

# Plasma mediated treatment along with Interferon $\beta$ mechanism for symptomatic Covid 19/20 treatment and generation of asymptomatic conditions for Covid 19/20 with contrast to IBV Avian virus.

Pratik Nandi<sup>1</sup>, Dippyoman Guha<sup>2</sup>.

1. Department of Life-science, Dr KKR's GROUP of INSTITUTION, Vijayawada, Andra Pradesh, India.
2. Department of Pharmaceutical Science & Technology, Birla Institute of Technology, Mesra, Ranchi, Jharkhand, India.

## Abstract-

*Covid 19 virus has shown its terror by causing severe acute respiratory disorder of human being's effects shows a type of viral pneumonia. To address the anomaly the paper carries the motive encountering the viral infection with the help of interferon type 1  $\beta$ . A basic discussion of effective INF $\beta$ 1 and its introduction in the effective cells by Corona virus, plasma mediated delivery system along with development of asymptomatic conditions in non-affected individual. The plasma therapy considers plasma transfusion into effected individuals to boost their immunity against Corona virus. The plasma consists of antibodies, antigens as well as interferon to mediate with the viral infection and providing high effective rate. Satisfying these 2 goals was the basic motto of the paper along with a generation of asymptomatic condition in effected individuals. IBV (infectious bronchitis virus) is a type of influenza virus which has structural, genomic as well as symptomatic similarities with corona virus. Vaccination of non-effected individuals with IBV vac may allow to address the symptomatic similarities of Corona virus such as fever and breathing troubles. The generation of active immunity may render the extent of symptoms allowing persons to remain asymptomatic against the Corona infection. The study of structural phylogenomic of IBV along with Corona virus, and a contrast of similarities to support the asymptomatic postulates of the infected individuals has been explained.*

## Introduction-

The first Covid outbreak came into light as severe cases of pneumonia in Wuhan, China. The cases gave valid clearance towards the impact of the virus issuing severe respiratory disorder and its spread turned towards unavoidable pandemic. Effective treatment against Covid 19 has yet to obtain certainty. FDA has granted the use of a antiviral drug remdesivir for treating severe corona symptoms. Patients suffering from severe respiratory troubles are suggested to get support from supplemental oxygen and ventilator. The US National Institute of Health suggested the use of corticosteroid dexamethasone. The therapies suggested till date has shown effectiveness in treatment but isn't the permanent solution against Corona virus. Assembling possible therapies that may shows extent of effective activity against Covid 19/20 symptomatic patients are interferon INF $\beta$ 1 responsible for its anti-viral activity and plasma therapy leading towards extension of a better treatment policy or maybe a better effective solution towards permanent healing protocol for Covid treatment. For generating asymptomatic conditions as the pandemic has seasoned a wide range of death may also be a possible counter mechanism. The corona virus has shown its symptoms quite similar to the influenza and flu disease where effective similarity is fever, pain, breathing troubles as symptoms. To address such symptoms, it is possible to develop conditions where the virus infecting a human cell may not yet be stopped at the moment but the human

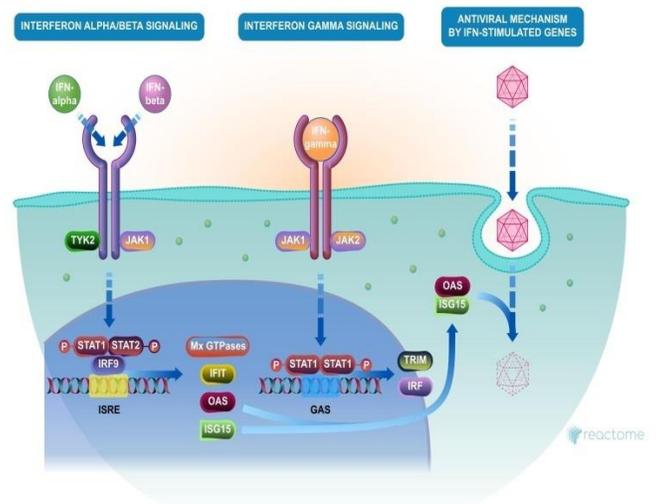
cell not showing symptoms may be a possibility that can be considered. By administration of the already available marketed vaccines of flu and influenza especially IBV (infectious bronchitis virus) having structural, symptomatic and cellular similarities that will help to immunize a non-effected individual who may get effected via Covid 19/20 virus but the avoidance of symptoms or generating a 1<sup>st</sup> line of defense in immunization against corona virus might be possible. Due to matches of avian IBV virus with Corona virus there is possibility of generating the immunized defense system against the symptoms of Corona virus. A detailed study of the therapies in present condition has been shown along with the tests for detection of Corona virus, flaws and achievements along with a approach to generate a probable most possible plasma mediated drug delivery system along with the mechanism of Interferon  $\beta$  has been studied in detail.

