



Medicinal Molecules &
Materials Group

Polymer-membrane interactions as a target for polymeric antivirals

CHARLOTTE FROST, PAUL DENMAN

DR. NATHAN BOASE

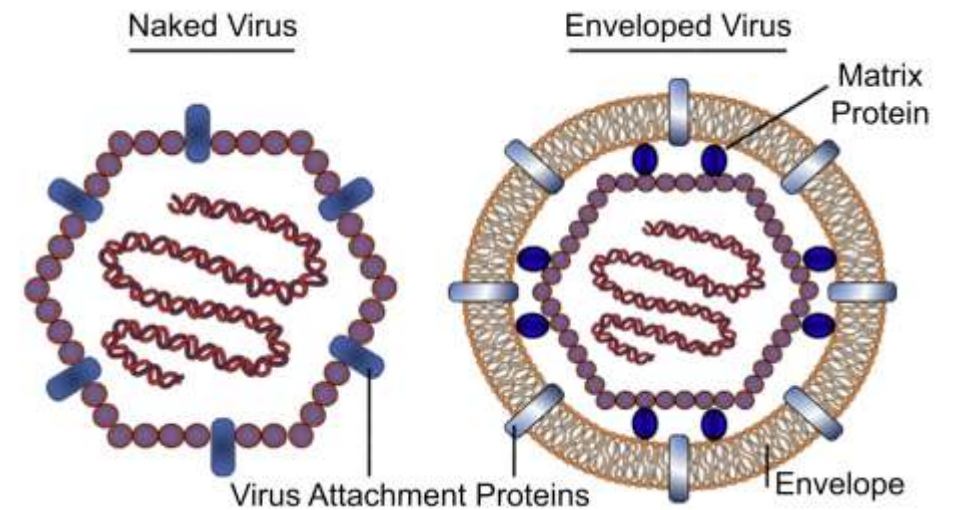
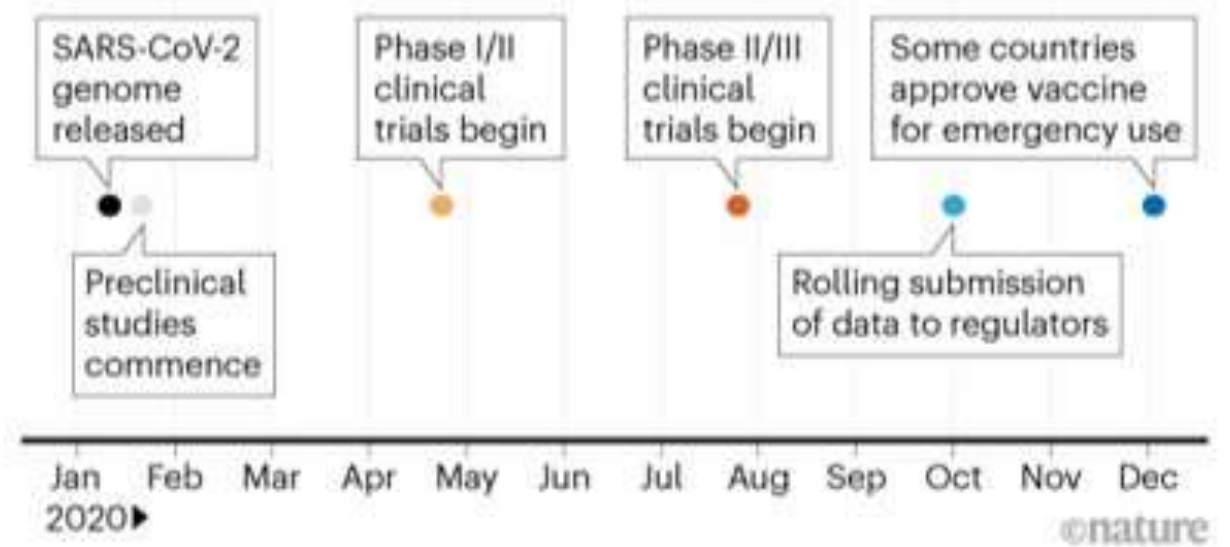
Macromolecular Chemistry and Physics (2023), 224,
2300315

