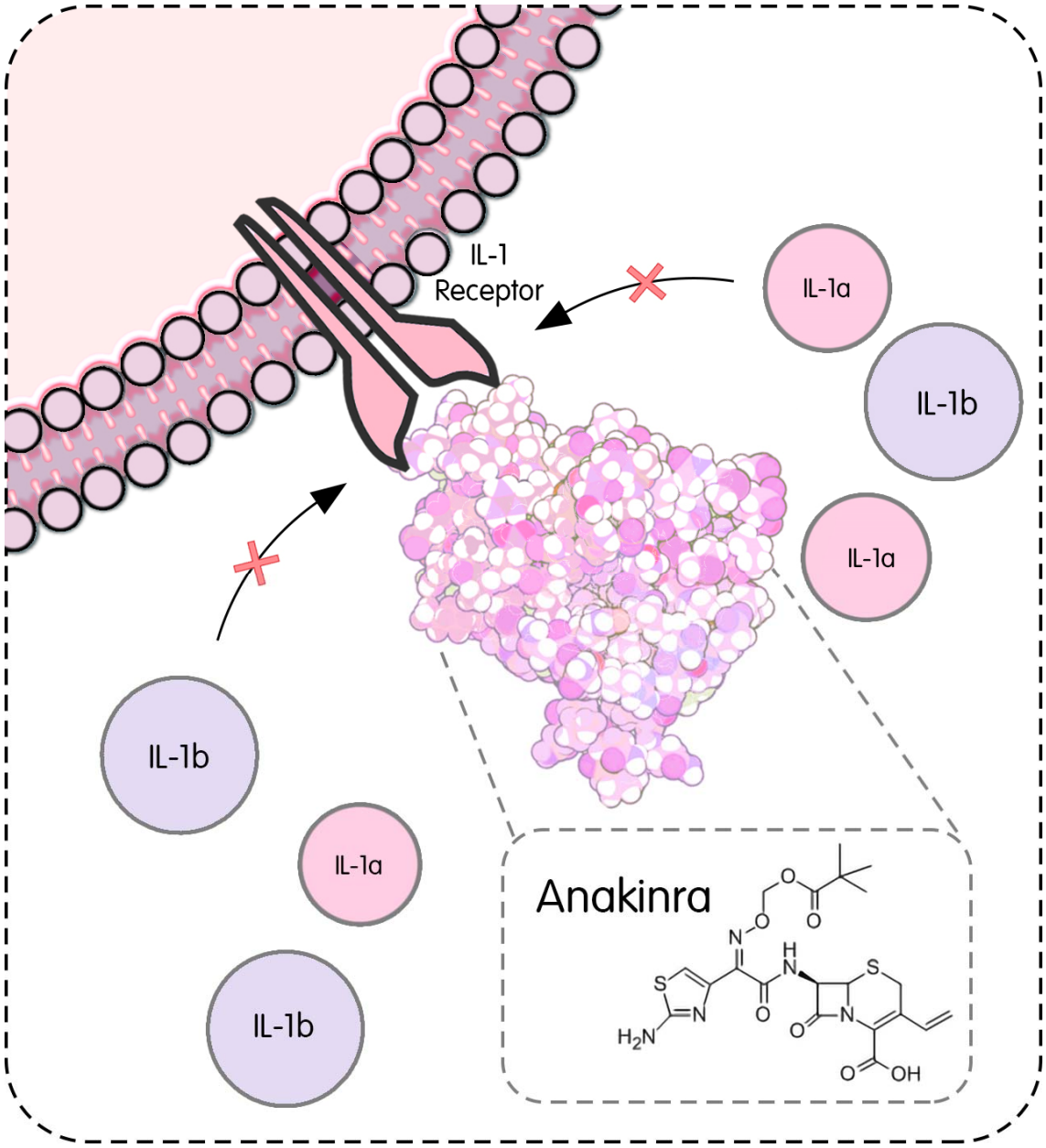

Figure 1: Anakinra

Anakinra as an interleukin-1 receptor antagonist, blocks the activity of IL-1α and IL-1β and inhibits binding of the IL-1 to its receptor.

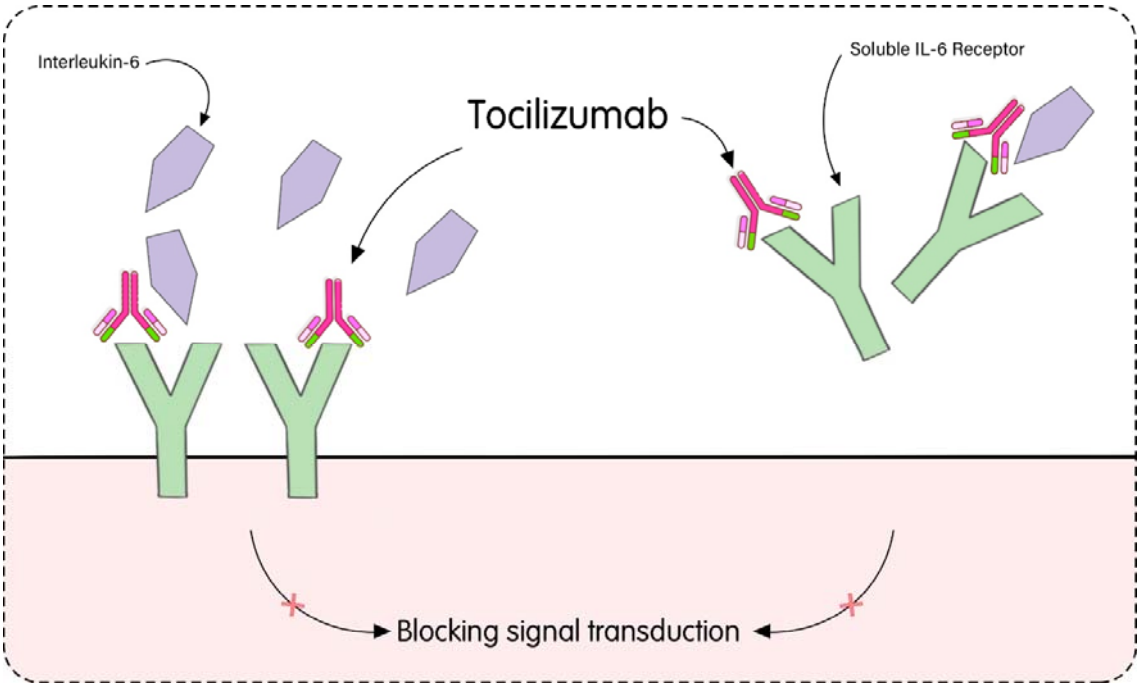

Figure 2: Tocilizumab

Tocilizumab suppresses the cytokine storm by blocking IL-6 receptors.