**Key words-**Interferon  $\beta$ 1, plasma therapy, asymptomatic conditions, IBV, Covid 19/20.

### 1. Interferons as a treatment.

The most trending question of this time is the different ways to combat with COVID-19. The use of the knowledge regarding Interferons (IFN) can be visualized with regards to this subject. As it is already known that IFNs are the body's natural defense mechanism against viral infection. Keeping in mind the category of nCoV this topic can also be pursued. However, the question remains on how the interferons can help with the anti-viral activity. To come up with the answer the basic knowledge of IFN is a must. IFNs are inducible cytokines that are released by the body as an innate response towards the viral infection. IFN are mainly of types IFN  $\alpha$ ,  $\beta$ ,  $\gamma$ . IFNs can be grouped into Type 1 IFN and Type 2 IFN. Type 1 IFN consist of the  $\alpha$ ,  $\beta$  whereas the Type 2 IFN consist of  $\gamma$ . Type 1 IFN is also considered as viral IFN and they are induced upon the viral infection. Type 2 IFN is also considered as immune IFN and are induced by mitogenic or antigenic stimuli. IFN  $\alpha/\beta$  is synthesized by the infected cells whereas the IFN  $\gamma$  is synthesized in response to the secretion of some cells of the immune system such as CD4 Th1 cells, NK

cells CD8 cytotoxic suppressor cells.



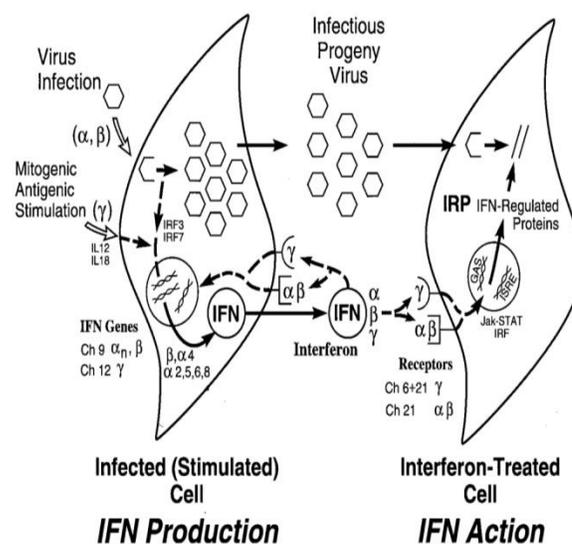
**Fig 1. Mechanism of IFN in an Overview** [1]

#### 1.a. Interferon Mechanism of Action to encounter viral infection

Where the response related to IFN is as helpful an important setback is an unchecked response which may lead to immune pathology and autoimmune disorders as well. For the detection of the viral genome, the immune system of the human body has various sensors. One such sensor is the Toll-like Receptors [2], TLR7, TLR3, TLR8, and TLR9 which scan the endosomal and extracellular space for the detection of DNA and RNA detecting viral genomes from lysed virus particles outside the cell and thus initiating the secretion of IFN and other pro-

inflammatory molecules<sup>[3]</sup>. Also, RIG-I detects the di-phosphate and tri-phosphate at the end of a dsRNA stem, a unique feature of the viral RNAs of the majority of the RNA viruses. For DNA viruses, the IFN induction is triggered by the presence of cytoplasmic DNA associated with their infection. To be specific, the IFN induction is stimulated when the cellular sensor cGAS binds to cytoplasmic DNA, becomes activated, and generates a di-nucleotide, cGAMP<sup>[4]</sup>. The activation of the cellular sensors brings upon the transcriptional induction of IFN. During these events, many adaptor molecules, transcriptional factors, and regulatory enzymes (IRFs) may function as our target for treatment against the viral infection. Interaction of secreted IFN with its subsequent receptor's triggers phosphorylation and thus the activation of STAT transcription factors which promote the IFN stimulated genes thus providing us an antiviral response.