Biomacromolecules (2024) *in preparation*

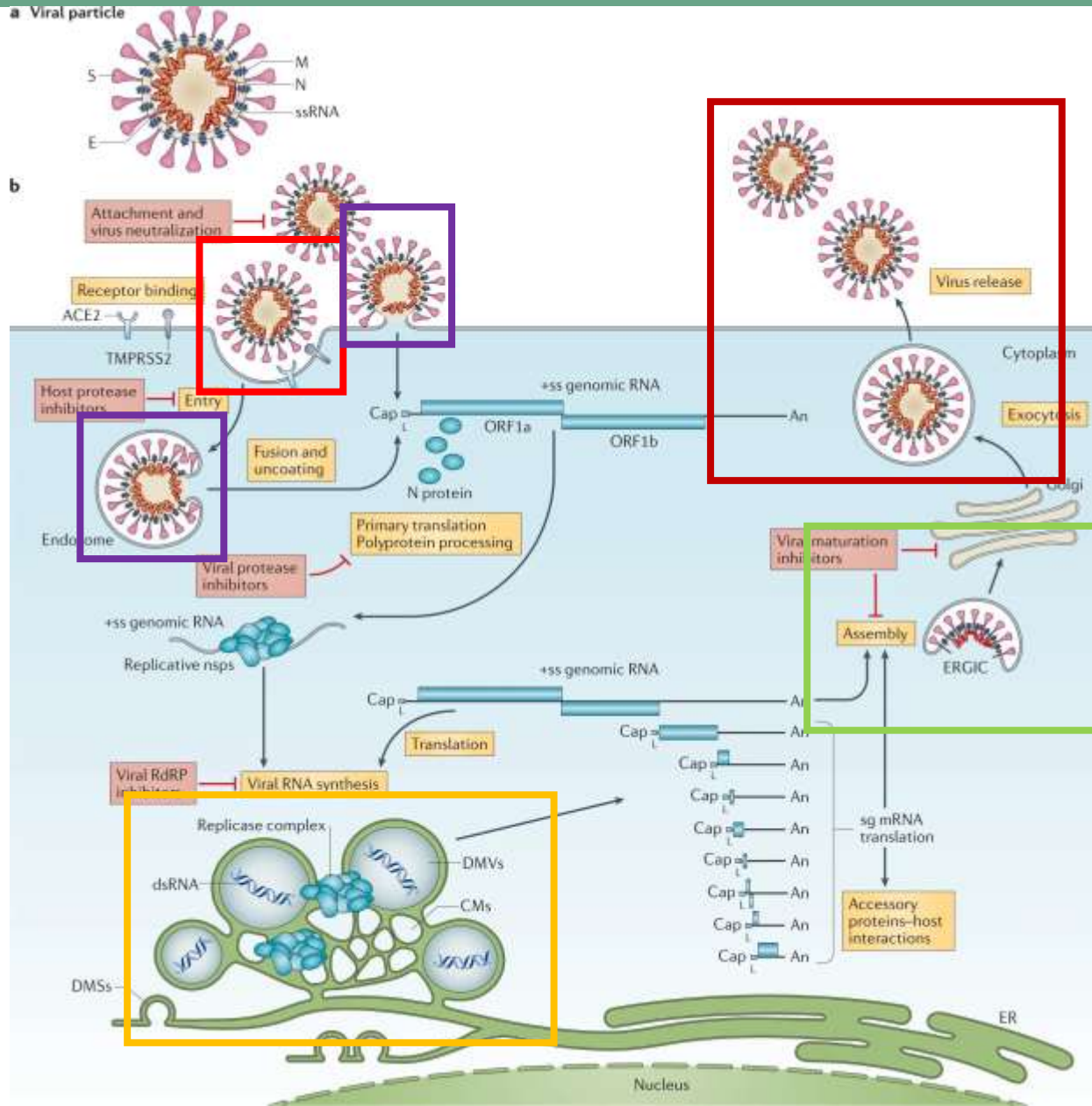


QUT

Impact of viral pandemics



Viral 'life' cycle



1. Attachment

Whitesides, G. M. *J. Med. Chem.* **1995**

VivaGel™ Starpharma, Tyssen, D. *PLoS One* **2010**

