A novel class of host-directed antivirals with broad spectrum activity against respiratory and systemic RNA viruses

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ABSTRACT

We have identified a broad spectrum antiviral candidate with low micromolar potency in multiple respiratory and emerging pathogens that functions through a novel host-mediated target. Broad-spectrum antivirals that retain potency in the presence of rapidly evolving viruses are in demand and host-directed antivirals remain an attractive therapeutic strategy. We previously reported the identification of a novel class of chromone drug candidates that modulate innate immunity along the RLR/IRF3 axis. Importantly, our compounds activate innate immune signaling downstream of numerous viral countermeasures and are a unique addition to conventional antiviral compounds in development or on the market. Through SAR, we have achieved broad spectrum in vivo activity against diverse RNA viruses including the respiratory pathogens, influenza, RSV, and HCoV with EC50s in the low nM range. While our development path is focused on broad respiratory indications, we have demonstrated potent in vitro activity against systemic and emerging viruses including dengue and ebola. Administration of lead compounds provides significant therapeutic benefit in murine models of respiratory infection, including influenza and RSV. Pharmacokinetic treatment reduces titers over 2 logs and more than one log in a delayed treatment model, translating to significant decreases in morbidity and mortality. These analogs demonstrate high permeability and sufficient metabolic stability to provide oral bioavailability compatible with twice-daily dosing. Finally, lead molecules exhibit a generous therapeutic index, show no off-target receptor activation and no genotoxic or cardiotoxic potential. In summary, our lead compounds proposed for development are non-direct acting antivirals that potentiate a cell autonomous effector response active against diverse RNA viruses, are less likely to elicit emergence of resistant viral variants, and have potential to be therapeutics for viral infections of undiagnosed etiology.

ADVANTAGES OF IRF3-MEDIATED ANTIVIRALS

- Inhibits single step in virus life cycle
- Well characterized for target and MOA
- Virus resistance readily developed
- Active against one or a few viruses
- Inhibit virus replication & activates immune cells for viral clearance
- Viral resistance less likely
- Enhance effects of direct-acting antivirals (in combination therapy)

LEAD COMPOUNDS HAVE DEMONSTRATED nM POTENCY IN MULTIPLE VIRUS FAMILIES

Medicinal chemistry optimization has improved broad spectrum antiviral potency

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<th>IRF3 translocation</th>
<th>FLU EC50 (nM)</th>
<th>RSV EC50 (nM)</th>
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<th>DENV EC50 (nM)</th>
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BROAD SPECTRUM IN VIVO EFFICACY IN MOUSE MODELS OF VIRUS INFECTION

- Reduction of FLU-H1N1 and MHV-coronavirus in the lung at day 3
- Inhibition of DENV-2 in the blood at day 3

Delayed treatment up to 48h post-infection provides protection from a lethal influenza challenge in mice

LEAD ANTIVIRAL PRECLINICAL SUMMARY

- Active against FLU, RSV, DENV, CoV, HBV, CMV, WNV, HCV, EBOV
- In vitro EC50 < 100nM
- Metabolically stable with good oral exposure
- Good permeability with no evidence of efflux
- Multi-dose studies show no adverse effects in vivo
- Animal models show inhibition of H1N1 Flu, coronavirus, and dengue virus replication
- Receptor/kinase panel (CEREPE) showed NO off-target binding/effects
- No genotoxic or cardiotoxic liabilities identified
- Drug activity is dependent on IRF-3

TARGETING INNATE IMMUNITY OFFERS POTENTIAL FOR A PAN-VIRAL THERAPY

- West Nile Virus
- Dengue Fever
- Ebola
- Lassa
- Hepatitis B
- Hepatitis C
- West Nile Virus
- Dengue Fever
- Ebola
- Lassa
- Arenaviruses
- Cytomegaloviruses
- Influenza
- H3N2
- H1N1
- Paramyxovirus: RSV, paraflu, Measles
- Coronavirus: SARS, MERS

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