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

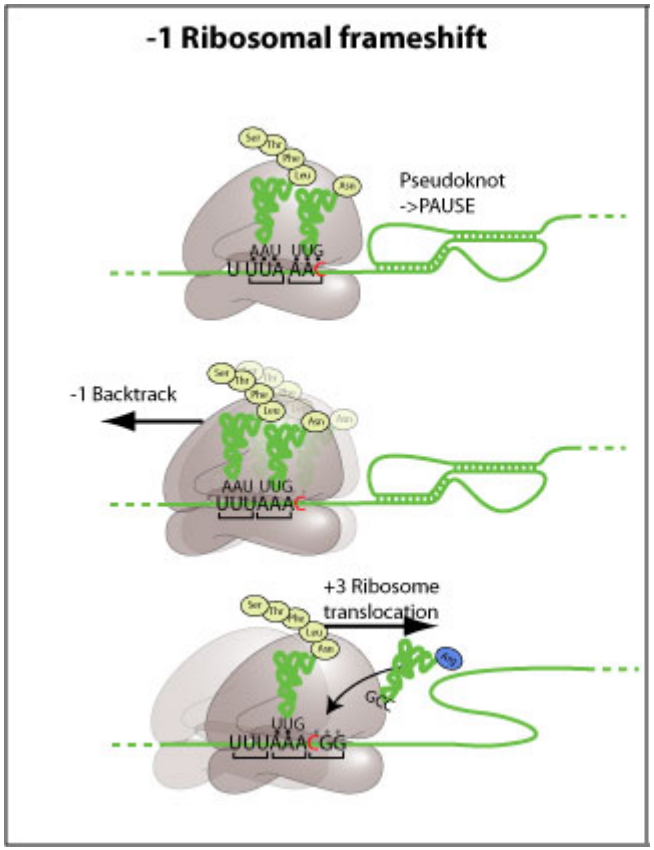
Junjie Guo

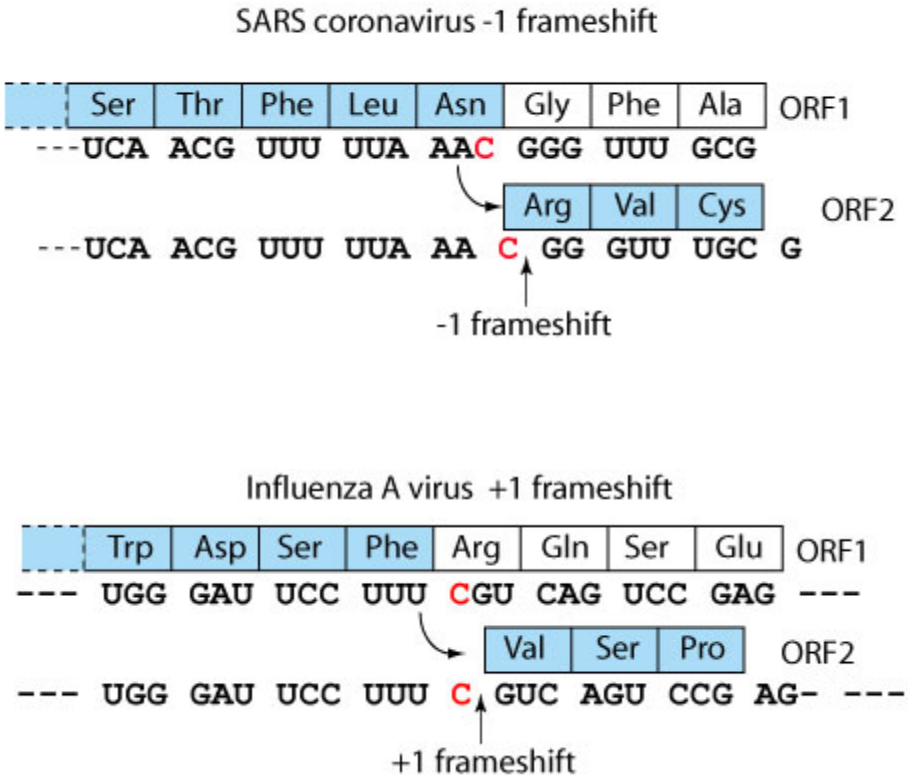
Department of Neuroscience

Yale Center for RNA Science and Medicine

Yale University School of Medicine

Programmed ribosomal frameshifting is prevalent in RNA viruses

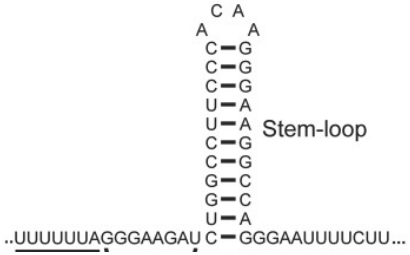




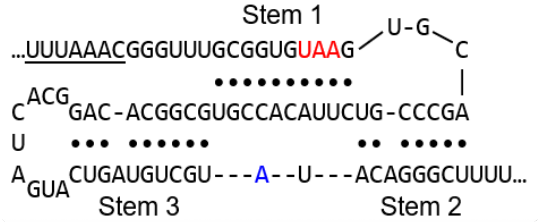
ViralZone, http://viralzone.expasy.org