2. Entry (membrane fusion)

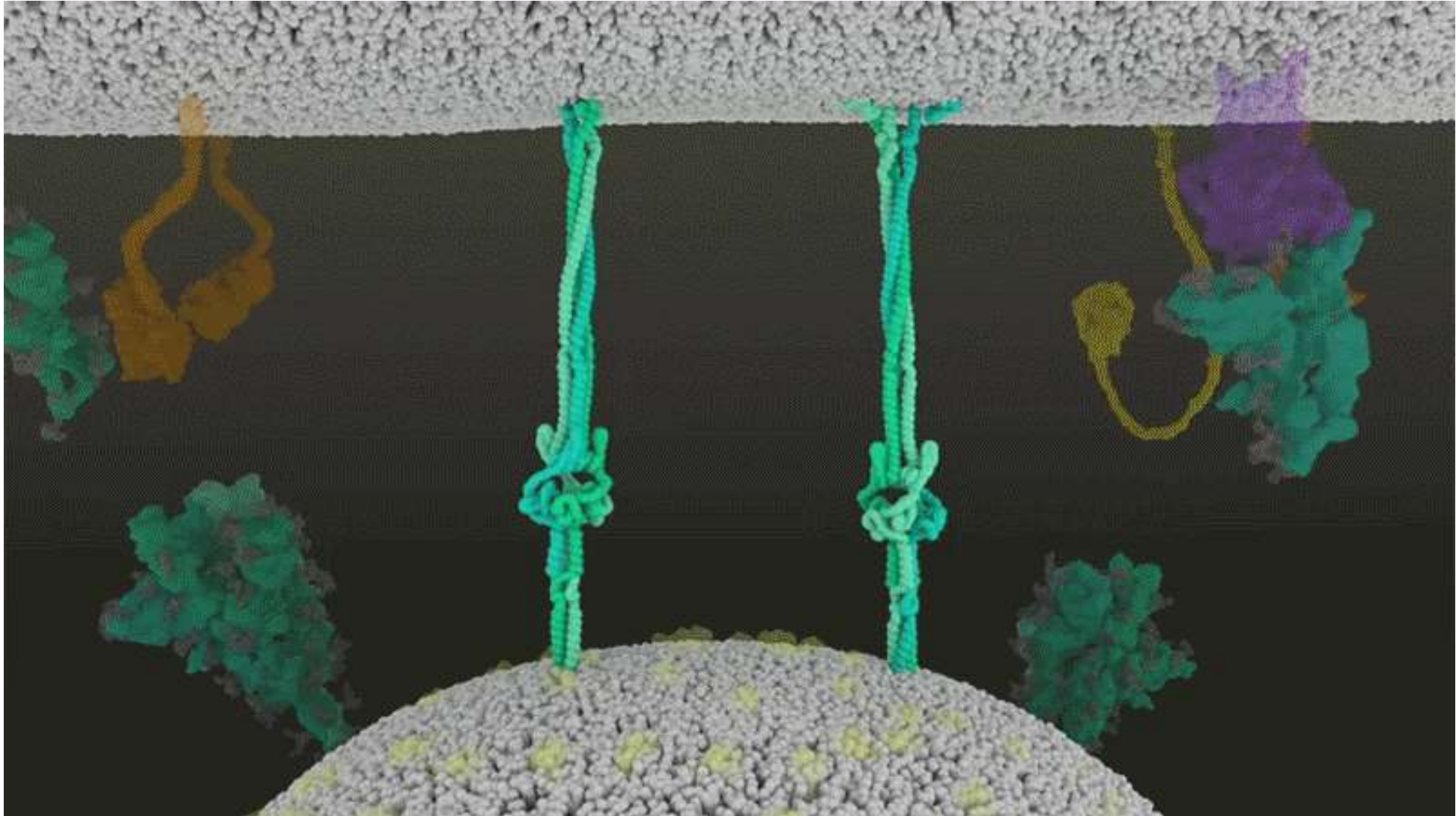
3. Replication

4. Assembly

5. Egress

V'kovski, P. *Nature Reviews Microbiology* **2021**, 19, 155

Membrane Fusion Process

