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A door step towards the most possible outcome to win against covid-19/20 pandemic, vaccination

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Abstract
SARS-COV-2 is the human corona virus that has been creating a global anomaly and responsible for the world wide pandemic. The main purpose of this article is to corelate with a solution following the paths of interferon effectiveness for the infection vaccination following the liposome mediated drug delivery system for the infected, non-infected SARS-COV-2 patients. SARS-COV-2 shows most sensitivity to interferon specially the IFNβ subtype. Due to the special characteristics and anti-viral effects in the context of any emerging viral epidemics as the first line of detectors and defence, the type 1 interferons (IFN1) are taken into consideration. Now for installation of the medication our goal is to a) installing the interferon by following the interferon cascade mechanism as vaccination of healthy individuals b) installation of interferon effectiveness by following the Liposome mediated drug delivery system. By approaching these 2 procedures our motive is to make it effective against COVID-19/20.

Keywords: covid19/20, interferon, liposome based drug delivery system, IFNβ1, JAK-STAT, PEGINFβ1

Introduction
The potential antiviral activity of interferon has been the primary objective of consideration while developing this article. Type-1 interferon with its broad antiviral effectiveness evaluated against SARS-COV AND MERS-COV has been evaluated under the sets of clinical trial (Gao *et al*., 2010; Loutfy *et al*., 2003; Omrani *et al*., 2014). Though the use of interferon comes with various side effects of fever, pain, shortness of breath [1] we can easily conclude that interferon treatment for a patient at last stages of COVID-19 would be a matter of risk. As TYPE-1 interferons are the first to be secreted in cell-site action against antiviral effectivity the effectiveness of this IFN1, specially IFNβ1 can be modulated in a different approach. The extracted IFNβ1 from a COVID-19 patient can be used to induce immunity in a healthy individual βof adenosine showing anti-inflammatory action. The plasmacytoid dendritic cells after getting exposed to viral components by the Pattern Recognition Receptors (Liu 2005) secret IFN1 as its first action against viral infection such as interference with viral replication, slowdown of viral cell metabolism, secretion of cytokines to promote activation of adaptive immunity, concluding type 1 interferons to be the first cytokines produced against a viral infection to be recognized by the IFNAR receptor present in the plasma membrane of most cells. For the affected individuals showing symptomatic/asymptomatic potentials extracted IFNβ1 is to be coated by liposome for crossing the first line of barrier in the viral cell and showing effectivity. The 2nd line of approach must be effective for both of a healthy and effected individual in this era of fight against COVID-19/20.

Explanation in details
1) Mechanism of covid-19/20 and immune response
COVID19/20 virus is a single stranded RNA, jacketed virus With the largest viral DNA genome [2]. The nucleocapsid of the virion is composed of phosphorylated nucleocapsid N protein, covered with phospholipid bilayer. The outer part also comprises of 2 different spike proteins (S) (Geng Li *et al*), spike glycoprotein trimmer and hemagglutinin-esterase (HE). The membrane and envelop protein are present inside the particular spike protein of the viral envelop.

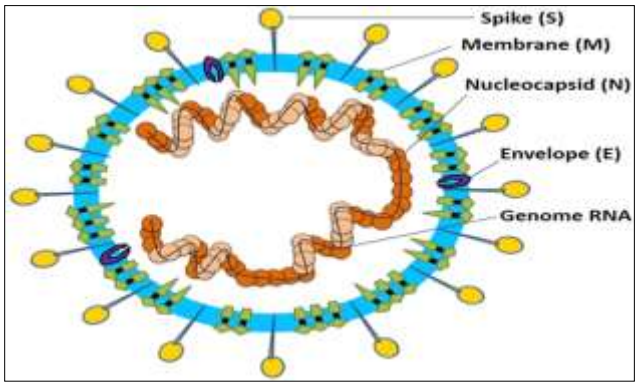

Fig 1: Structure of COVID-19/20 [2]

Corona virus family has several subtypes among which the specific α and β COVs are the ones infecting human. The interferon mechanism takes into action by following the JAK-STAT signal pathway [2]. INF-type1 limits the virus spread by showing immunomodulatory role responsible for macrophage phagocytosis of antigens and causing restriction to infected cells pausing the effective viral outbreak. The JAK-STAT pathway blockage may cause the risk of interferon to be non-working that must be overcome by introducing foreign helper interferons that will be active against unblocking the pathway.

