Exploring the morphology of host cells for innovative drug repurposing in viral infections

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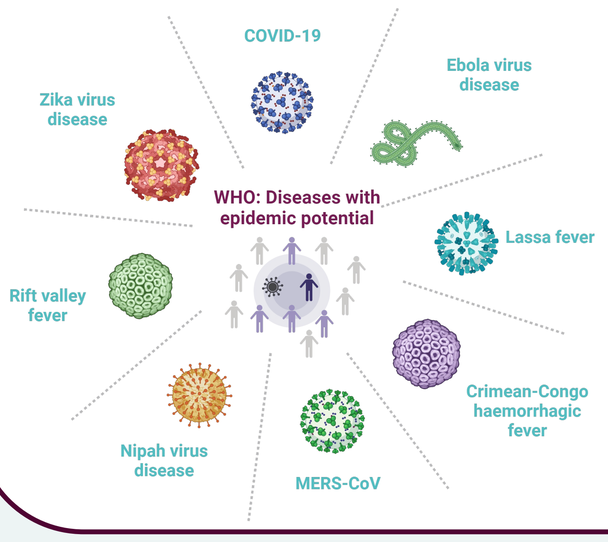
Ten antivirals vs hundreds of viruses



>200 viruses infectious to humans

19 vaccines

10 antivirals

Antiviral demand

Increased viral threat

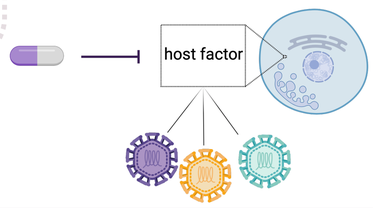
Exploiting the virus dependency on host cell pathways

Host-directed antivirals

- ⊕ Larger target repertoire
- ⊕ Broad spectrum opportunity
- ⊕ Reduced drug resistance
- ⊖ Increased risk of toxicity

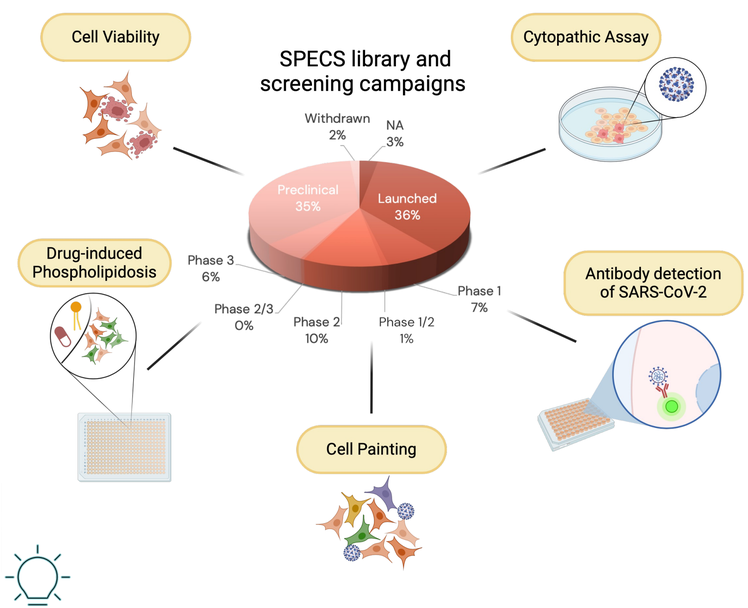
Elevating possibilities for viral infections by drug repurposing

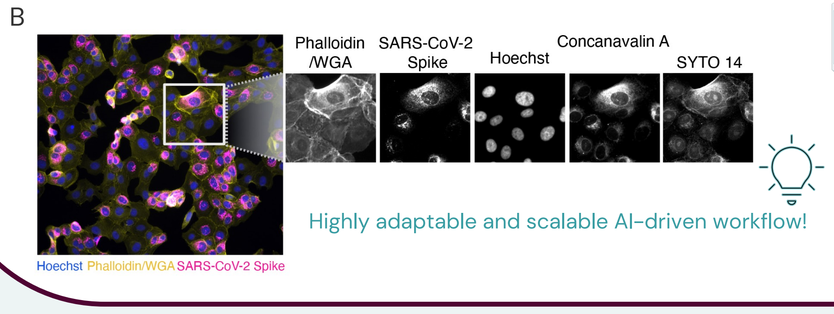
- ✓ Cost-benefit
- ✓ Time-benefit
- ✓ Lower safety-risk



Morphological profiling unveils antiviral compounds

- SPECS library screenings identifies 324 compounds with antiviral activity
- Cell Painting creates a unique fingerprint with >2000 morphological parameters
- SARS-CoV-2 induces a unique phenotype, reversed by reference antivirals
- Cell Painting pinpoints 36 potential SARS-CoV-2 repurposing candidates





Highly adaptable and scalable AI-driven workflow!