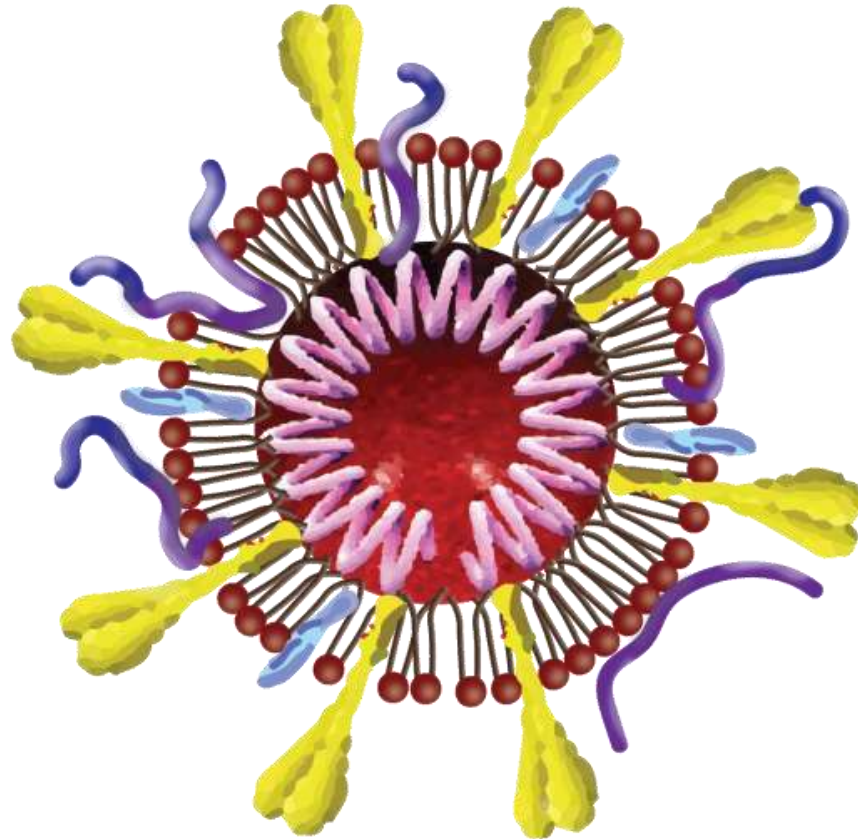
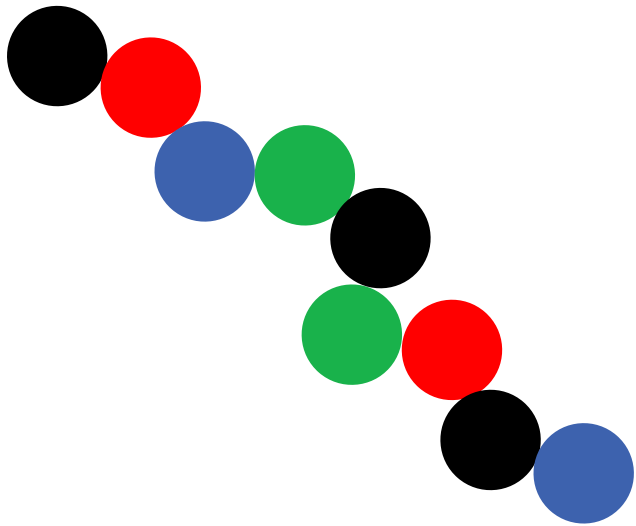


Scudellari, M. 'How the coronavirus infects cells — and why Delta is so dangerous'. *Nature* **2021**.

Vigant, F. *Nat Rev Microbiol* **2015**, *13* (7), 426-37.

