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How the world lost one of its most effective anti-malarials to mutations in a Malarial multi-drug resistance protein: a molecular perspective

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Progress towards the eradication of Malaria, one of humanity's deadliest diseases, is faltering due to the development of drug resistance. Of the six WHO recommended antimalarial combination therapies, five consist of a partner drug whose susceptibility can be modulated by mutations in the *P. falciparum* Chloroquine resistance transporter (PfCRT). As the name suggests, mutations in the protein were responsible for the evolution of resistance to the once powerful and effective drug, Chloroquine. PfCRT evolved the ability to transport Chloroquine away from its target, thereby gaining resistance.

Resistance to Chloroquine has emerged multiple times and with some specific mutations appearing to be essential to allow Chloroquine transport. However, not all of the mutations arising in the resistant malaria strains increase the protein's ability to transport Chloroquine. This suggests that some of the mutations may have been required to rescue PfCRT's natural function as a peptide transporter, yielding an evolutionary compromise in function under drug pressure.

To investigate the molecular basis for the evolution of Chloroquine resistance, we have performed molecular dynamics simulations of Chloroquine susceptible and resistant isoforms of PfCRT with high concentrations of Chloroquine and a series of peptide substrates. These demonstrate the accessibility of the binding cavity, the likely binding sites, and the access routes of each substrate. The simulations suggest plausible roles for a number of mutations in modulating substrate access and binding, aiding in understanding the evolutionary history of PfCRT, a fulcrum point of antimalarial resistance.