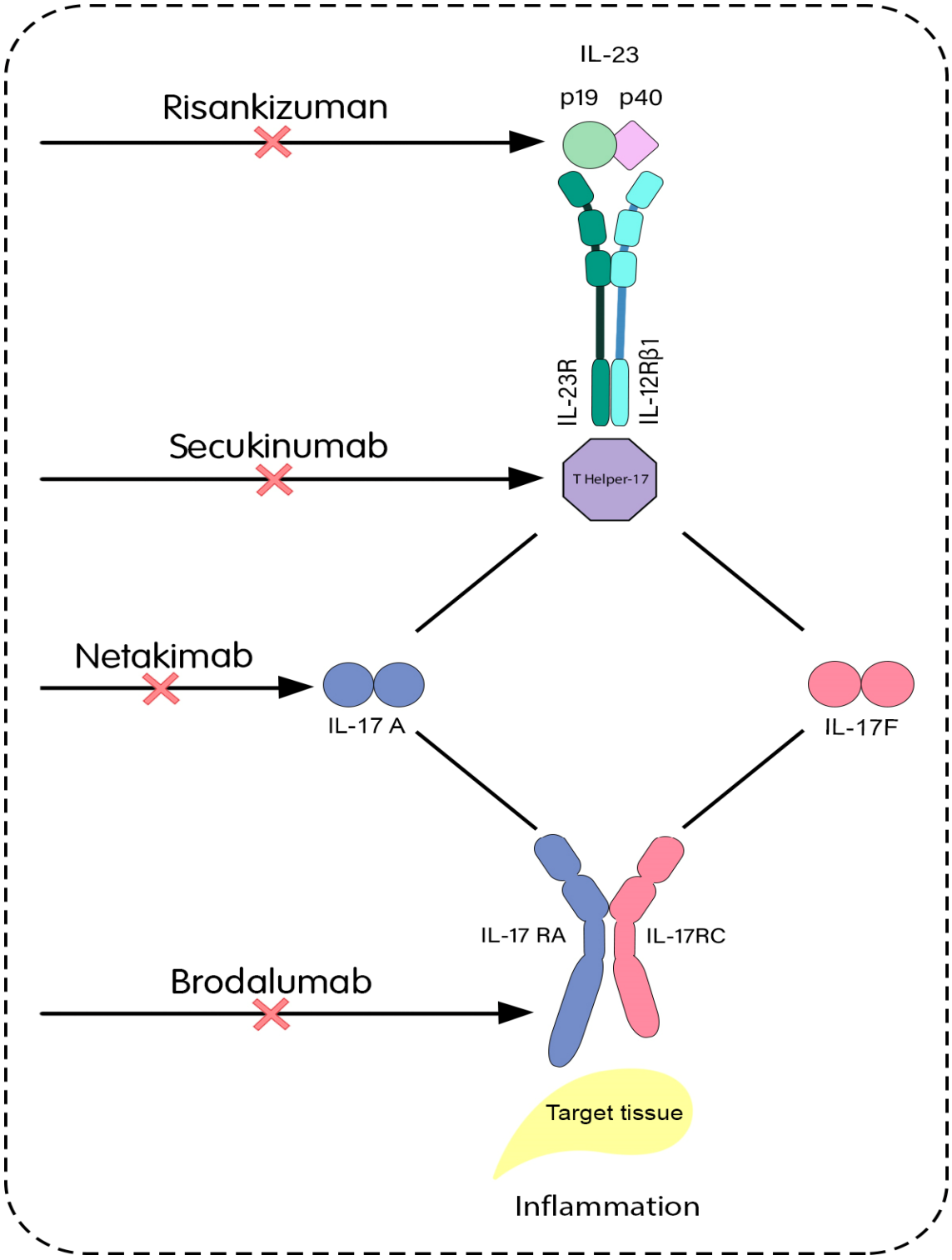

Figure 3: Netakimab

Netakimab, hinders interleukin 17-A, and Brodalumab blocks its receptor of IL-17A (IL-17RA), Secukinumab suppresses T-helper 17, Risankizumab, binds to the p19 and inhibits IL-23.

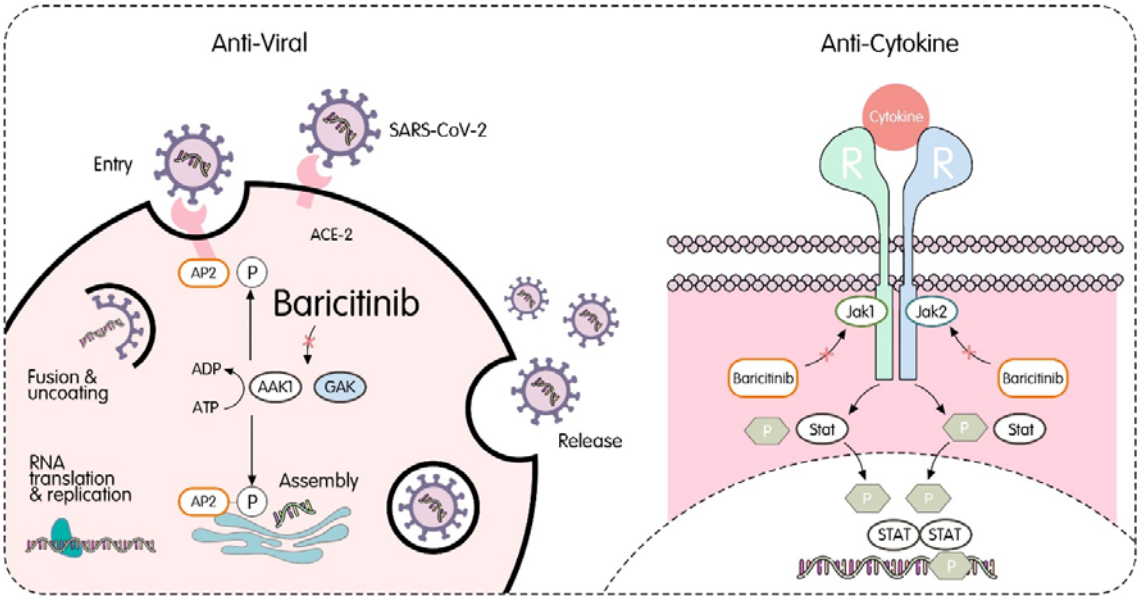

Figure 4: Baricitinib

Baricitinib targets the Janus kinase family, with specificity towards JAK1 and JAK2 and results in the prevention of downstream phosphorylation and activation of Signal Transducers and Activators of Transcription (STAT) proteins. In addition to its anti-inflammatory profile, Baricitinib exhibits antiviral effects by blocking the entry of SARS-CoV-2 into lung cells by reducing the endocytosis of SARS-CoV-2 through the inhibition of AP2-associated protein kinase 1 and cyclin G associated kinase.