A platform to rapidly identify drug candidates targeting viral FSEs

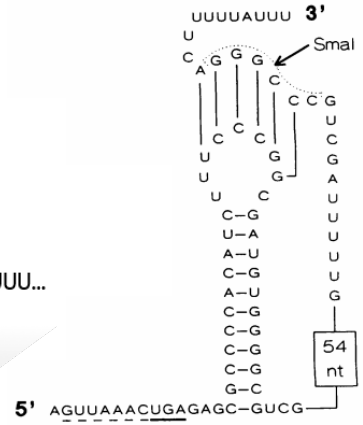
HIV-1 FSE



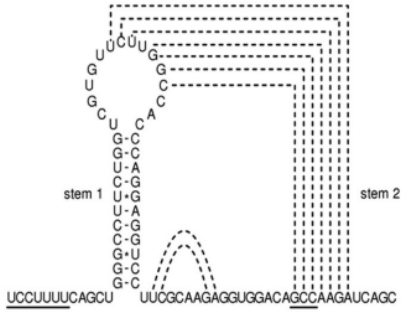
SARS-CoV-2 FSE



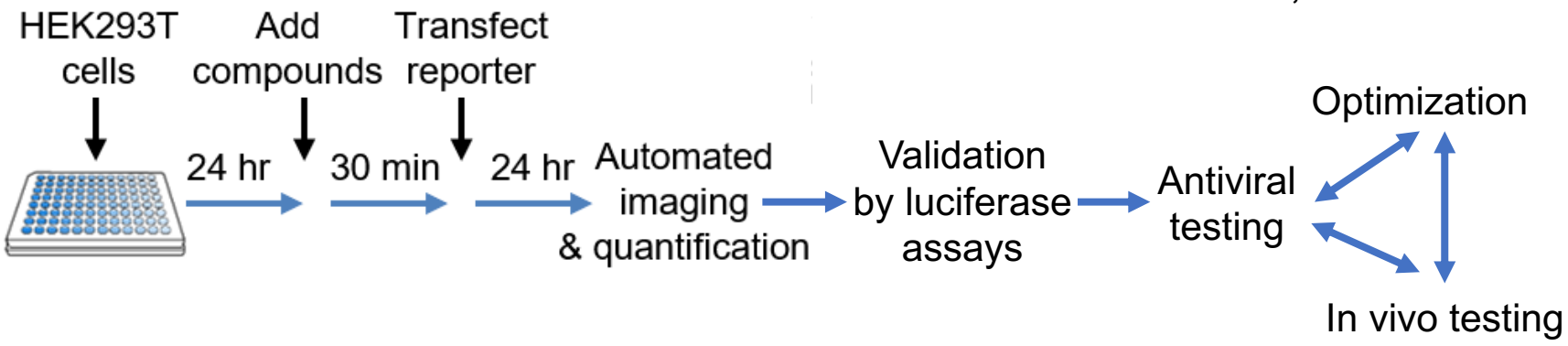
Equine arteritis virus FSE



West Nile virus FSE



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



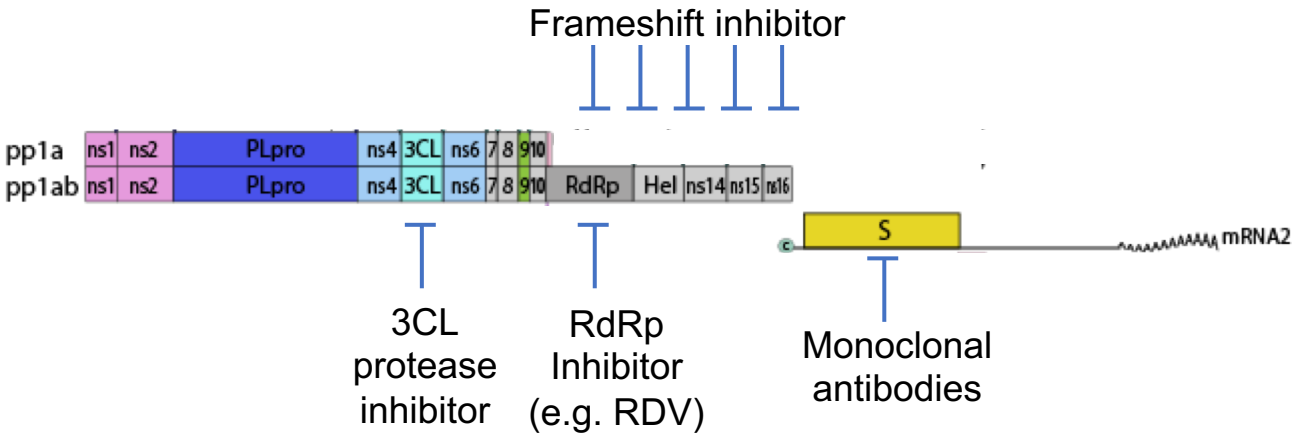
Advantages of FSE-targeting drugs over existing classes of antivirals

- **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.

