Targeting Host Factors as Therapeutics for Influenza and Other Viral Diseases

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Resistance to antiviral therapy is a major public health concern, often undermining the clinical utility of whole classes of drugs targeting specific viral components. In the cases of rapidly mutating viruses such as influenza, HIV, and hepatitis C, resistance to antivirals can occur as the result of treatment with single agents. Host pathways critical for virus replication could be targets for a new generation of drugs with high barriers to resistance and broad spectrum activity. The repurposing of FDA-approved drugs targeting host factors for viral infections could dramatically reduce the timeline and costs of bringing a product to market.

Based on these assumptions, we screened a small molecule library of >1000 FDA-approved drugs in the presence of sub-optimal concentrations of amantadine (AMT) and oseltamivir (OSL) against Influenza A/H1N1 in Madin-Darby canine kidney (MDCK) cells. Of the drugs tested, >40 produced inhibition of 50-100% at one or more concentration(s). Analysis of the classes of the drugs revealed that a number of hits clustered along distinct cellular pathways important for virus replication. Among these, ADS-324, an antifolate, emerged as the most promising candidate with the best activity and selective index against influenza.

To confirm that ADS-324 was synergistic with direct acting antivirals (DAAs), we investigated the activity of combinations of ADS-324 with AMT and OSL by testing all three drugs at multiple concentrations in double and triple combinations in MDCK cells infected with A/H1N1. Double combinations of AMT, OSL, and ADS-324 were additive to modestly synergistic. However, the triple combination was highly synergistic (>10-fold over any double combination) over multiple concentrations of each drug. Synergy resulted in the enhanced antiviral activity of ADS-324, as demonstrated by a reduction in the EC₅₀ of >10-fold in the presence of AMT and OSL. In addition, the activity of ADS-324 was evaluated in combination with other host targeted drugs (HTDs) identified from the screen. The results demonstrated that combinations of HTDs were synergistic at inhibiting influenza replication, suggestive that targeting multiple host pathways may result in enhanced antiviral activity. To determine the spectrum of activity of ADS-324 against other viruses, we evaluated the activity of ADS-324 as a single agent and in combination against the flavivirus yellow fever. The results demonstrate that ADS-324
had strong antiviral activity (EC\textsubscript{50} = 0.03 μM) as a single agent and was synergistic with interferon at inhibiting yellow fever virus replication.

The identification of FDA-approved drugs that inhibit virus replication by targeting one or more host cellular pathways may result in the discovery of new, safe, and effective antiviral treatments. We surmise that antiviral therapies that target host factors will have high barriers to resistance and broad spectrum activity against zoonotic and emerging pathogens.