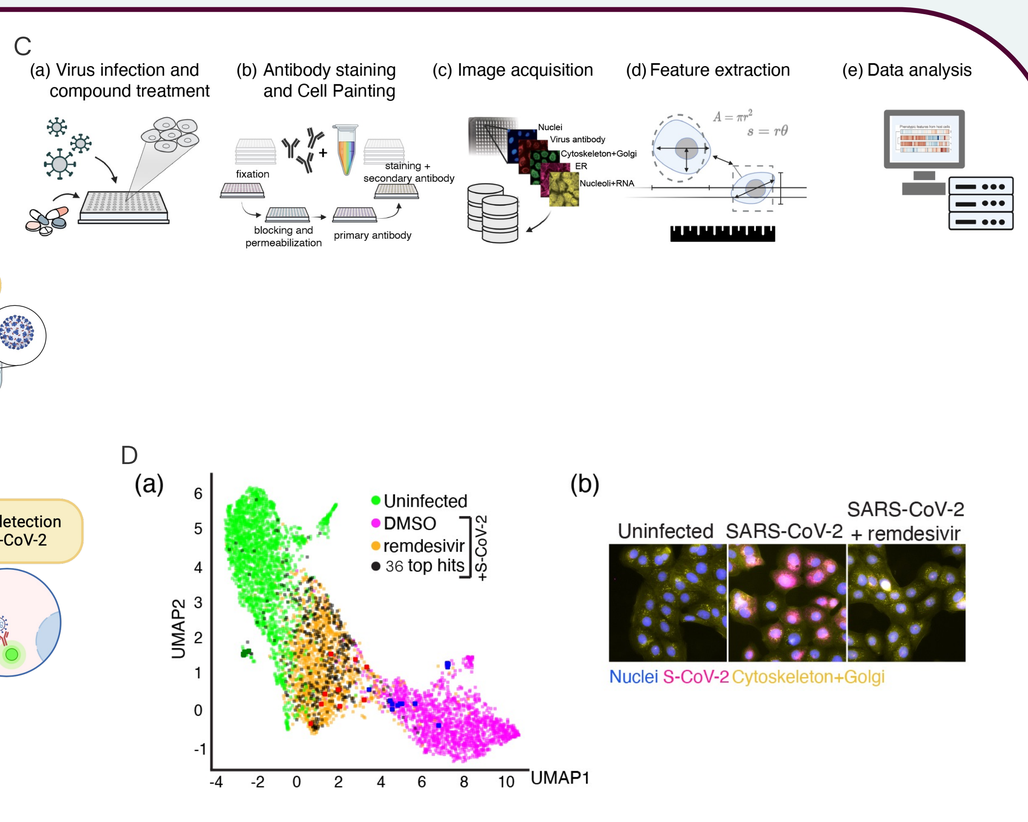
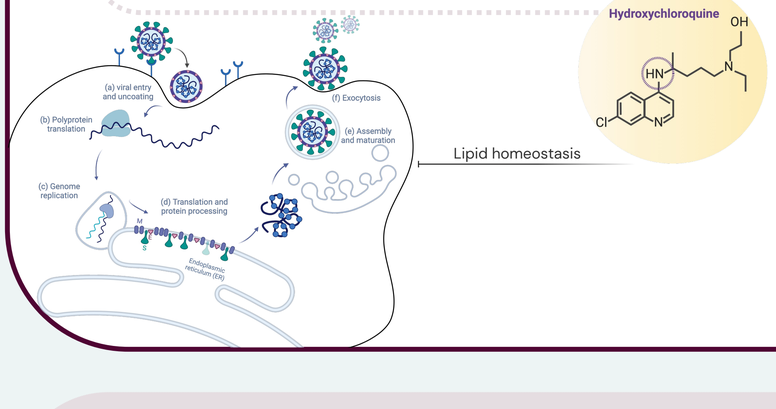


Fig. 1. (A) Overview of the screening methods using SPECS drug library of 5275 compounds. (B) Representative picture of fluorescent dyes with SARS-CoV-2 Spike antibody. (C) Cell painting workflow. (D) Cell Painting summary and representative images. UMAP plot representing populations of uninfected cells (green) and infected cells treated with DMSO (pink), remdesivir (orange) and screening hits (black).

Drug-induced phospholipidosis

- Predominantly induced by cationic-amphiphilic drugs
- Characterized by accumulation of the drug in cellular compartments
- Disrupts the lipid homeostasis



- Confounds drugs for SARS-CoV-2
  - Correlation with SARS-CoV-2 inhibition in vitro
- Does not reflect specific target-based activities of the drug
- Cell-line specific activity
- 157 compounds in the SPECS library (3%) induce phospholipidosis
- 61 antiviral compounds (19%) induce phospholipidosis

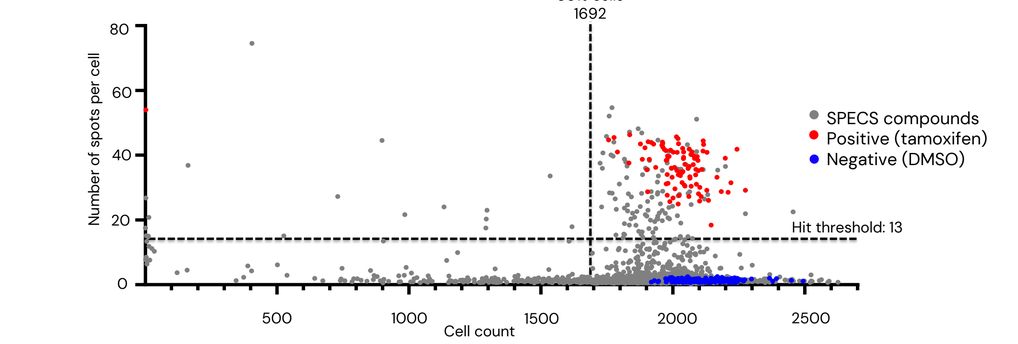


Fig. 2 (A) Workflow of the phospholipidosis (PL) screen. (B) Uninfected A549-ACE2 cells treated at a single dose screened for PL. Displayed are SPECS compounds (gray), positive control (red), and DMSO (blue).

Conclusions and future outlook

- Cell Painting enables unbiased morphological profiling for finding repurposing antiviral candidates
  - → Applicable for emerging viruses to combat future pandemics
- Several antiviral compounds have phospholipidosis activity
  - → Future research is required to understand the importance of phospholipidosis in viral drug discovery

Next step: Explore antiviral drug targets and drug combinations

This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No 101057442

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Acknowledgement: Analysis of data for figure 2 made by Kun Qian (CBCS)