Identification and Characterization of Novel Chemical Scaffolds with anti-HIV Activities

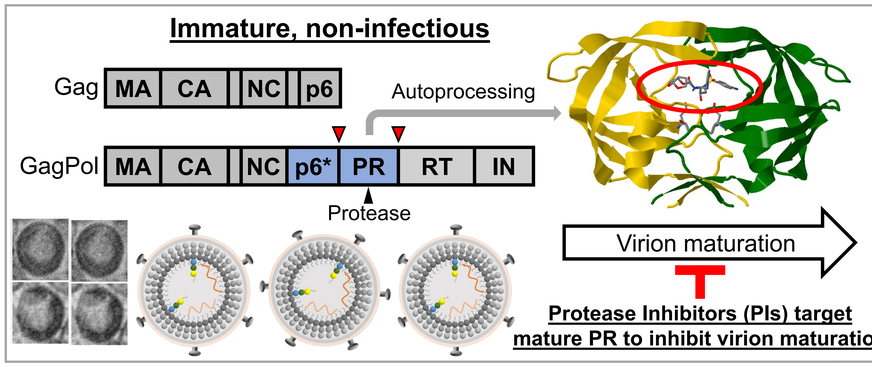
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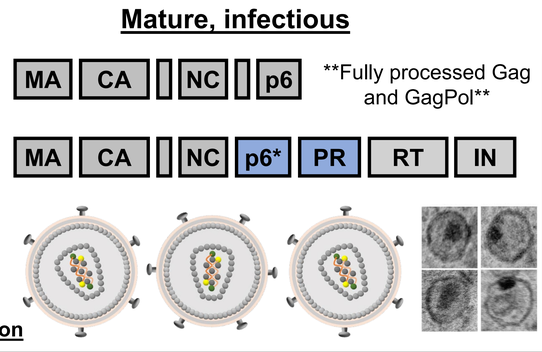
[3]Life Sciences Institute, University of Michigan, Ann Arbor, MI 48109, USA; "*", equal contributions

Poster 707

Immature, non-infectious



Mature, infectious



Virion maturation

Protease Inhibitors (PIs) target mature PR to inhibit virion maturation

GAP

- PIs target mature PR with high potency
- PIs have far less potency against PR precursors compared to mature PR
- No structures of PR precursors exist

APPROACH

- Identify and characterize novel compounds for Autoprocessing inhibition via cell-based assays & functional screens

GOAL

- New class of HIV-1 antiretroviral for expanded ART
- Insight into autoprocessing/drug resistance mechanisms

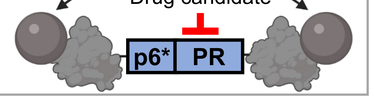
Preliminary AlphaLISA HTS

~350,000 small molecule/NPE compounds

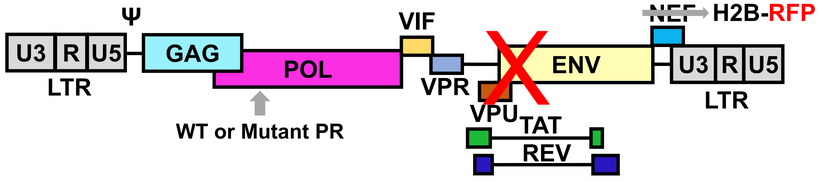
157 validated hits (triplicate)