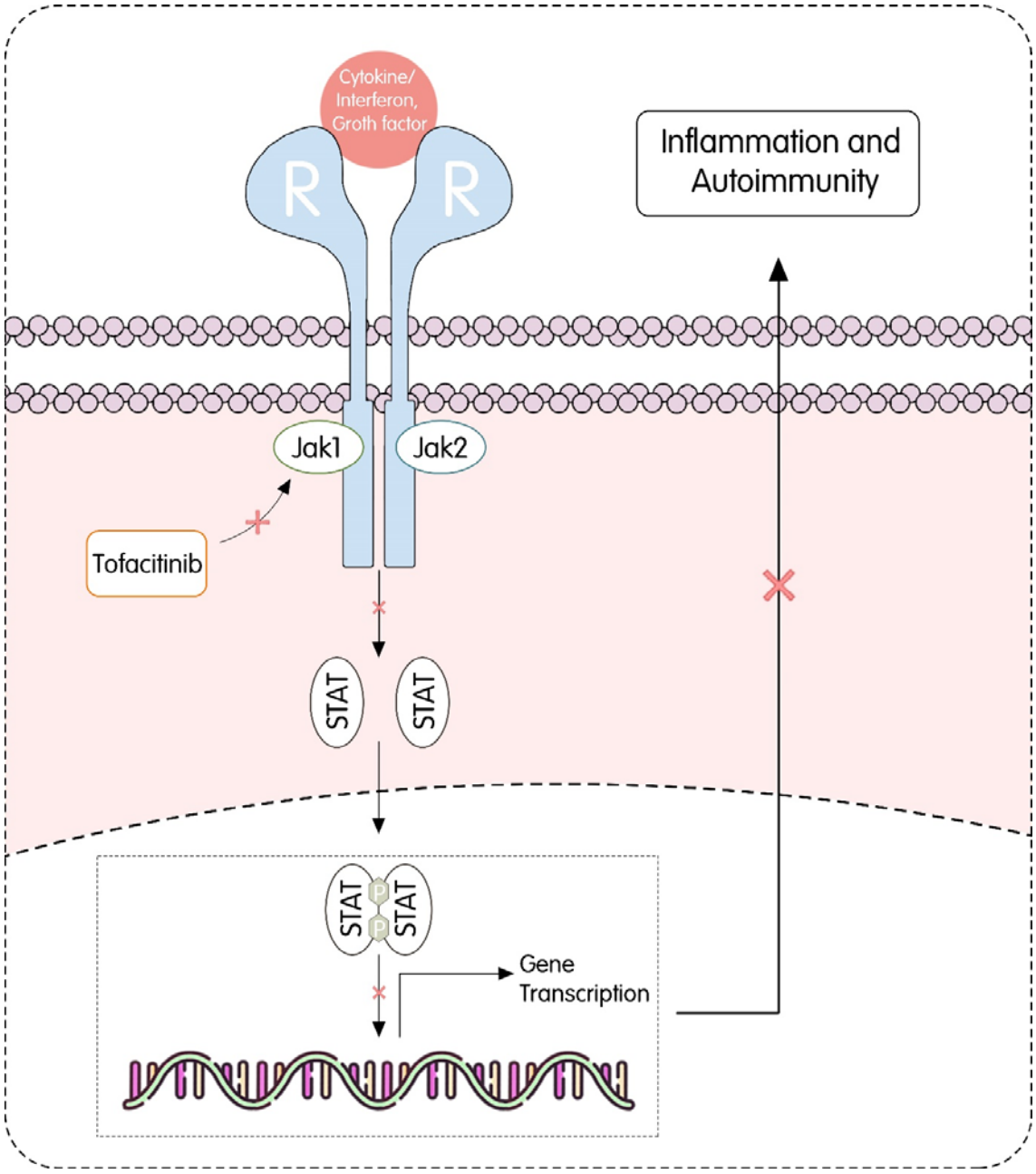

Figure 5: Tofacitinib

Tofacitinib functions by binding to Janus kinases, which inhibits the activation of the JAK-STAT signaling pathway, leading to a potential reduction in the production of pro-inflammatory cytokines.

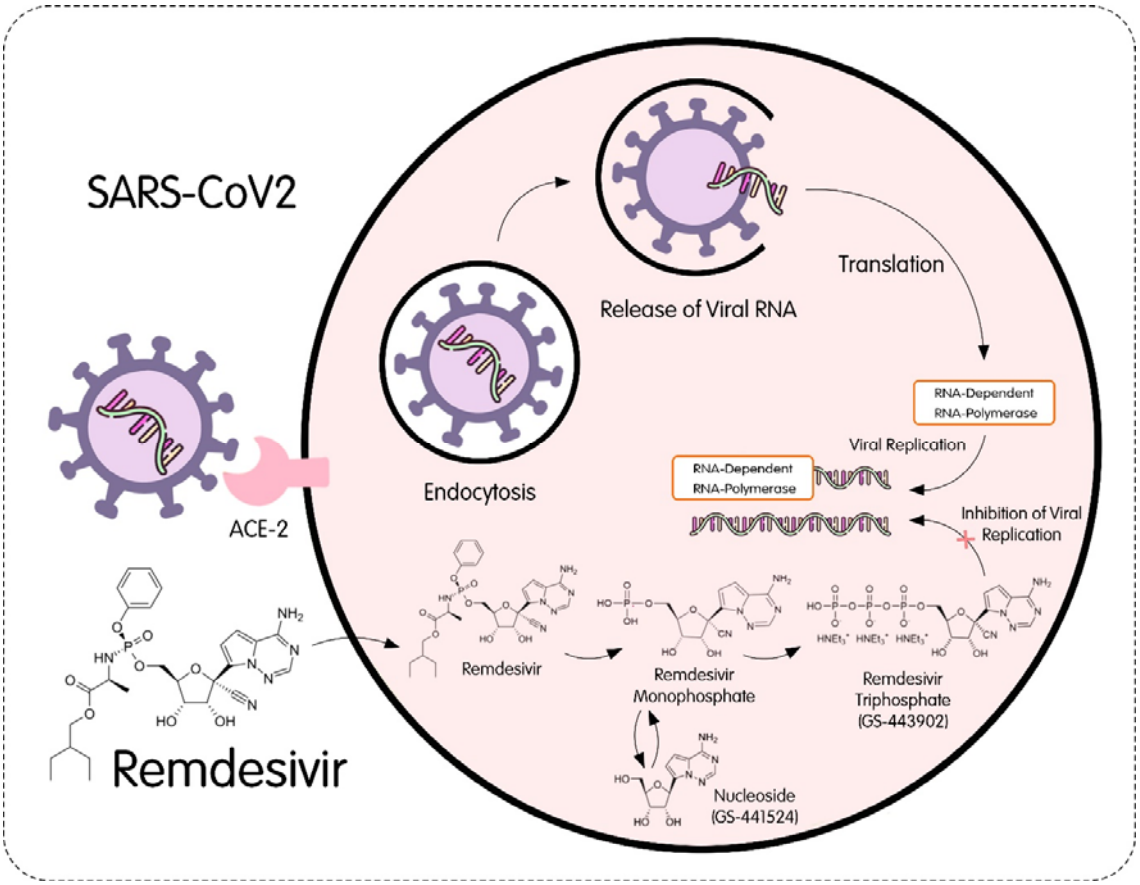

Figure 6: Remdesivir

Remdesivir is metabolized into the pharmacologic active analog adenosine triphosphate and in a competition with ATP interrupts RNA-dependent RNA polymerase (RdRp) function and RNA synthesis.

