

# Hyaluronic Acid - Hydroxychloroquine Conjugate Proposed for Treatment of COVID-19

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**ABSTRACT:** We propose to develop a drug conjugate from Hyaluronic acid (HA) biomaterial, which is present in extracellular matrices, the synovial fluid of joints, and Hydroxychloroquine (HCQ), which is being considered for the treatment of COVID-19 but it exhibits some toxicity, the HA-HCQ is expected to show reduced toxicity and enhance efficacy.

**KEYWORDS:** COVID-19, Hyaluronic acid, Hydroxychloroquine, drug delivery, drug conjugation

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## 1. INTRODUCTION

A number of antiviral drugs are used for the treatment of different viral diseases; these include: *Hydroxychloroquine* for malaria, rheumatoid arthritis, and the same is now considered for the treatment of COVID-19; *Lopinavir* and *Ritonavir* for HIV/AIDS and other antiretroviral; Favipiravir, antiviral drug with activity against RNA viruses, and effective against COVID-19; *Remdesivir* (GS.5734), originally considered for the *Ebola* virus disease, *MERS* and *SARS* Viruses (SARS-CO-2); *Cyclodextrins*, a sugar based polymers, show some promise in the treatment of COVID-19. However, almost all of these drugs exhibit some systemic toxicity.

Our objective is to modify one of the leading drugs, Hydroxychloroquine, considered for COVID-19, by conjugating it with hyaluronic acid to reduce its toxicity and increase its efficacy.

Hyaluronan also known as hyaluronic acid, HA [1] is a naturally occurring polysaccharide of a linear repeating disaccharide unit consisting of  $\beta$ -(1 $\rightarrow$ 4)-linked D-glucopyranuronic acid and  $\beta$ -(1 $\rightarrow$ 3)-linked 2-acetamido-2-deoxy-D-glucopyranose (Fig. 1), which is present in extracellular matrices, the synovial fluid of joints, and scaffolding that comprises cartilage. Despite the simplistic structure of hyaluronan, it behaves quite differently from other glycosaminoglycans in its mechanism of synthesis, its size, its physico-chemical properties such as the network-forming, viscoelastic, and its charge characteristics are important to many biochemical properties of living tissues. It mediates its biological functions through specific protein receptors present on the different cell surfaces, which include CD44 [2], HARE [3], RHAMM [4], and LYVE [5].

Hyaluronan molecules are involved in the activation of signalling pathways that control cell proliferation, differentiation, adhesion and migration [6-12].

Our research work on specific conjugation of hyaluronic acid (Fig.1) with pharmacologically active compounds such as camptothecin, methotrexate, methylprednisolone, propofol led to a number of drugs for the treatment of diseases such as cancer, arthritis, osteoporosis; hyaluronic acid is not only interesting because of its biocompatibility and bio absorbability, but also because of its own therapeutic efficacy [13-15].

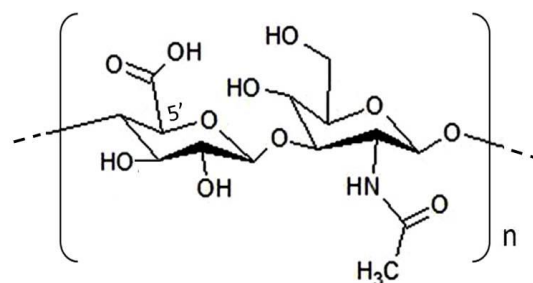


Figure 1. Hyaluronic Acid (HA)

### Why HA-HCQ Conjugates?

In the light of our research on HA-conjugates with a variety of pharmaceutical compounds to yield drugs with specific targeting strategy, we reasoned the possible application of the conjugated HCQ to HA (Fig.1), to study its biological activity against the COVID-19. The advantages envisaged in this strategy to

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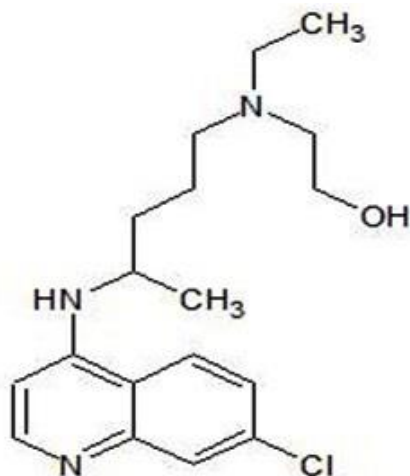
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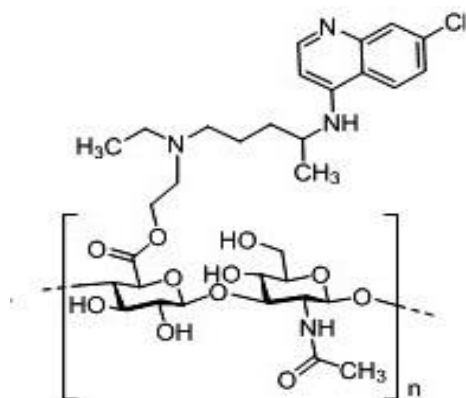
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conjugate the drug Hydroxychloroquine with hyaluronic acid to afford HA-HCQ (Fig.3), are to reduce the intrinsic toxicity and to increase its bioavailability, localization and controlled release of the drug, and enhance the efficacy of the conjugated drug (Fig. 3).



**Figure 2. Hydroxychloroquine (HCQ)**

The conjugation of HCQ (Fig.2) to hyaluronic acid (Fig.1) can be achieved through the hydroxyl group of the HCQ by a variety of linkages known in the classical organic chemistry. However, initially, we have chosen the simplest approach to link the hydroxyl group of the compound (Fig. 2) to hyaluronic acid (Fig.1) through the C5'carboxylic group of the glucuronic moiety forming an ester linkage. For the detail methodology of our proposed strategy, see our patent [15] on the conjugation methylprednisolone with HA.



**Figure 3. Hyaluronic Acid-Hydroxychloroquine conjugate**

## CONCLUSION

A number of "HA-HCQ" drug conjugates, using different molecular weight of hyaluronic acid and different degree of substitution of HCQ in the conjugates, will be prepared and evaluated against COVID-19.

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