Project Aims

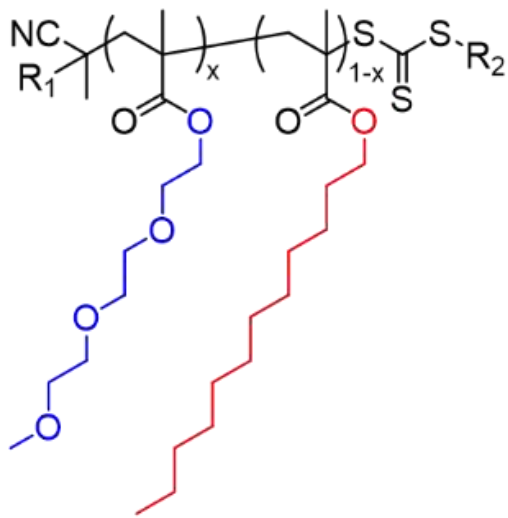
- Design amphipathic copolymers with high affinity for viral envelope that can inhibit viral infection
- Study physicochemical factors that drive interaction and inhibition



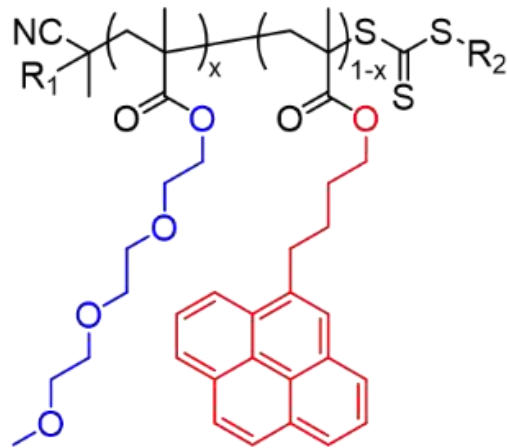
Studying polymer-membrane interactions