Once activated, both STING (DNA-sensing) and MAVS (RNAsensing) signaling platforms recruit multiple kinases, ubiquitin ligases, and adaptors leading to the phosphorylation and activation of latent transcription factors involved in IFN promoter activation. Among these transcription factors, the IRF factors, especially IRF3 and IRF7, are critical for IFN induction<sup>[5]</sup>. Besides, IRF7 is also required for IFN induction upon TLR activation. STAT1 and STAT2 are also among the essential transcription factors, together with IRF9, that mediate IFN signaling and IFN-induced expression of ISGs thus providing us a situation to be considered which may cause hindrance in the INF activation. Activation of the IRFs and STATs transcription factors is triggered by the specific kinases, including JAK1 and TYK2 for STAT1 and STAT2 and IKK $\epsilon$  and TBK1 for IRF3 and IRF7, that become activated upon initiation of signaling.



**Fig 2. Mechanism of IFN Production and Action<sup>[6]</sup>.**

IFNs show their action through cognate cell surface receptors that are largely species-specific. A common receptor having two subunits, IFNAR-1 and IFNAR-2 are possessed by IFN  $\alpha$ ,  $\beta$ , and  $\omega$ . IFN  $\alpha/\beta$  (the phosphorylated forms of Stat-1 $\alpha/\beta$  and Stat-2), along with an additional non-STAT protein, p48 (also known as IRF-9), translocate to the nucleus and form a complex ISGF-3. The ISGF-3 trimeric complex then binds to a cis-acting DNA element, ISRE, found in IFN  $\alpha/\beta$ -inducible genes. For IFN1, the phosphorylated Stat-1 $\alpha$  factor homodimerizes, translocates to the nucleus, and binds to a different cis-acting element, designated the gamma-activated sequence (GAS), commonly found in IFN1-inducible genes. An invasion by virus triggers the transcription of many cellular genes either by direct activation of IRF3 or by indirect induction of IFN $\alpha/\beta$ . The IRF3 is the key transcriptional activator. However, from the studies conducted by Krystal Matthews et al<sup>[7]</sup>, we can't depend totally on the IRF3 due to the presence of IRF3 inhibiting factor in SARS COV-2 which hampers the induction of IFNs. The topic of the use of the IFN mechanism is incomplete without considering the viral IFN

signaling antagonists. The viruses encode proteins that inhibit the induction of the IFN pathway.

Fig 3. Anti-viral Actions of Interferon.<sup>[6]</sup>

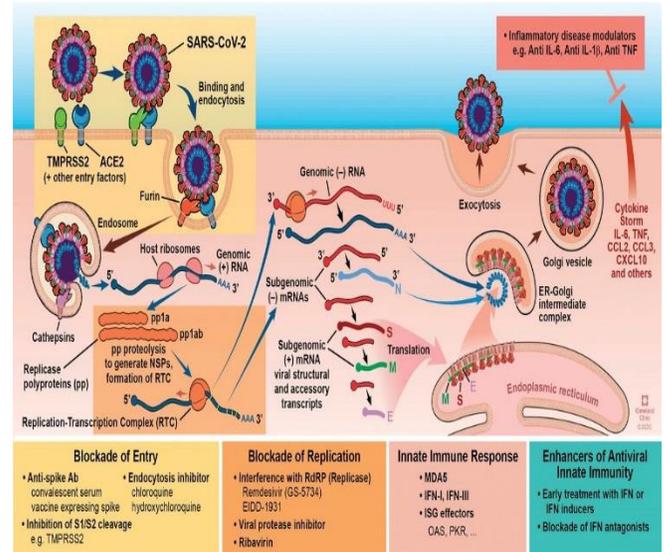
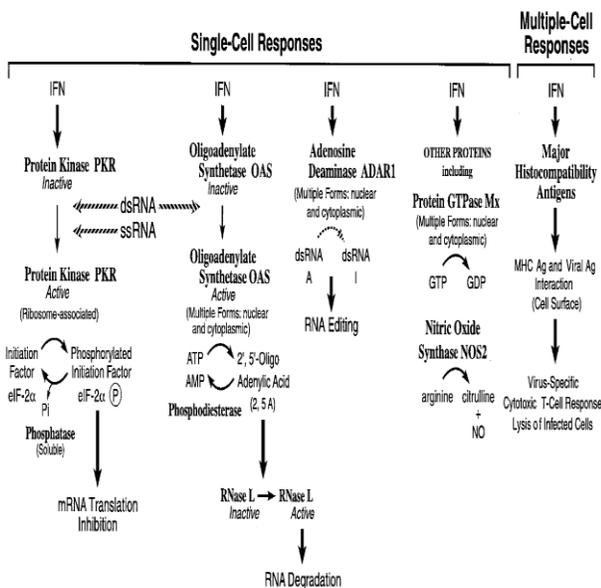


