e-therapeutics

Network-driven Drug Discovery

EXPLORING BIOLOGICAL AND CHEMICAL SPACES USING NETWORK-DRIVEN DRUG DISCOVERY: INFLUENZA PROGRAMME

BACKGROUND

Influenza viral infections cause annual outbreaks with associated health and economic losses.

Vaccination is the main tool to minimize influenza infections. However, vaccine production requires surveillance of circulating strains and has limited effectivity. Small-molecule therapeutics would therefore be ideal for the treatment of this highly changing virus. Antivirals targeting the viral neuraminidase protein (*e.g*. oseltamivir & zanamivir) are the current standard of care for influenza infections, but the treatment is far from optimum, with a short treatment window after the onset of the disease and moderate benefits. Furthermore, drug resistance is a problem for influenza treatment and has been observed for neuraminidase inhibitors. Agents targeting other viral proteins are in clinical development (*e.g.* inhibitors of the influenza polymerase complex). Although a drug targeting the viral polymerase is safe in clinical studies and efficacious at treating existing viral resistant strains, variants conferring reduced sensitivity have been reported to arise *in vitro*. Moreover, due to differences in the viral polymerase across strains this inhibitor has broad activity against influenza A strains but lacks activity against influenza B strains. Therefore, an opportunity exists to develop new anti-influenza compounds with high barrier to resistance, better treatment window, and wider strain cover.

THE OPPORTUNITY

e-therapeutics has successfully applied its **Network-driven Drug Discovery** (NDD) platform to identify small-molecule antivirals against influenza virus. The programme yielded two lead-series that are chemically different and have distinctive antiviral profiles - with one series active against influenza A and B strains and the other series lacking anti-influenza B activity. The molecules were discovered using human protein interaction networks and showed antiviral activity in relevant human cell lines.

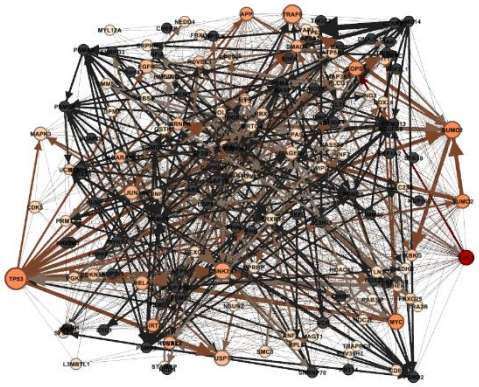
e-therapeutics' platform can be used to discover novel and differentiated hits for subsequent hit-to-lead and lead optimisation.

THE APPROACH

Network-driven Drug Discovery

Our approach to developing influenza antivirals was to target the network of host proteins required for viral replication.

Targeting the host proteins, as opposed to the viral ones, should allow us to capture the complexity of the viral infection and more efficiently identify drug-like compounds for *in vitro* screening and subsequent medicinal chemistry improvement. These compounds should be better at addressing the problems of existing anti-influenza drugs targeting viral proteins (*e.g.* resistance, lack of strain coverage, and poor treatment window).



Example of an influenza network based on host proteins required for viral infection (black dots)

ACTIVITIES

Networks, Compounds, Screening and Medicinal Chemistry Optimisation

Protein interaction networks were constructed using host factors that are essential for the virus life cycle as seeds.

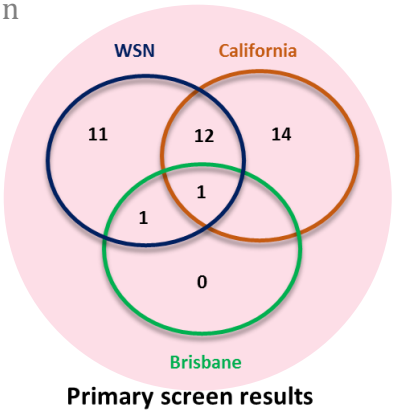
Network construction approaches

- Early viral entry steps: binding, internalization
- Viral genome replication and transcription
- Virus-like particle formation
- Incorporation of vRNPs into virion
- Intracellular localization of viral protein
- Combined interactome

Using network analysis and proprietary analysis tools, 1000 compounds with desirable physicochemical characteristics were identified for *in vitro* testing. Compounds were initially screened for antiviral activity in two influenza A strains, namely WSN & California.

Thirty-nine compounds were active in at least one of the two strains tested and fulfilled the screening filter criteria (activity < 10 µM and no cellular toxicity). Further screening indicated that two compounds were also active against influenza B Brisbane strain.

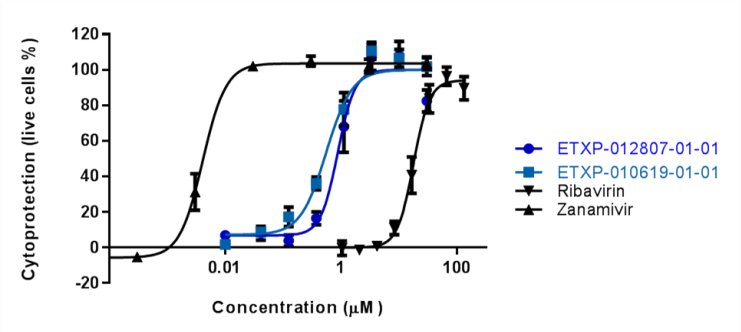
Compounds selected from 2D-3D similarity and compound foot-print matching searches confirmed SAR, and two chemotypes were selected for medicinal chemistry optimisation. A few rounds of design-make-test-analyses cycle improved the potency of the hits, with one series showing activity against influenza A virus only, and the other series against both influenza A and B strains.



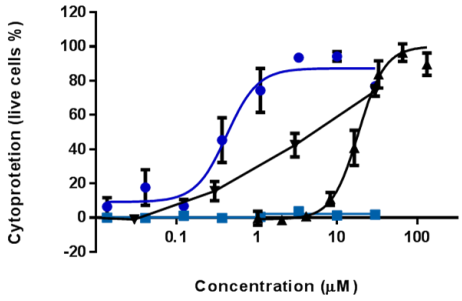
Primary screen results

Screening filter criteria	
Antiviral IC_{50}	<10 µM
Cytotoxicity IC_{50}	> 30 µM

Interesting hits: simple chemical structure, low molecular weight, chemical tractability, and positive IP. Suitable for medicinal chemistry improvement



***In vitro* activity against WSN strain**



***In vitro* activity against Brisbane strain**

New molecules with increased potency against influenza A and B strains

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