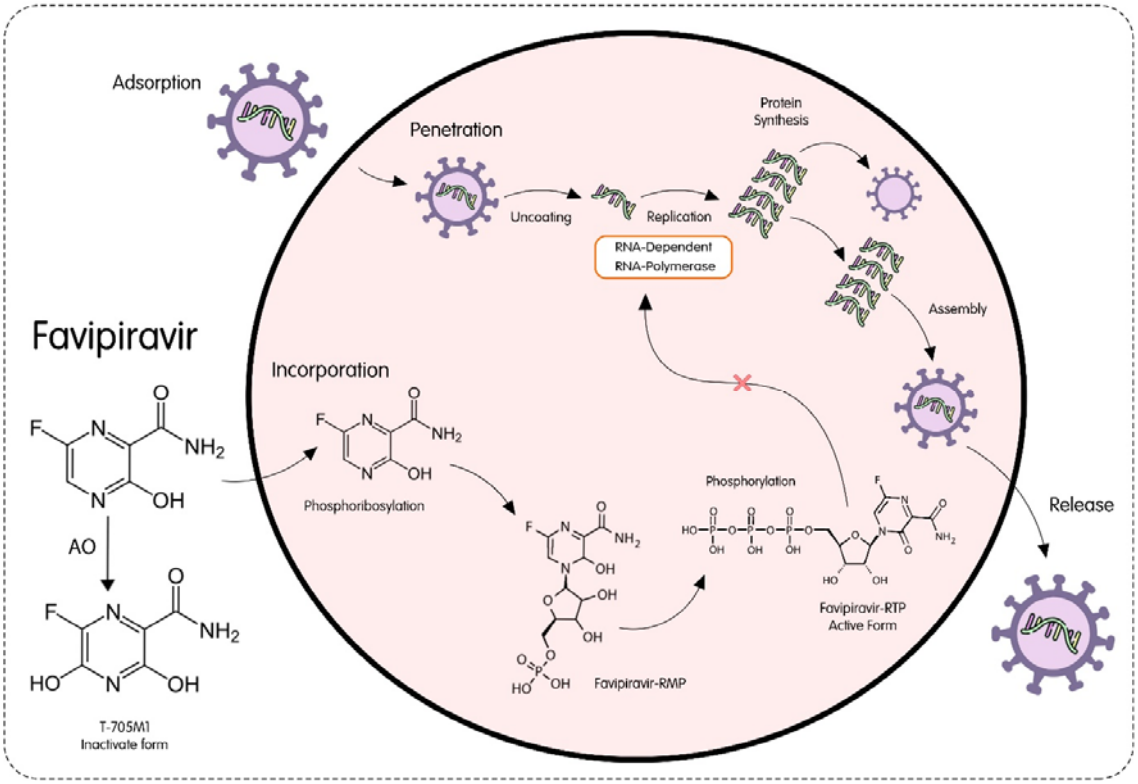

Figure 7: Favipiravir

Favipiravir is metabolized into the active form, ribofuranosyl-5B-triphosphate (favipiravir-RTP) and interferes with RNA-dependent RNA polymerase (RdRp) function and RNA synthesis.

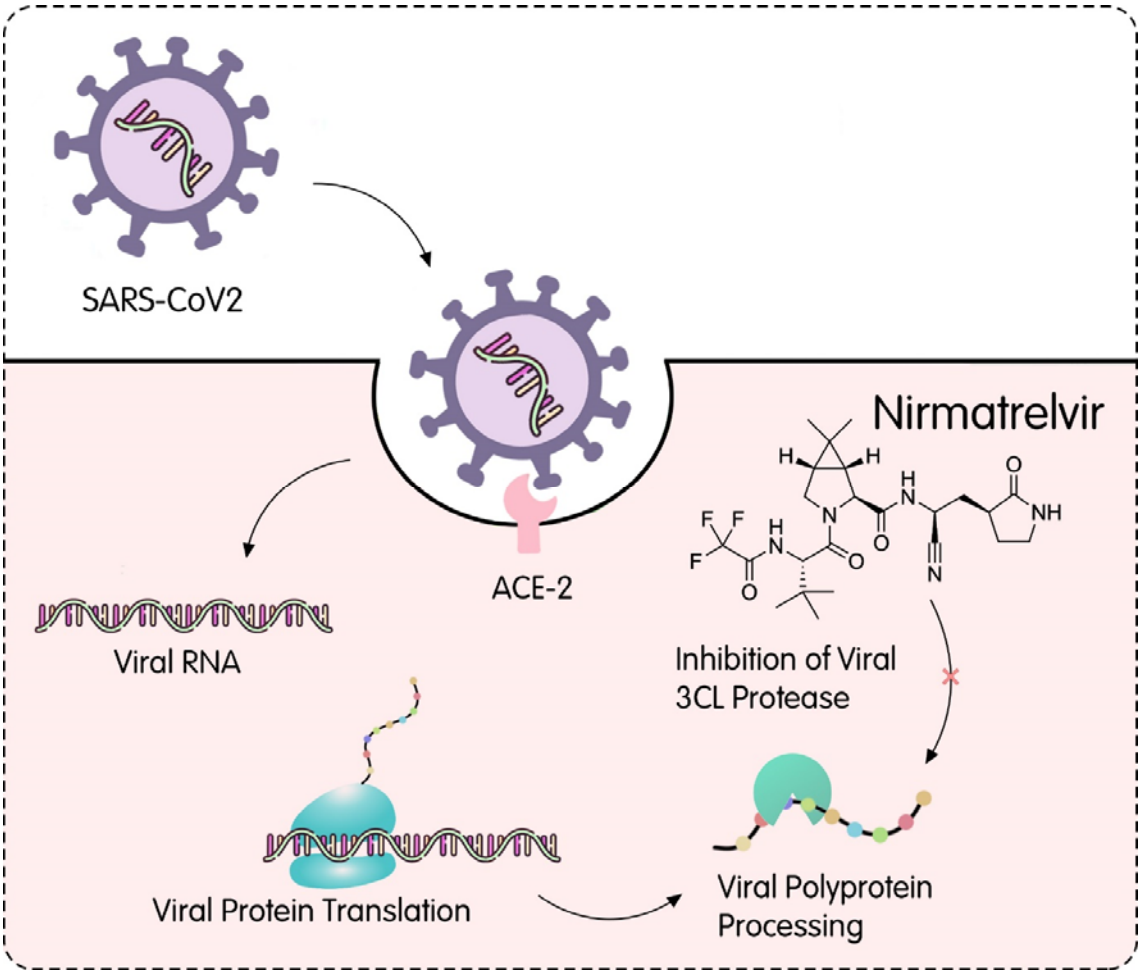

Figure 8: Nirmatrelvir

Nirmatrelvir targets the 3C-like protease enzyme required for COVID-19 viral replication and results in the prevention of virus replication.