Fig 4. Replication of Sars-cov-2. <sup>[16]</sup>

1.b. Possible Outcomes of use of Interferon mechanism.

From this study, we can conclude the possibility of the use of various signaling receptors to identify the viral genome upon infection more readily and enhance the induction of IFN in the cellular immune response. By targeting the IFN 1 as the first step we can induce IFNs in the immune response thus providing us the possibility to counter the deadly virus. The detection of the viral genomes from the infected cells can also be detected more readily if there is a stimulation to TLRs. As SARS CoV2 being a single-stranded RNA virus, the detection can be made more sensitive by the stimulation of RIG-I which readily detects the RNA viruses thus inducing IFN production. Thus, in short, the TLRs and the RIG-I receptor families are the key components in the detection of the RNA virus. The signaling pathways initiated by these may help in the antiviral action and the containment and prevention of further proliferation of the virus by signaling the neighboring cells showing an adaptive immune response. The release of IFN followed by the JAK-STAT pathway will provide the antiviral action. Possibility for the detection of virus is approximately very high in case of interferon,

Antiviral Actions of Interferon



henceforth if provided more potent scavenging property to IFN there is a possibility of total destruction for Corona virus.

## 2. Plasma Therapy

The body's immune system includes the formation of antibodies upon the detection of foreign cells. Using this response as an advantage the concept of Plasma Therapy can be used as an effective way to encounter the deadly virus. Plasma Therapy has recently been considered as a treatment by many researchers and doctors. Amongst this outbreak, all the possible treatment methods are to be kept in mind and applied to help overcome the hard times. Antibodies can remember the pathogens it has encountered before. The use of antibodies from the blood of the recovered patients can be a promising path towards the treatment. This is where Plasma Therapy comes in the discussion. Plasma Therapy has been used for over a century to combat bacterial and viral infections. The use of Plasma Therapy can thus be considered when considering the SARS CoV2.

### 2.a. How can the Plasma Therapy be used?

When a patient encounters the virus their body's natural defense mechanism includes the release of antibodies. These antibodies react to the presence of the virus and thus if we can use the blood plasma of those patients who have recovered from the disease, there is a possibility to overcome the disease by natural body mechanisms. The blood plasma of the recovered patients contains the neutralizing antibodies which can be useful in combating the viral infection. The plasma of the recovered patients can be isolated from their blood samples and administered into the infected patients. This will be possible if the recovered patients are voluntarily donating their blood samples for the noble cause. According to some studies, the use of Convalescent Plasma Therapy has been very useful and thus can be considered<sup>[8]</sup>. The use of Plasma Therapy can provide passive immunization to the patients

administered. It has been considered as a preventive measure and thus the therapy can be used as a vaccine against the SARS COV2 virus<sup>[9]</sup>. Upon administration of the plasma rich in the antibody, it will circulate in the blood, reach the tissue, and thus protect against the virus<sup>[9]</sup>. Depending on the concentration of the antibody present and created by the body the effect will last from a few weeks to months.

### 2.b. Risks Involved

Transfer of Blood substances includes the transfer of some infectious agents and other risks are involved. In some patients, the transfer of the antibodies may increase the pathogenicity of the viral infection. The antibody administration may result in the body's natural immune response to be affected greatly thus involving the risk of re-infection in the patients. Recently it was observed that the blood samples collected should be from the patients who have recovered recently<sup>[10]</sup>.