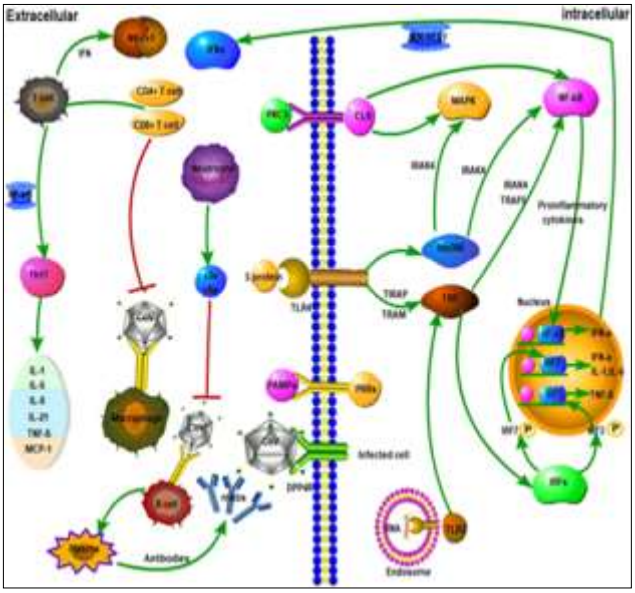

Fig 2: Activity of viral infection against innate and adaptive immune response [2]

2) Mechanism of interferon action

Macrophages, lymphocytes and tissue cells are able to release small protein structures named as Interferon after being infected by a virus. The activity of interferon is to diffuse the surrounding cellular structures after binding to the surfaces of the surrounding cells. The activity shown after binding with the surrounding cell is the production of protein that prevents synthesis of viral proteins hence preventing spread of virus throughout the body. The INF1 act first after an individual getting effected by a viral infection and provides utility on implication of first line activity against the infection [3].

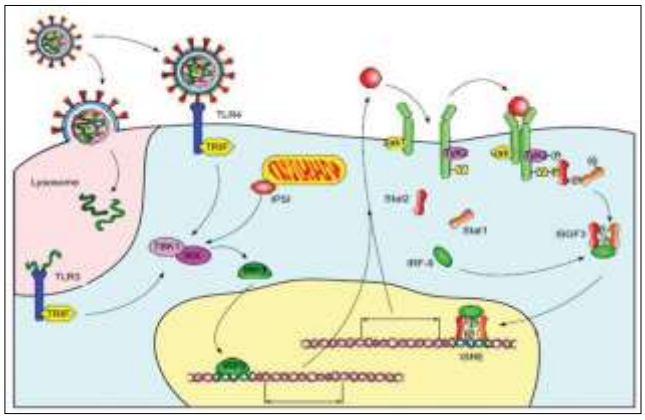

Fig 3: Mechanism of action of Interferon in virus infected cell [4]

3) Antiviral mechanism of interferon

a) Blocking of Viral-mRNA synthesis.
b) Block translation of Viral-mRNA.
c) 2'-5' oligo(A) synthetase and ribonuclease C

1. This enzyme gets activated by dsRNA
2. Unique ability to synthesize oligos(A) in the 2'-5'linkage.
3. Poly (A) oligos bind ribonuclease L and activate it resulting in mRNA destruction. This may result in destruction of both cellular and viral cells [5].

4) Virus mechanism to counteract interferon

a. Specific viral proteins may result in blocking the induction of IFNβ1 expression.
b. May block the activation of the key PKR protein kinase.
c. May activate a cellular inhibitor for PKR.
d. May block IFN induced signal transduction.

5) Virus evading interferon response

The virus potential lies to its adaptation of interferon response by making proteins that neutralise PKR. The evasion mechanism proceeds via producing VI-A-RNA (160 nt long) that binds with the PKR molecule. This RNA takes a double stranded form without activating the PKR molecule as well as showing no eIF2 phosphorylation. The viral translation proceeds as expected producing E1A which sequesters p300/CPB the cofactors needed for interferon expression [6].

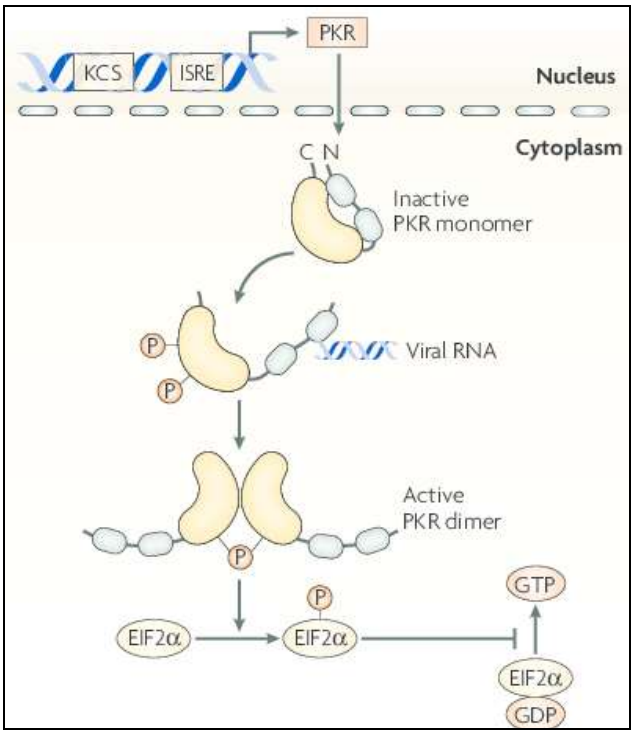

Fig 4: Mechanism of action of PKR with respect to interferon [7]