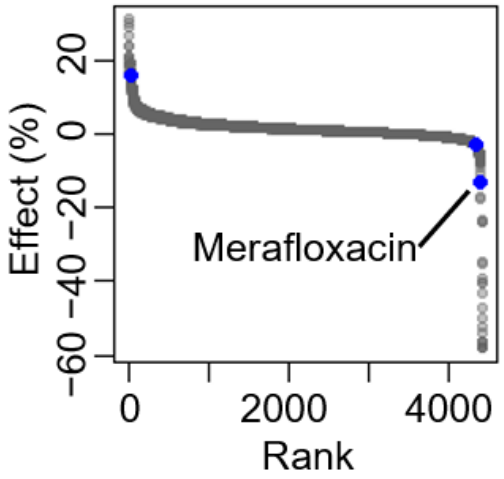
- **Robustness**
  Natural mutations that confer resistance are unlikely to arise.

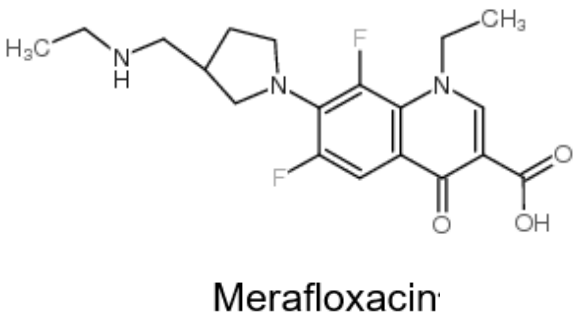
- **Targeting multiple viral components simultaneously**



Discovery of a SARS-CoV-2 frameshift inhibitor

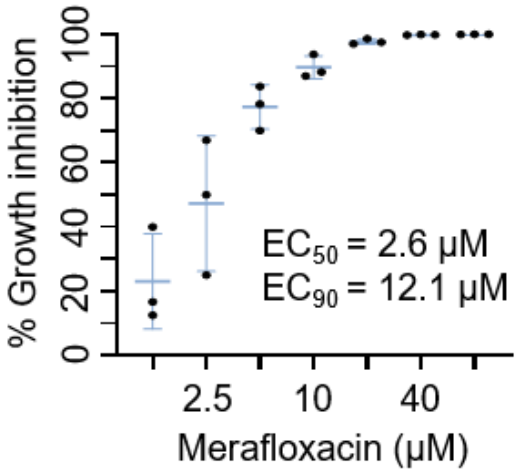
Effects of 4,434 compounds
on SARS-CoV-2 frameshifting





Merafloxacin

Antiviral activity
in Vero E6 cells



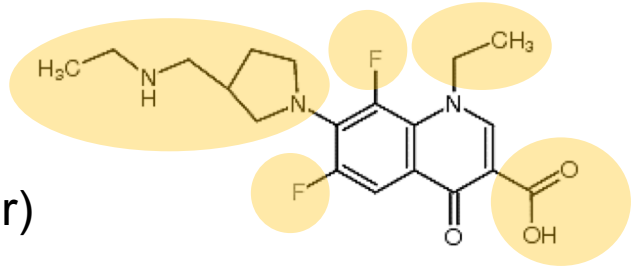
- 4,434 approved drugs and drug-like compounds screened
- Highly robust microscopy screens: Z' = 0.91-0.95
- Rapid validation by an orthogonal, luciferase-based assay
- 1 frameshift enhancer (ivermectin) and 1 inhibitor (merafloxacin) validated

* 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 sprectra
- ~$55,000 total (Yale Center for Molecular Discovery, ~50% subsidized)

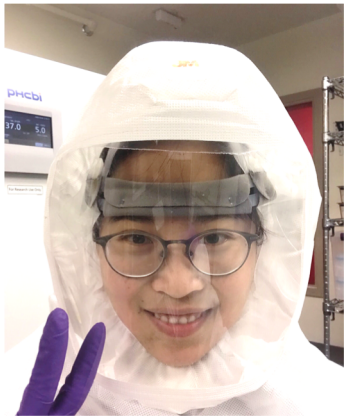
Expected outcomes: startup formation; licenses to pharmaceutical companies

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

Our Team

Junjie Guo, PhD
PI
Assistant Professor
Neuroscience

Brett Lindenbach, PhD
Consultant
Associate Professor
Microbial Pathogenesis



Yu Sun, PhD
Staff scientist
Neuroscience

Yulia Surovtseva
Consultant
Director, YCMD

Laura Abriola
Staff scientist
YCMD