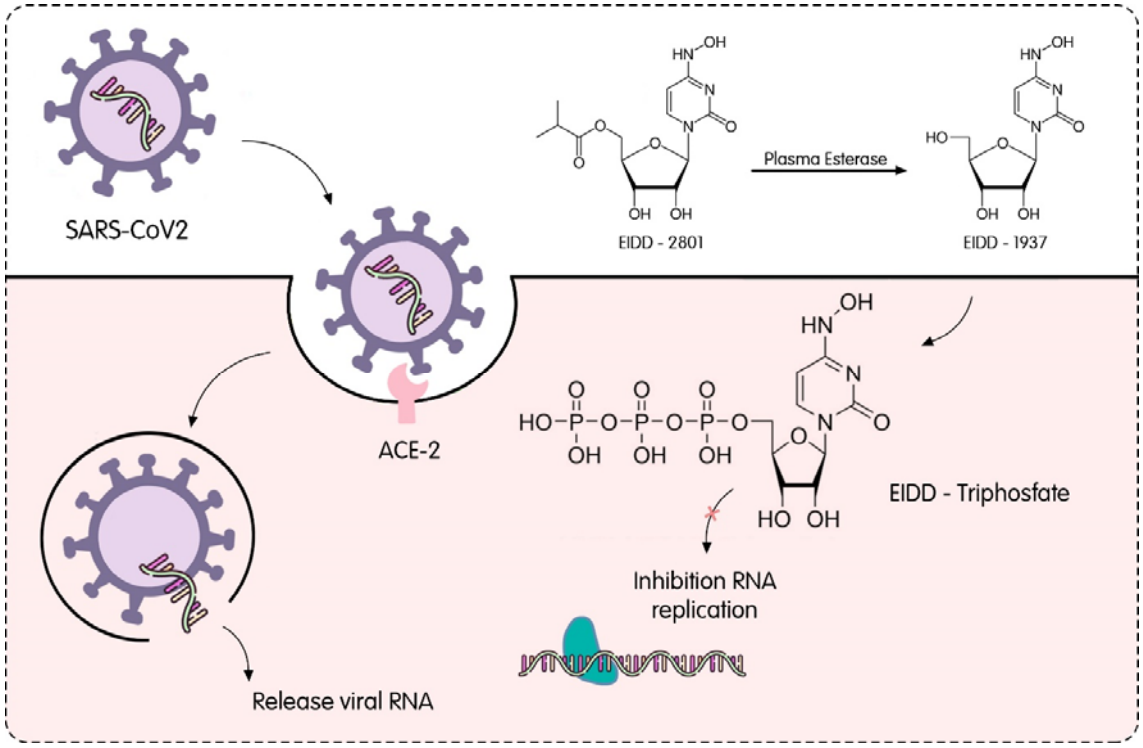

Figure 9: Molnupiravir

Molnupiravir is a prodrug that is a ribonucleoside small molecule derivative known as β-D-N4-hydroxy cytidine (NHC). NHC circulates in the body and undergoes intracellular phosphorylation to form NHC triphosphate. Subsequently, viral RNA polymerase combines with NHC triphosphate to misdirect the virus to bind to either guanosine or adenosine when replicating This results in the accumulation of destructive mistakes in the viral genome, ultimately rendering the virus non-infectious and unable to replicate.

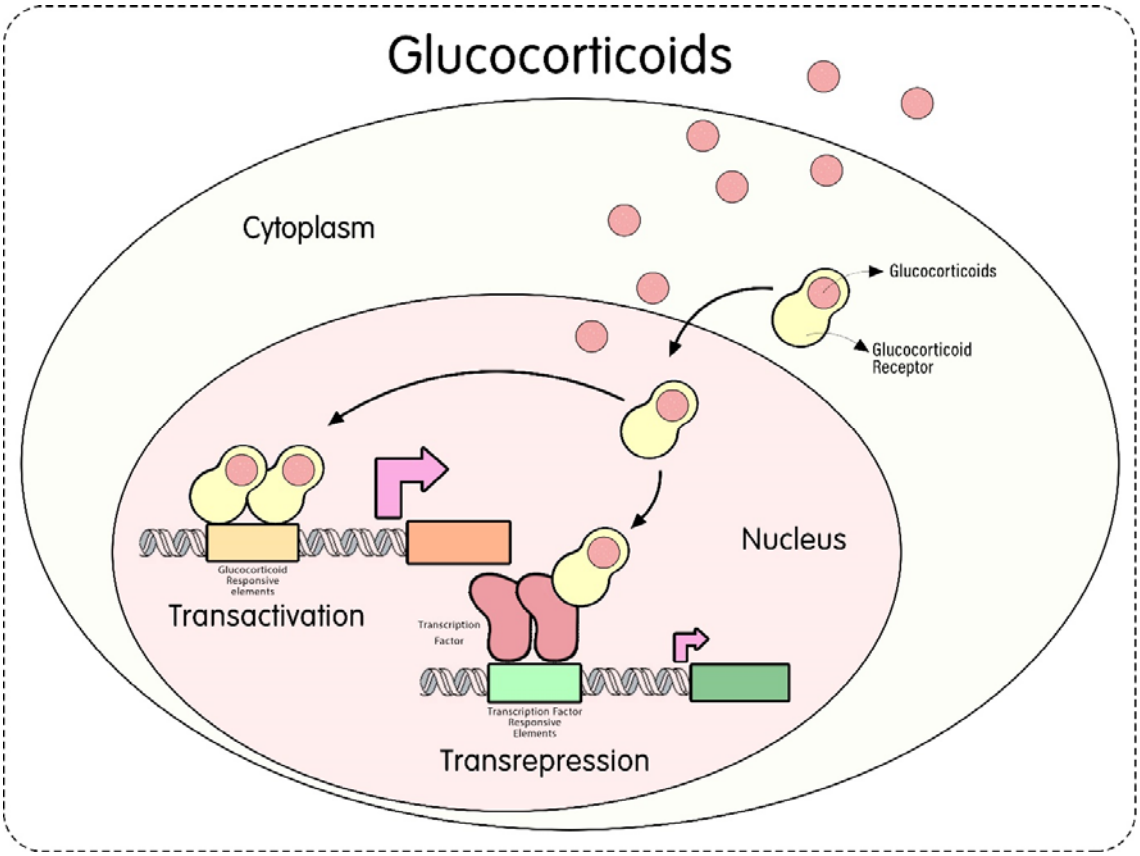

Figure 10: Corticosteroids

Corticosteroids bind with receptor proteins in the cytoplasm and make a steroid-receptor complex. This complex pass into the nucleus and can stimulate or inhibit the synthesis of specific proteins via DNA connection.