6) Liposome based drug delivery system especially stealth

Liposomes are nanoscale drug particles introduced since 1995[8]. Now a preliminary condition may appear regarding the viral structural aspects, how we may proceed with the coating part for allowing entry of the interferon into the viral host cell. As COVID-19 is an adeno virus we may take a sustainable approach of coating the interferon with polyeytheleneglycol (PEG). Studies have shown [9] that PEGylated IFN-β proteins are special for providing higher in-vitro bioactivity, pharmacokinetic property because of its selective modification in the N-terminus. The improved pharmacological properties of IFNβ with PEG was stated by Kinstler *et al.* (1996), Basu *et al.* (2006), Bell *et al.* (2008). IFNβ comprises of 11 lysine residues involve in receptor binding along with N-terminal amino acid. By following the site specific PEGylation technology [10] modification of cystine analogs along with the IFNβ1 developing of procured vaccination may show possibility. This site specific PEGylation is achieved by the incubating the reactive PEG with the target COVID19 moiety reasons in

improvement of reducing in renal clearance that will allow to achieve prolongation in systemic circulation, reduced toxicity and dosage frequency [10] the critical factors for vaccination. Liposome mediated drug delivery system comprises of the following types a) Conventional liposome- It is a type of lipid bilayer molecule showing positive, negative or neutral lipid cholesterol bilayer enclosing an aqueous core. Hydrophobic as well as hydrophilic particles can be initiated inside. b) PEGylated liposome- Our field of choice because of its hydrophilic polymer coating that provides steric stabilization. c) Ligand targeted liposome- Second choice of action because of its target-oriented characterization of its surface or terminal end. d) Theranostic liposome- Single system made of nanoparticle, targeting element and therapeutic molecule.

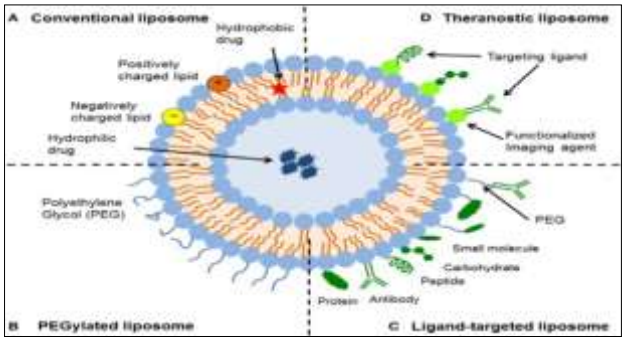

Fig 5: Diagrammatic representation of Liposomal drug delivery systems a) Conventional liposome, b) PEGylated liposome c) Ligand targeted liposome d) Theranostic liposome [9].

7) Pharmacologic modification of interferon

Interferons has a relative short life hence repetitive dosage is required to maintain the efficacy or the biological effective concentration in plasma level [11]. The pharmacologic approach to evade this interferon efficacy as well as supplementing the decreasing toxicity is to coat the recombinant INF with a polyethylene glycol moiety. This allows slow metabolism of the interferon, along with providing more sustained level of exposure. It also diminishes INF specific activity as steric interference declines its binding affinity with its receptor [12].

8) Pharmacology and hypothetical clinical efficacy

PEGINFβ1 is the substantial modified form of interferon having a PEG group attached to it. This attachment will allow prolongation in its half-life reducing the dosage frequency. The advance trial was a 3-phase study comparing placebo to subcutaneous INFβ1 may be provided with an effective dose of 125 mg every 2 to 4 weeks for 1 year. Patients taking PEGINFβ1 every 2 to 4 weeks showed a reduction in ARR disability progression compared to those on placebo at 48 weeks [13].

Conclusion

Our main moto in this article was to achieve a hypothetical progress in vaccination of the COVID-19/20, as well as providing with a conceptual action on persons already sustaining through the viral infections. The substantial treatment for an adeno viral infection requires effectiveness of vaccination because of its continual change in mutation and its wide scope of activity. To ensure a proper and healthy society against the COVID-19/20 pandemic sustainable requirement of vaccination is highly essential. This field of work require more study and effective clinical phase trial modulations to be active in near future but the possibility of using the interferon may show a ray of hope to win this fight against COVID-19/20 both in field of vaccination and effective medication.

Acknowledgement

Foremost we would sincerely like to express our gratitude to all the corona fighters over the world risking themselves everyday to defeat the pandemic and reinsure a win. Beside them we would thank our parents for every support and blessings till date. We would solely like to dedicate our sincere approaches towards vaccination a small project that we have worked on for the betterment of India and others suffering from this pandemic.

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