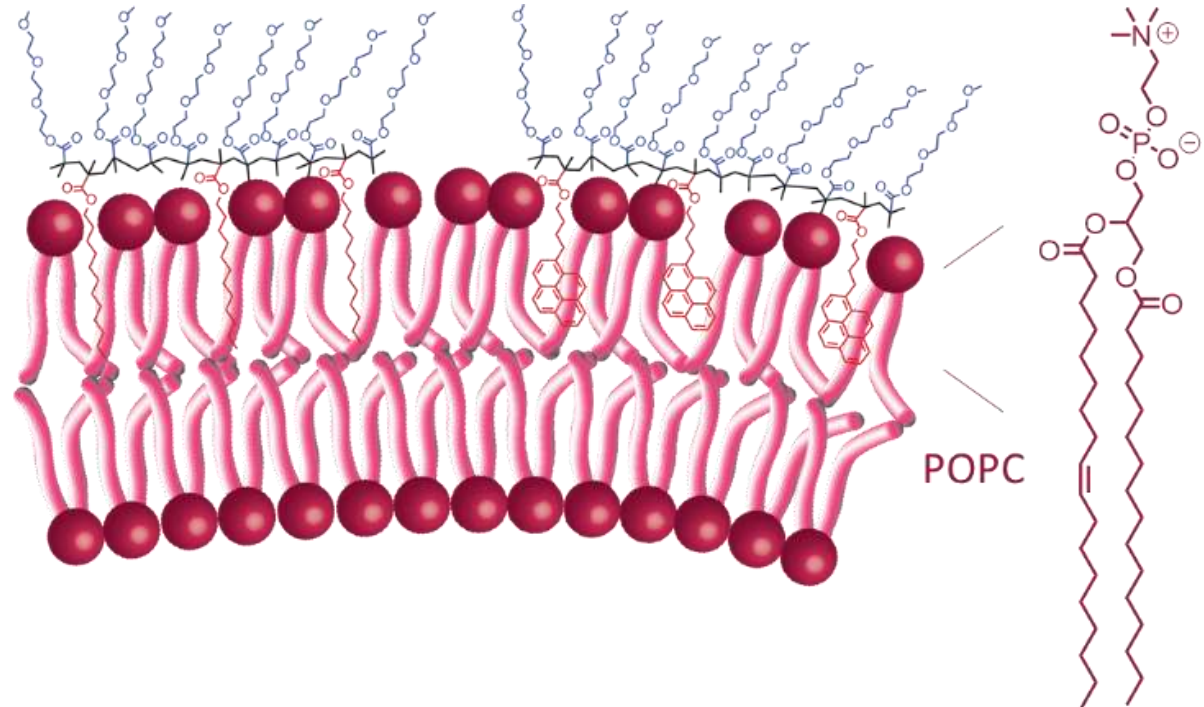
Charlotte Frost



TEGMA-co-LMA



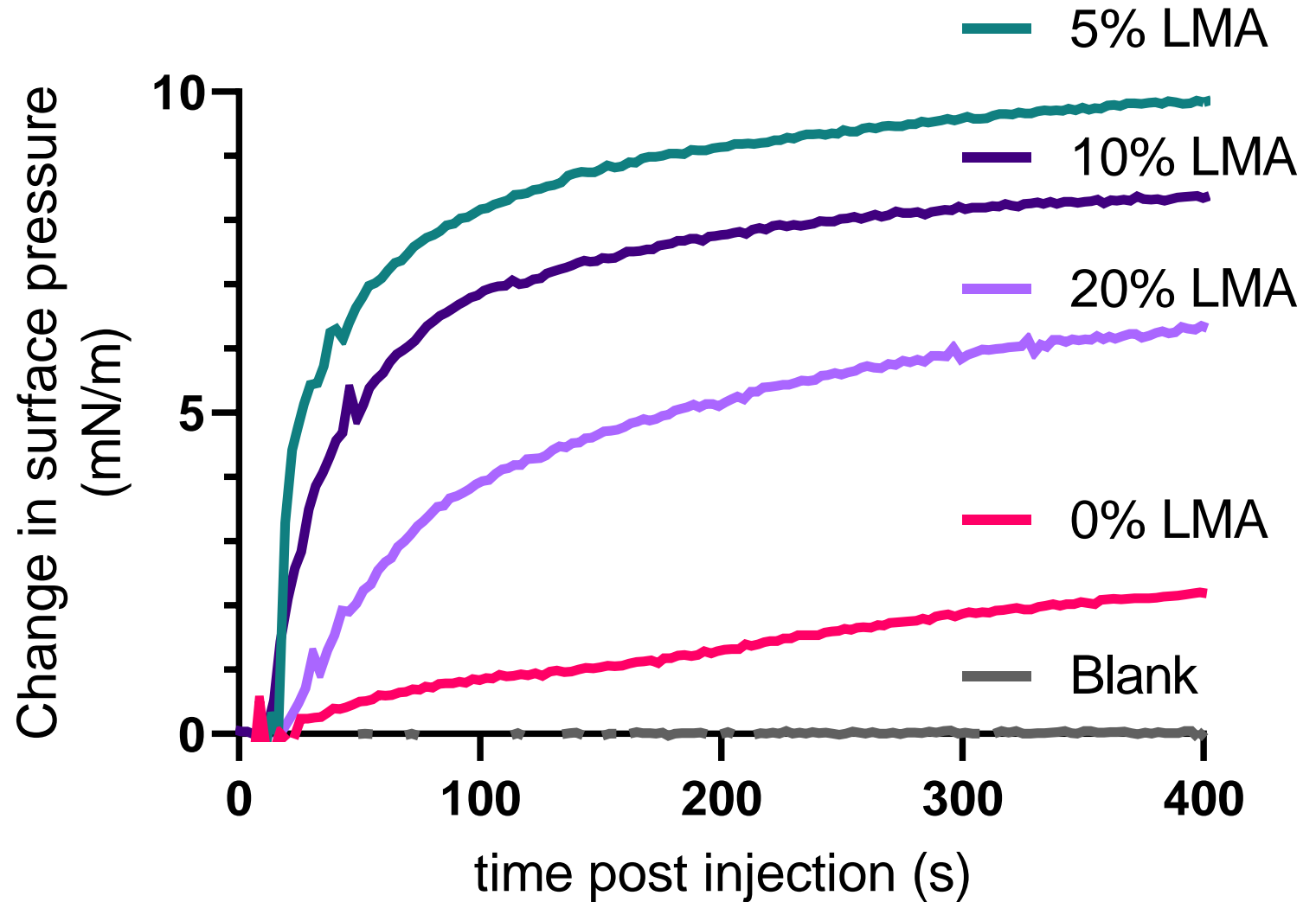
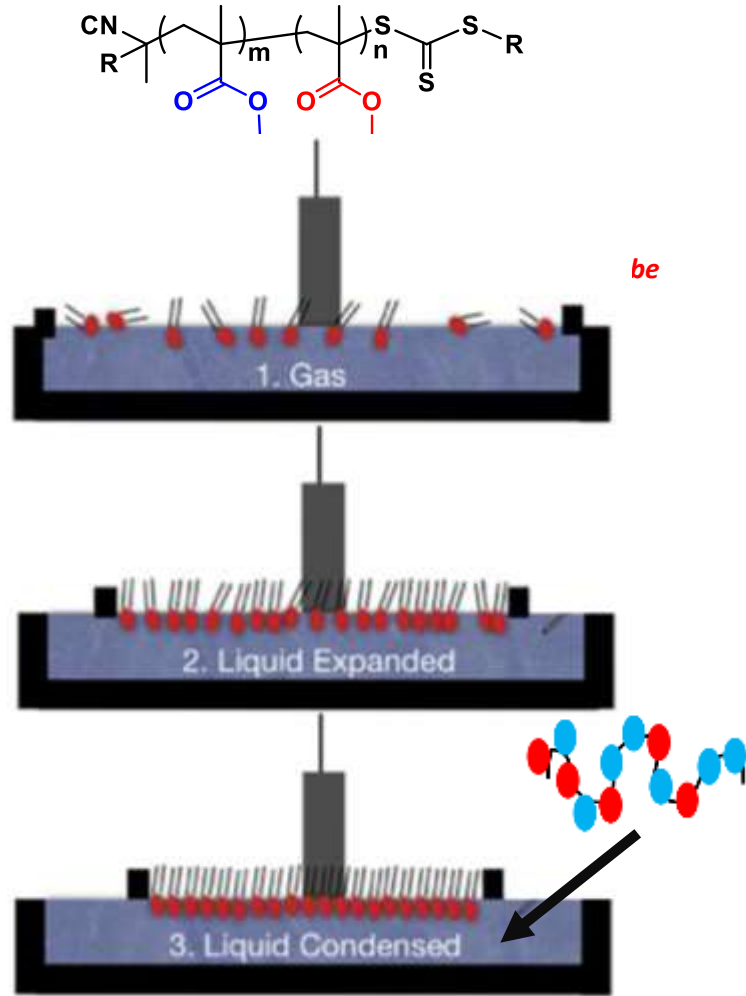
TEGMA-co-PyBuMA



