Formulation and Delivery Strategies for COVID-19 Drugs

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With a vaccine at least a year away, it may be possible to rapidly repurpose existing drugs to prevent SARS-CoV-2 infections and treat patients already infected with COVID-19, writes Kevin McHugh, an assistant professor of bioengineering at Rice Univ., in the current issue of AIChE's open-access journal *Bioengineering & Translational Medicine* (https://doi.org/10.1002/btm2.10163). More than 40 different drugs are currently being explored for efficacy against COVID-19. Unfortunately, many of them have side effects that limit their use to the most severe cases and prevent their use as prophylactics. Drug formulation and delivery strategies such as controlled release and targeted delivery could expand the use of such existing drugs.

Many of the drugs being evaluated to treat COVID-19 infection are repurposed small-molecule antivirals and immune-modulating antibodies that are already approved for other indications (*e.g.,* chloroquine, hydroxychloroquine, ribavirin, favipiravir) or in clinical trials but not yet approved by the U.S. Food and Drug Administration (FDA) (*e.g.,* remdesivir, galidesivir, leronlimab). If proven effective, these drugs offer several advantages from a rapid-response perspective, such as the availability of safety data. In addition, several of these drugs offer broad-spectrum activity that makes it more likely they will remain functional even if the SARS-CoV-2 virus mutates.

Thus far, there has been little discussion about using these drugs to prevent the disease from occurring, presumably due to their potential side effects. For example, the malaria drug chloroquine, when used as directed, commonly produces nausea, diarrhea, vomiting, and muscle weakness, among other side effects; at higher concentrations, only two to three times the daily dose, it can cause potentially fatal acute cardiovascular toxicity. Even if chloroquine is found to be effective against an active infection, its severe side effects make it unattractive as a preventive measure.

There is precedent for pre-exposure prophylaxis (PrEP) when the side effects of an antiviral are low. One such drug is emtricitabine/tenofovir disoproxil (Truvada), which inhibits reverse transcriptase to prevent HIV from creating DNA from its RNA, thereby preventing it from integrating into the host cell genome and replicating. Because this enzyme is not native or necessary for human cell function, use of Truvada is not associated with highly pervasive or severe side effects, enabling the drug's widespread used as both a prophylactic and a post-exposure therapy. If an effective drug for treating COVID-19 with infrequent and/or mild side effects is identified, it may be possible to rapidly transition to evaluating its use for PrEP. However, if that drug does have side effects, perhaps its toxicity could be reduced to make its use as a prophylactic viable.

Drug delivery systems can be used to administer drugs that have promise but are not sufficiently safe in a traditional formulation. A drug delivery system may improve absorption, increase intracellular delivery, maintain drug concentrations within a small therapeutic window, or provide a high concentration gradient between the organ of interest (*e.g.,* lungs) and systemic circulation.

For instance, the HIV drug combination lopinavir and ritonavir, which is under evaluation as a COVID-19 treatment, has side effects that include diarrhea, nausea, and liver damage. These drugs have a half-life of about 4–6 hr and systemic concentrations can vary by a factor of eight between peak and trough. Developing a controlled-release formulation that maintains the minimum effective drug concentration could mitigate side effects by reducing the steady-state drug concentration by as much as eight-fold and reducing the burden on the liver by 81%.

Targeted drug delivery may offer a similar or better ability to reduce toxicity in some cases, particularly for respiratory infections. Because the lungs comprise only about 2% of the total body weight, targeted delivery could reduce the amount of drug required by a factor of 50 or more compared to oral administration. A promising approach is the hitchhiking of drug-loaded nanocarriers on red blood cells — intravenous administration of these constructs improved delivery to the lungs by about 40-fold — which could be used to achieve an effective local concentration without requiring a high systemic drug concentration. The preparation of inhalable particles for local delivery is a simpler approach.

"On the spectrum of rapid response readiness, the repurposing of existing drugs with broad-spectrum activity and known side effects that can be mitigated with advanced drug-delivery techniques should be a top priority. If we can augment the protection provided by personal protective equipment (PPE) with effective, low-toxicity prophylactics, we may be able to stymie the spread of the disease and maintain a healthcare workforce operating at full capacity when they are most needed," McHugh says. CEP

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