### 2.c. Outcomes

The possible outcome that can be given is that the use of plasma therapy can prove to be of great importance against the SARS COV2 virus. The plasma can be obtained from the blood of patients who have recently recovered from the disease. The most recent samples of the plasma are required as the possibility of the neutralizing antibodies being present will be most likely. Plasma Therapy is an age-old technique that has been considered in counteracting with deadly diseases. However, Plasma Therapy has its cons as it can be time taking and also alter the body's immune response. Convalescent Plasma Therapy can be used to treat patients who are infected and also be administered to individuals as a preventive measure against the viral infection. Plasma Therapy provides passive immunization to the patients.

## 3. How COVID-19 is different from flu and other respiratory disorders?

While the symptoms of COVID-19 are similar to the symptoms of flu and other respiratory disorders, the difference between the symptoms is a major factor determining the course of the treatment. Some patients experience a wide range of symptoms upon infection with SARS CoV2 ranging from mild to severe illnesses, while others may not show symptoms at all. The time period of the virus is 14 days. The symptoms of being infected with SARS CoV2 are fever, cough, breathing difficulties or shortness of breath, experiencing fatigue and chills, headache, sore throat, severe olfactory loss, congestion or runny nose, nausea or emesis, diarrhea and so on. The most likely people to be infected with the viral disease are of the older age group (60 years and over), people with chronic medical conditions like patients suffering from diabetes or lung disease, people under long term care facility or with unhealthy conditions, also patients with a weakened immune system due to solid organ transplants. Patients suffering from asthma, neurologic conditions, high blood pressure, obese people with BMI > 30, or other immuno-compromised diseases.

#### **4. Effective administration of asymptomatic conditions against Corona virus-**

The basic mechanism and effectiveness have got a wide range of similarity in case of viruses. While corona virus shows symptoms quite similar to influenza virus as they are contagious and respiratory disorders. The vaccination of influenza virus based on the 32 serotypes as well as climatic conditions dependent on hemispheres according to WHO <sup>[11]</sup>. Another symptomatic similarity of Corona virus matches Flu. The effective symptom's similarity retaliates with fever, pain, cough, breathing troubles, sore throat, fatigue, vomiting and diarrhea. The dissimilarity contributes loss of taste or smell.

Now as the condition against rate of infection are getting worser day-wise, a possible postulate may be idealized in current situation. Creation of non-infectious environment is impossible, but possibility

towards development of asymptomatic conditions may conclude a solution.

Corona virus belongs to the sub-family of coronavirinae. Coronavirinae has following types Alpha-corona virus, beta-corona virus, gamma-corona virus and delta-corona virus. The Sars-Covid-2 belongs to beta-corona-virus gene and has shown particular similar genomic structures and characteristics at genetic level with IBV (infectious bronchitis virus) avian infection which comes from gamma-corona-viruses. Similarity is based upon structural actuation that is presence of spike protein in genome structure of both IBV and Corona virus. <sup>[12]</sup> On the basis of phylogeny the 3'-terminal-end of both genera produce structural proteins whereas the 5' terminal-end contains the non-structural proteins which can be encoded due to the presence of open reading frame<sup>[12]</sup> in case of both the viruses. The clinical symptoms of IBV matches with corona virus that is similar in case of pneumonia symptoms.

Use of vaccine for IBV in non-effective patients may ascertain immunity response against the symptoms such as fever, pain, cough, breathing troubles that turns out deadly on the later stages of viral infection. Due to high genetic similarity and same mechanism of infection, use of IBV vaccination may be supportive towards the asymptomatic theory<sup>[13]</sup>. This in turn may contribute to turn the individual asymptomatic against Covid 19/20 and such will provide proper time to generate vaccine and API.

