Discovery and Optimization of Novel Compounds Targeting Programmed Ribosomal Frameshifting in RNA Viruses

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Programmed ribosomal frameshifting is prevalent in RNA viruses

A platform to rapidly identify drug candidates targeting viral FSEs

Equine arteritis virus FSE

HIV-1 FSE

SARS-CoV-2 FSE

West Nile virus FSE

Totiviruses, Astroviruses, Picornaviruses, Alphaviruses, Influenza A Virus, etc.

HEK293T cells
Add compounds
Transfect reporter
24 hr
30 min
24 hr
Automated imaging & quantification
Validation by luciferase assays

Antiviral testing
Optimization
In vivo testing
Advantages of FSE-targeting drugs over existing classes of antivirals

- **Rapid screen design and lead identification**
  Only the viral genome sequence is needed. Suited for future viral pathogens.

- **Broad spectra**
  The same compound inhibits frameshifting in most known beta coronaviruses, and possibly future emerging ones.

- **Robustness**
  Natural mutations that confer resistance are unlikely to arise.

- **Targeting multiple viral components simultaneously**

![Diagram showing targeting of multiple viral components](image)
Discovery of a SARS-CoV-2 frameshift inhibitor

- 4,434 approved drugs and drug-like compounds screened
- Highly robust microscopy screens: $Z' = 0.91-0.95$
- Rapid validation by an orthogonal, luciferase-based assay
- 1 frameshift enhancer (ivermectin) and 1 inhibitor (merafloxacin) validated

* Provisional patent application filed (Yale Case OCR 7981) “Compounds and Compositions for Disrupting Programmed Ribosomal Frameshifting”
Use of Blavatnik funding

Part I Optimization of merafloxacin

- Optimize for stronger potency and antiviral activity
- 2 cycles of compound design and synthesis
- 25-30 compounds per cycle
- ~$54,000 total (New England Discovery Partner)

Part II Expanded screening for additional scaffolds

- Merafloxacin was identified from a small-scale screen of 4,434 compounds
- Plan to screen Life Chemicals Diversity Collection (126,639 compounds)
- Search for frameshift modifiers with higher activity and broader spectra
- ~$55,000 total (Yale Center for Molecular Discovery, ~50% subsidized)

Expected outcomes: startup formation; licenses to pharmaceutical companies

Future plan: In vivo testing, administration (IV vs. intranasal), pharmacokinetics
Our Team

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