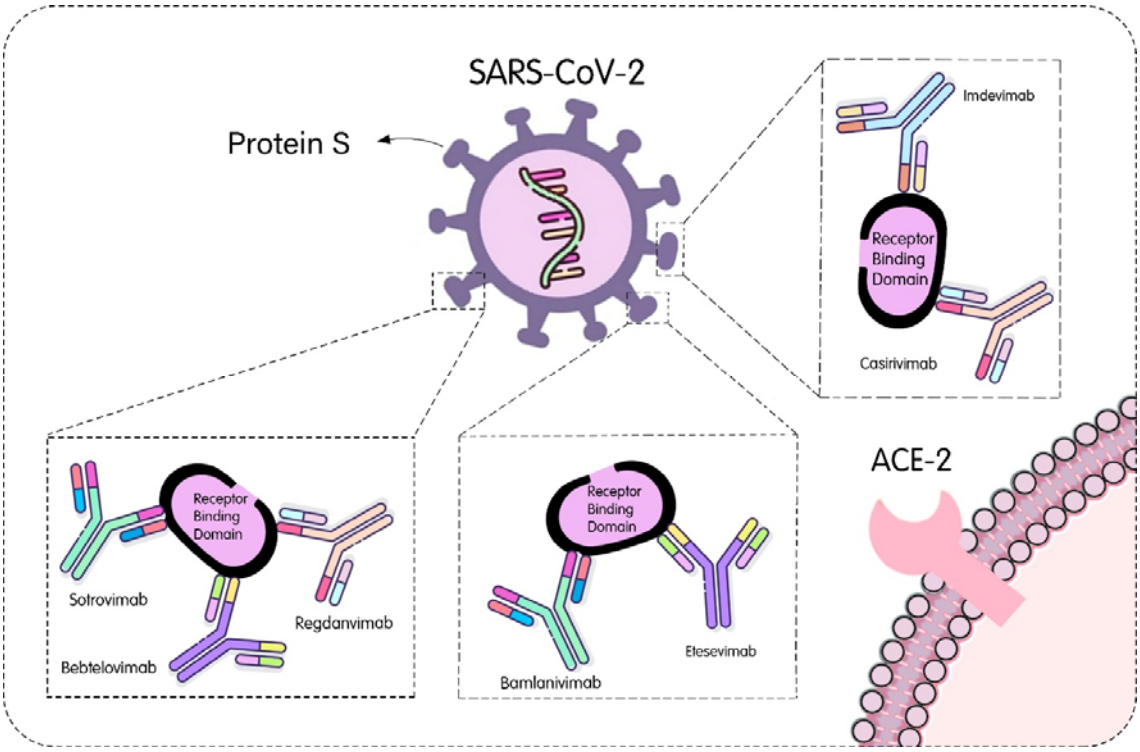

Figure 11: Monoclonal antibodies

Bamlanivimab plus etesevimab, sotrovimab and Casirivimab plus imdevimab target spike protein of SARS-CoV-2.

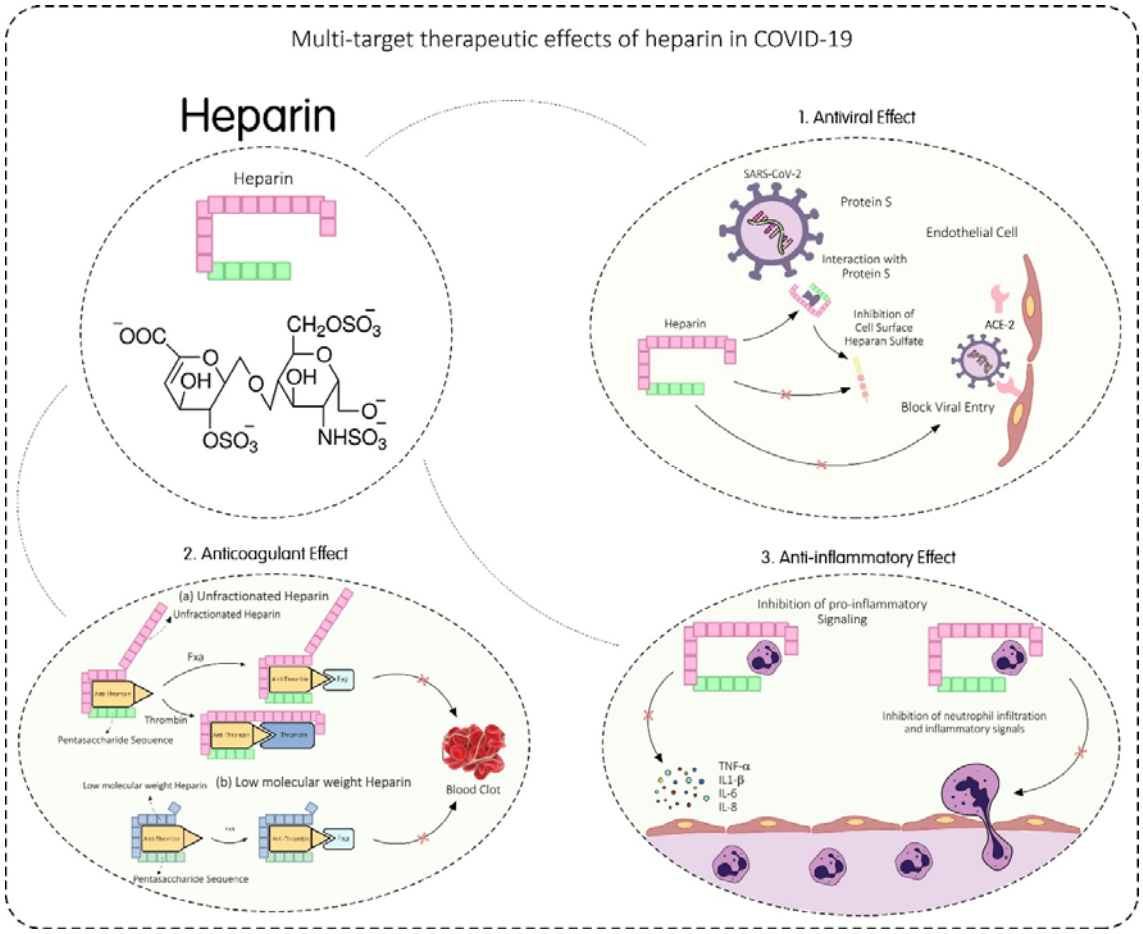

Figure 12: Heparin antiviral (1), anti-inflammatory (2), and anticoagulant (3) properties.

