

# Chloroquine and Hydroxychloroquine

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The chloroquine family of antimalarials has a long history of use, spanning many decades. Despite this extensive clinical experience, novel applications, including use in autoimmune disorders, infectious disease, and cancer, have only recently been identified. While short term use of chloroquine or hydroxychloroquine is safe at traditional therapeutic doses in patients without pre-disposing conditions, administration of higher doses and for longer durations are associated with toxicity, including retinotoxicity. Additional liabilities of these medications include pharmacokinetic profiles that require extended dosing to achieve therapeutic tissue concentrations. To improve chloroquine therapy, researchers have turned toward nanomedicine reformulation of chloroquine and hydroxychloroquine to increase exposure of target tissues relative to off-target tissues, thereby improving the therapeutic index.

chloroquine

hydroxychloroquine

Nanoformulation

cancer therapeutics

## 1. Introduction

Chloroquine (CQ) and hydroxychloroquine (HCQ) have been used for decades in the prevention and treatment of malaria and in the treatment of some autoimmune diseases such as lupus erythematosus and rheumatoid arthritis due to their immunomodulatory properties<sup>[1][2][3]</sup>.

## 2. Effect

Despite being considered old drugs, CQ and HCQ have generated new interest due to their anticancer activity both in preclinical and clinical studies<sup>[4][5]</sup>. Researchers have shown these drugs act through a variety of antineoplastic mechanisms such as autophagy disruption, tumor vessel normalization, immunomodulation, and inhibition of metastasis, acting both directly on the tumor parenchyma and tumor microenvironment<sup>[6][7]</sup>. Chloroquines have been shown effective either as monotherapies or as adjunct therapies, sensitizing cancer cells to existing cytostatic agents as well as targeted therapies<sup>[7]</sup>. For example, HCQ has been shown to synergize with MEK pathway inhibitors for effective treatment of RAS-driven cancers, and CQ has been shown to inhibit melanoma growth through modifying tumor-associated macrophage (TAM) from the M2 immunosuppressive/pro-tumor phenotype to M1 immunostimulatory/antitumor phenotype<sup>[8][9]</sup>.

CQ and HCQ have also recently received worldwide attention due to their potential use in treating coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Previous studies showed in vitro efficacy of these drugs against Middle East respiratory syndrome coronavirus

(MERS-CoV) and severe acute respiratory coronavirus (SARS-CoV), and a recent study demonstrated CQ could effectively inhibit viral infection of SARS-CoV-2 in vitro<sup>[10][11][12]</sup>. As a result, scientists suggested their assessment in patients, leading to emergency use authorization for HCQ and the initiation of several clinical trials. CQ and HCQ are both basic amphiphiles that concentrate in the lysosome and inhibit lysosomal function as their primary mechanism of action<sup>[13]</sup>. While CQ and HCQ also have similar toxicity profiles and are equipotent, chloroquine is much more toxic (2-fold)<sup>[13]</sup>. Although short-term administration of either drug is generally well-tolerated, except in patients predisposed to arrhythmia, chronic dosing and high-dose regimens can cause severe side effects such as irreversible retinal toxicity<sup>[14][15][16]</sup>. CQ and HCQ have similar pharmacokinetic (PK) properties, including high volume of distribution and prolonged plasma half-lives between 40 and 50 days, which requires weeks of dosing to achieve steady-state therapeutic concentrations<sup>[17]</sup>. Reformulation of CQ and HCQ to improve their PK and safety profile may support the use of these drugs for applications such as cancer and infectious diseases.

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