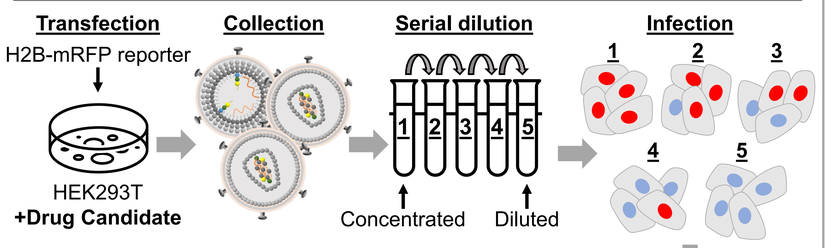
40 hits with inhibitory activity

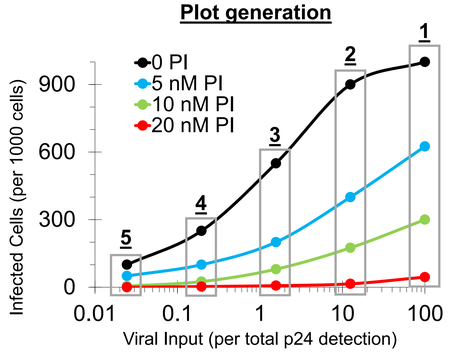
Positive hit

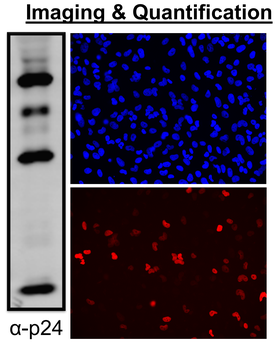


Hit Validation via Novel Infectivity Assay

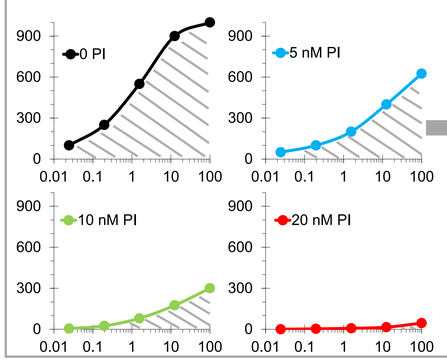


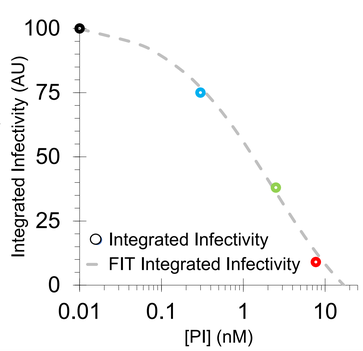




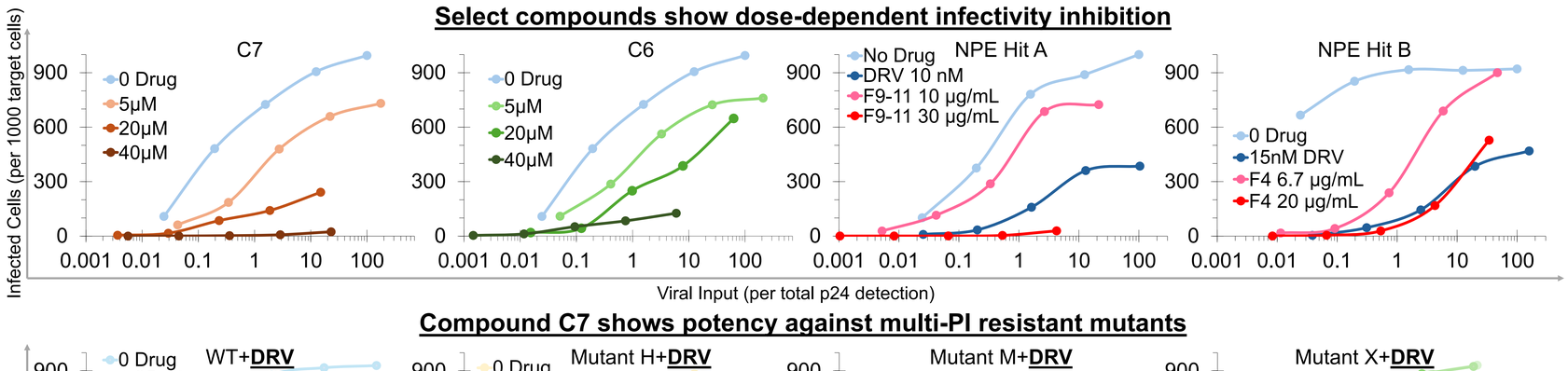


Infectivity percentage; Western blot normalization

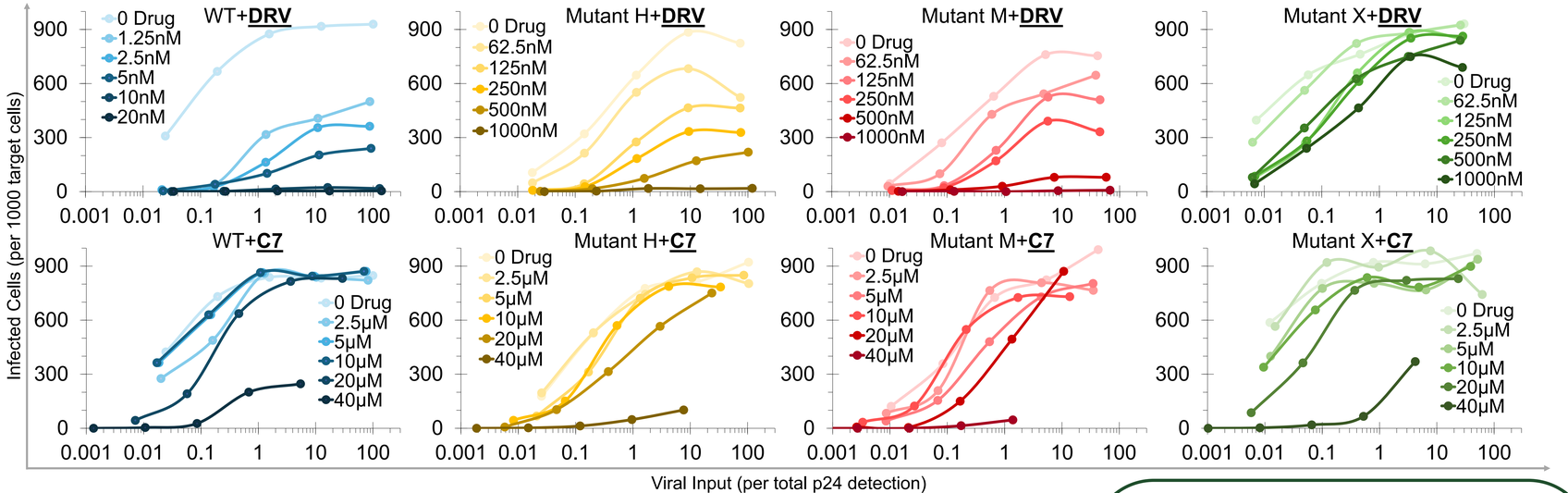




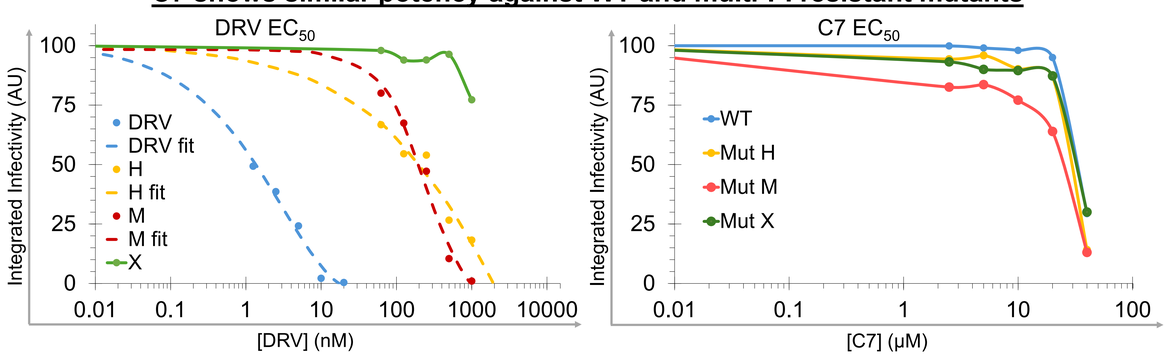
Select compounds show dose-dependent infectivity inhibition



Compound C7 shows potency against multi-PI resistant mutants



C7 shows similar potency against WT and multi-PI resistant mutants



Key Takeaways + Next Steps

- Validation of candidates displaying infectivity inhibition at low-micromolar doses
- **Similar EC_{50} of candidates against wild-type and highly drug-resistant viruses**
- Further SAR analysis and analog-by-catalog

Acknowledgements

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NIH National Institute of Allergy and Infectious Diseases
NIAID

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