1. Heparin can also attach to the spike protein of SARS-CoV-2 and serve as a competitive suppressor for virus entry, thus reduce infectivity
2. it can reduce inflammation through impeding neutrophil infiltration and inhibiting the production of inflammatory factors, such as IL-8, IL-6, and TNF-α
3. Moreover, both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) can bind to antithrombin III which inhibits the activation of FX. Unfractionated heparin (UFH) also can blocks thrombin by consisting heparin-antithrombin-thrombin complex and leading anticoagulation.

Table1: anti-inflammatory drugs used against COVID-19, their direct targets and SNPs, and SNPs association with other disease and drugs

Anti covid medicine	target	SNP	position	SNP association with other drugs	SNP association with diseases	reference
anakinra	IL-1R1	rs10490571	Intron	-	Rheumatoid Arthritis, osteonecrosis of the femoral head, lumbar disc herniation, breast cancer, IgA nephropathy	(75),(76),(77), (78), (79)
		rs12712127	Intron	-	-	-
		rs13019803	Intron	-	GVHD	(80)

		rs13020778	Intron	-	No evidence	-
		rs1558641	Intron	-	atopic asthma	(81)
		rs2110726	3 Prime UTR	-	Less Breast Pain in Women Prior to Breast Cancer Surgery	(82)
		rs2160227	Intron	-	invasive pneumococcal disease	(83)
		rs2192752	Intron	-	location of papillary thyroid carcinoma	(84)
		rs2234650	Intron	-	sudden sensorineural hearing loss, risk of vertical HIV transmission, systemic sclerosis	(85), (86), (87)
		rs2287047	Intron	-	severe hand osteoarthr	(88), (89)

					itis, Invasive Pneumococcal Disease	
		rs3917225	Intron	-	osteoporosis predisposition, osteonecrosis of the femoral head, thyroid cancer, ankylosing spondylitis, IgA nephropathy, severe hand osteoarthritis	(90), (76), (91), (92), (79), (88)
		rs3917254	Intron	-	invasive pneumococcal disease	(83)
		rs3917267	Intron	-	invasive pneumococcal disease, Hepatitis B Virus Infection	(83), (93)

					of Children	
		rs949963	Intron	-	development of secondary lymphedema following breast cancer surgery, Childhood asthma	(94), (95)
tocilizumab	IL-6R	rs11265611	Intron	-	atrial fibrillation	(96)
		rs12083537	Intron	Tocilizumab(73),(97),(98),(99),(7(742)	ischemic stroke in patients with metabolic syndrome, severe heart failure, lung function in Chinese patients with asthma, coronary heart disease,	(100), (101),(102),(103)

		rs12133641		-	Abdominal aortic aneurysm	(104)
		rs12730935		-	No evidence	-
		rs2228144		-	No evidence	
		rs2228145	Missense	Tocilizumab(73),(72)	Multiple disorders such as: rheumatoid arthritis, asthma and dermatitis risk, COVID-19 risk, psoriasis, morbidity of preterm newborns, Alzheimer's Disease, obesity, Gulf War Illness, ischemic stroke, type 2 diabetes, bipolar disorder,	(105), (106), (107), (108), (109), (110), (111), (112), (113), (114), (115), (101)

					heart failure	
		rs2229238	3 Prime UTR	-	Preeclampsia	(116)
		rs4129267	Intron		Asthma, Ankylosing Spondylitis, cardiovascular diseases, Diabetic Ischemic Heart Disease, cardiovascular diseases and inflammatory disease	(117), (118), (106), (119), (106)
		rs4537545	Intron	-	joint damage in rheumatoid arthritis,	(120)
		rs4845617	5 Prime UTR	-	atherosclerotic lipid profiles, Neurological Status,	(121), (122), (108)

					psoriasis	
		rs4845618	Intron	-	Melanoma, cardiovascular diseases and inflammatory disease, rheumatoid arthritis	(123), (106), (120)
		rs4845622	Intron	-	Melanoma, severe heart failure	(123), (101)
		rs4845625	Intron	-	atrial fibrillation, dyslipidemia, chronic kidney disease, cardiovascular disease, Atherosclerosis, cardiovascular diseases and inflamma	(96), (124), (125), (126), (127), (106), (119)

					tory disease, Diabetic Ischemic Heart Disease	
		rs6684439	Intron	-	Melanoma, multiple myeloma, severe heart failure	(123), (128), (101)
		rs6694817	Intron	-	No evidence provideed	-
		rs7529229	Intron	-	Diabetic Ischemic Heart Disease, cardiovascular diseases and inflammatory disease, severe heart failure	(119), (106), (101)
secukimab	IL-17R	rs1057518744	Frame shift	-	-	-
		rs1057518745	Stop Gained	-	-	-

		rs1057518746	Frame shift	-	-	-
		rs1057518747	Frame shift	-	-	-
		rs1057519079	Missense	-	-	-
		rs12159217	Intron	-	Cerebral Malaria	(129)
		rs2229151	Synonymous Variant	-	new-Onset Diabetes after Transplantation	(130)
		rs2241049	Intron	-	primary graft dysfunction after lung transplantation, psoriatic arthritis	(131),(132)
		rs387906913	Stop Gained	-	-	-
		rs41396547	Intron	-	Cerebral Malaria	(129)
		rs41433045	2KB Upstream Variant	-	Cerebral Malaria	(129)

		rs4819554	2KB Upstream Variant	anti-TNF drugs(133), etanercept(134)	Prognosis of Non-Small Cell Lung Cancer Patients Receiving Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors, Hashimoto's thyroiditis , Preeclampsia, Toxoplasma gondii infection, ardiovascular mortality in patients with congestive heart failure	(135), (136),(137),(138), (139)
		rs879574	Intron	-	chronic rejection after lung transplantation,	(140),(141)