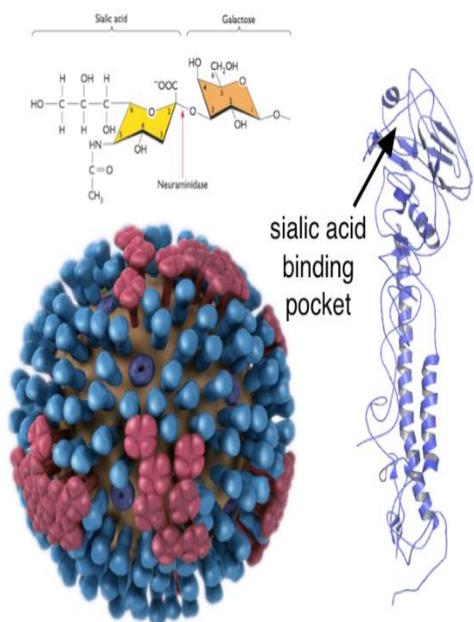


Fig-5. IBV virus [14]

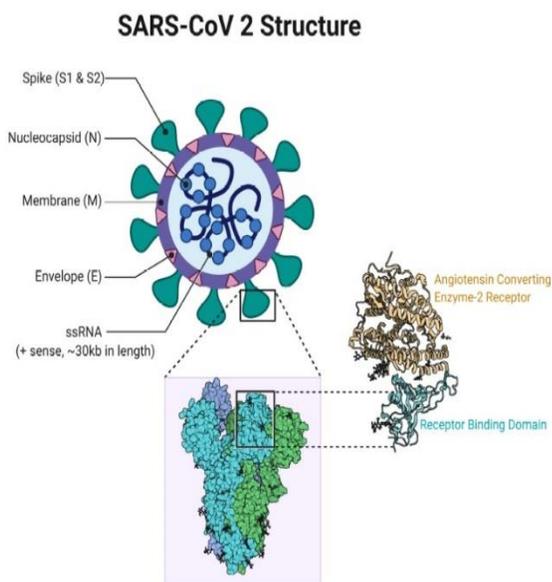


Fig-6. Sars-cov-2 structure [15]

5. Tests for detecting COVID-19 [17]

Antigen Test - The antigen test provides results within a few minutes however; they are not as sensitive as molecular tests. In this test, the nasal swabs are taken and the fragments of the virus are detected quickly. The positive results from antigen

tests are highly accurate but the negative results may need to be confirmed with molecular tests.

Molecular Test – In this type of test the genetic material of SARS- CoV-2 is detected. The test results are accurate and can be considered as the means to diagnose the disease.

Antibody (serology) Test – This test detects the body’s immune response to COVID-19 by looking for the antibodies in the blood to determine prior exposure. This test does not detect the virus but detects the antibodies. **6.Results and discussion-**

Plasma therapy	Interferon	Use of IBV (infectious bronchitis virus) avian infection vaccine as route for asymptomatic mechanism.
In plasma therapy the plasma needs to obtain from clinically recovered patients in recent times.	To identify the viral genome use of various signaling receptors are considered as an important breakthrough.	IBV shows similarity by structural phylogenomics well to an extent symptomatic similarity.
The plasma sample of effective individuals have the highest probability to contain neutralizing antibodies.	IFN is induced as a cellular immune response upon being infected by the virus.	Vaccination with IBV serotypes provide artificially acquired active immunity.

Administration of plasma therapy provides passive immunization to the patients.	As sars-cov-2 is a single stranded RNA virus the detection can be made more efficient RIG-1 is stimulated and thus the interferon production is induced.	The active immunity will allow to show a constant hindrance towards the symptoms of corona virus- fever, ache, respiratory disorders.
It is a broad spectra effective therapy where initial cellular components play the major role as antiviral therapy.	Interferons may be applicable in both cases, 1] detection- TLR and RIG-1 receptor family detection and induce IFN production. 2] Interferon also allows the prevention of further proliferation of the virus thus showing an adaptive immune response.	Injecting the vaccine in non- infected individuals may show asymptomatic covid19/20disease as the degree of symptoms might lose its potential providing enough time to consider an approachable treatment. <sup>[13]</sup>

**Abbreviation-**

IFN	Interferon
FDA	Food and drug administration
IBV	Infectious bronchitis virus
TLR	Toll like receptors
RIG1	Retinoic acid-inducible gene I
cGAS	Cyclic GMP-AMP synthase
IRF	Interferon regulatory factor
STING	Stimulator of interferon gene
MAVS	Mitochondrial antiviral signaling protein
JAK	Januskinase
STAT	Signal transducer and activator of transcription
TYK	Tyrosine kinase
IKK	Inhibitor of nuclear factor kappa B kinase
TBK1	Tank binding kinase 1
IFNAR	Interferon alpha beta receptor
ISGF	Interferon stimulated gene factor

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