					Crohn's disease	
		rs882643	3 Prime UTR	-	Crohn's disease	(141)
netakimab	IL-17A	rs10484879	intron	etanercept(134), tolerance to FOLFOX chemotherapy in colorectal cancer treatment(142)	Psoriasis, Age-Related Macular Degeneration, Chronic Periodontitis, Risk of Vulvovaginal Candidiasis, chronic hepatitis B virus infection, colorectal cancer	(132), (143), (144), (145), (146), (147)
		rs1974226	3 Prime UTR	-	atopic asthma, Chronic Obstructive Pulmonary Disease, Gram-positive infection and mortality	(148), (149), (150)

					of severe sepsis	
		rs2275913	2KB Upstream	steroid - response(151), Antitumor Necrosis Factor Agents(152), etanercept(134), biologic and MTX treatment(153), anti-TNF therapy (154),	IgA nephropathy, polycystic ovary syndrome, cervical cancer, systemic lupus erythematosus, schizophrenia, colorectal cancer, Rheumatoid arthritis, hepatocellular carcinoma, gastric cancer, Chagas disease, appendicitis, Prostate Cancer, syphilis, influenza, acute respiratory distress syndrome, leprosy	(155), (156), (157), (158),(159), (160), (161),(162), (163), (164), (165), (166), (167), (168), (169), (170), (171),(145), (172), (173), (174), (175),(176), (177), (178),(179), (180), (181),(182), (183),(184), (185),(186), (187)

					type 1 reaction, non-alcoholic fatty liver disease, Vulvovaginal Candidiasis, recurrent aphthous ulcer, osteoarthritis, bladder cancer, asthma, ischemic stroke, ankylosing spondylitis, celiac disease, laryngeal cancer , Recurrent Pregnancy Loss , severe viral bronchiolitis, lung cancer, Intestinal Behcet's disease,	

					breast cancer, periodontitis, panuveitis, Oral squamous cell carcinoma	
		rs3748067	3 Prime UTR	FOLFOX tolerance (142),	breast cancer, gastric cancer risk, Graves' disease, tuberculosis, Pemphigus Foliaceus, asthma, brucellosis, gastric cancer, Cervical Cancer, obstructive sleep apnea syndrome	(184),(188), (189), (190), (191), (192), (193) , (194), (195),(196)
		rs3804513	Intron	tolerance to FOLFOX(142)	ulcerative colitis	(197)
		rs3819024	2KB Upstre	-	gastric cardia	(198),(199), (200),

			am Variant		adenocarcinoma, metabolic syndrome, allergic bronchopulmonary aspergillosis in asthma, periodontitis and type 2 diabetes, brucellosis, colorectal cancer, syphilis, rheumatoid arthritis	(201),(193), (147), (147), (202),
		rs3819025	Intron	cytokine inhibitors(133)	breast cancer, Henoch-Schonlein purpura, brucellosis, rheumatoid arthritis	(184), (203),(193),(204)
		rs4711998	2KB Upstream Variant	response to blinatumomab (205), sustained responses to PEG-IFNa-2α(206)	HBV related hepatocellular carcinoma, brucellosi	(207), (193),(208), (209)

					s, osteitis after BCG vaccination, hepatitis B virus-related liver cirrhosis	
		rs7747909	3 Prime UTR	cytokine inhibitors(133)	colorectal cancer, age-related macular degeneration, giant cell arteritis	(147),(143), (210)
		rs8193036	2KB Upstream Variant	Anti-Jo1 Antisynthetase Autoantibodies(211)	acute respiratory distress syndrome (ARDS), osteitis after Bacillus Calmette-Guerin vaccination, metabolic syndrome, allergic Rhinitis, restless legs syndrome, skin	(169), (208), (199),(199),(212),(213),(214), (183),(150),(215),(216)

					structure infections, Parkinson's disease with cognitive impairment, intestinal Behcet's disease, Gram-positive infection, breast cancer mortality, rheumatoid arteritis	
		rs8193037	2KB Upstream Variant	cytokine inhibitors.(133)	Graves' disease, Coronary Artery Disease, congestive heart failure, nonsmall cell lung cancer, ulcerative colitis	(189),(217), (139),(218),(197)
		rs8193038	Intron	-	ulcerative colitis, brucellosis	(197),(219)

barcitinib	JAK1	rs1057519753	Missense	-		
		rs10789166	intron	-	Dengue hemorrhagic fever	(220, 221)
		rs11208534	Intron	-	-	-
		rs151047872	missense	-	-	-
		rs17127114	Intron	-	-	-
		rs2254002	Intron	-	-	-
		rs2780815	Intron	-	Behcet's disease	(222)
		rs2780831	Intron	-	Dengue hemorrhagic fever	(220)
		rs2780885	Intron	-	-	-
		rs2780889	3 Prime UTR	-	-	-
		rs2780890	intron	-	-	-
		rs2780895	Intron	-	-	-
		rs310230	Intron	-	Vogt-Koyanagi-Harada (VKH) syndrom	(223)

		rs310236	Intron	-	Vogt-Koyanagi-Harada (VKH) syndrome	(223)
		rs310241	Intron	-	Behcet's disease with ocular involvement, Vogt-Koyanagi-Harada (VKH) syndrome, allergic rhinitis, Psoriasis	(222), (223), (224), (225)
		rs310245	Intron	-	-	-
		rs3790532	Intron	-	Behcet's disease with ocular involvement	(222)
		rs3806277	Intron	-	-	-
		rs478665	Intron	-	-	-

		rs4916008	Intron	-	-	-
		rs578481	Intron	-	head and neck squamous cell carcinoma	(226)
		rs705509	Intron	-	head and neck squamous cell carcinoma	(226)
		rs869312953	Missense	-	-	-
tofcitinib	JAK2	rs10119004	Intron	-	ankylosing spondylitis	(227)
		rs1057519721	Missense	-	-	-
		rs1057519722	missense	-	-	-
		rs1057519723	missense	-	-	-
		rs1057520016	missense	-	-	-
		rs10815144	Intron	-	-	-
		rs10815149	Intron	-	-	-
		rs10974944	Intron	-	myeloproliferative	(228), (229), (230),

					neoplasms, essential thrombocythemia	
		rs121912472	missense	-	-	-
		rs121912473	missense	-	-	-
		rs12340895	Intron	-	myeloproliferative neoplasms	(231)
		rs12342421	Intron	-	polycythemia vera, myeloproliferative neoplasms	(232), (231)
		rs12343867	Intron	anti-TNF response(233)	Myeloproliferative Neoplasms, cytogenetically normal acute myeloid leukemia	(234), (235)
		rs12349785	Intron	-	myeloproliferative neoplasms, splanchnic venous	(231), (236)

					thrombosis	
		rs2230722	Synonym variant	-	-	-
		rs2230724	Synonymous Variant	-	recurrent spontaneous miscarriage, gastric cancer, acute myeloid leukemia	(237), (238), ,(235),
		rs2274471	Intron	13-*cis*-retinoic acid (13-cRA)(239)	Psoriasis, colon and rectal cancer	(240), (241),
		rs368927897	missense	-	-	-
		rs3780374	Intron	-	-	-
		rs3780378	Intron	-	myeloproliferative neoplasms	(231)
		rs4495487	Intron	-	myeloproliferative neoplasm	(242)
		rs56118985	Missense	-	breast cancer, acute leukemia	(243), (244)

		rs7737 5493	Misse nse	-	myelopro liferative	(245),
		rs7849 191	Intron	-	breast cancer, myelopro liferative neoplasm s	(246), (231)
		rs7851 969	Intron	-	-	-
		rs7857 730	Intron	-	Algerian, myelopro liferative neoplasm s, ankylosin g spondyliti s	(247), (231), (227)