Hydrophobe

0-30%

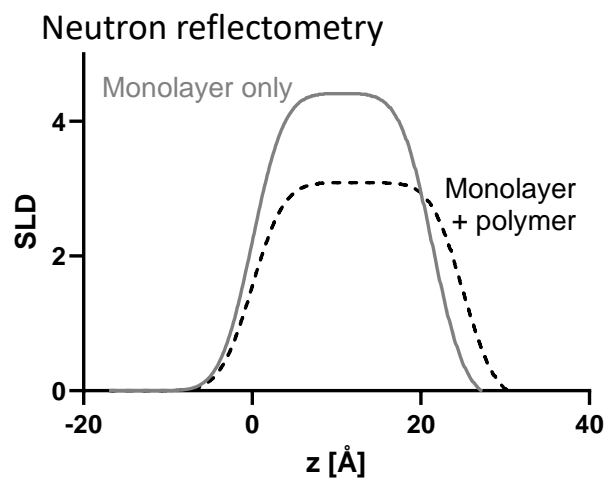
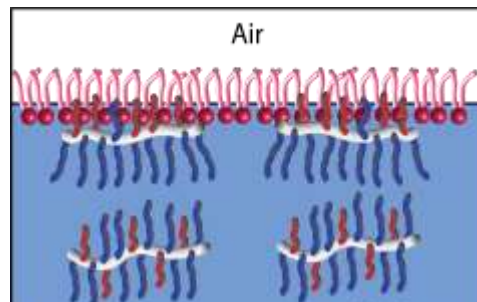
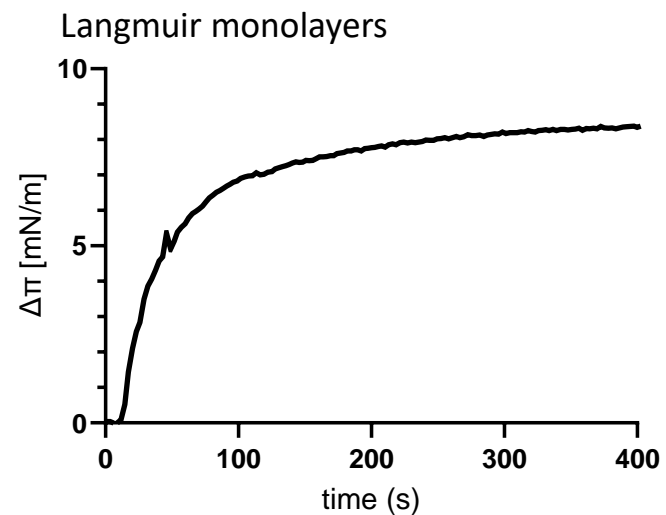
Studying polymer-membrane interactions



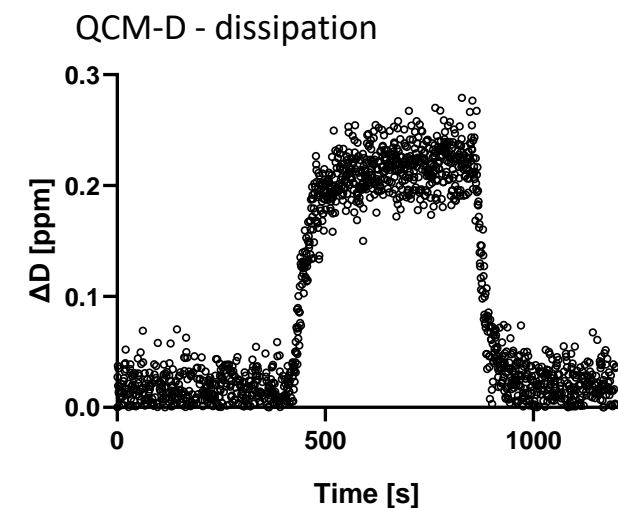
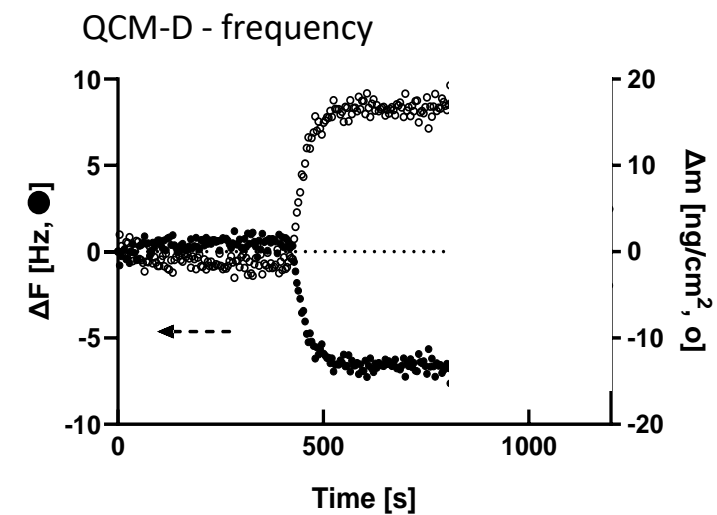
Polymer concentration 50 $\mu\text{g}/\text{mL}$

Frost, Boase, et al., *Macromolecular Chemistry and Physics* (2023), 224, 2300315

Polymer-membrane interactions at equilibrium conditions

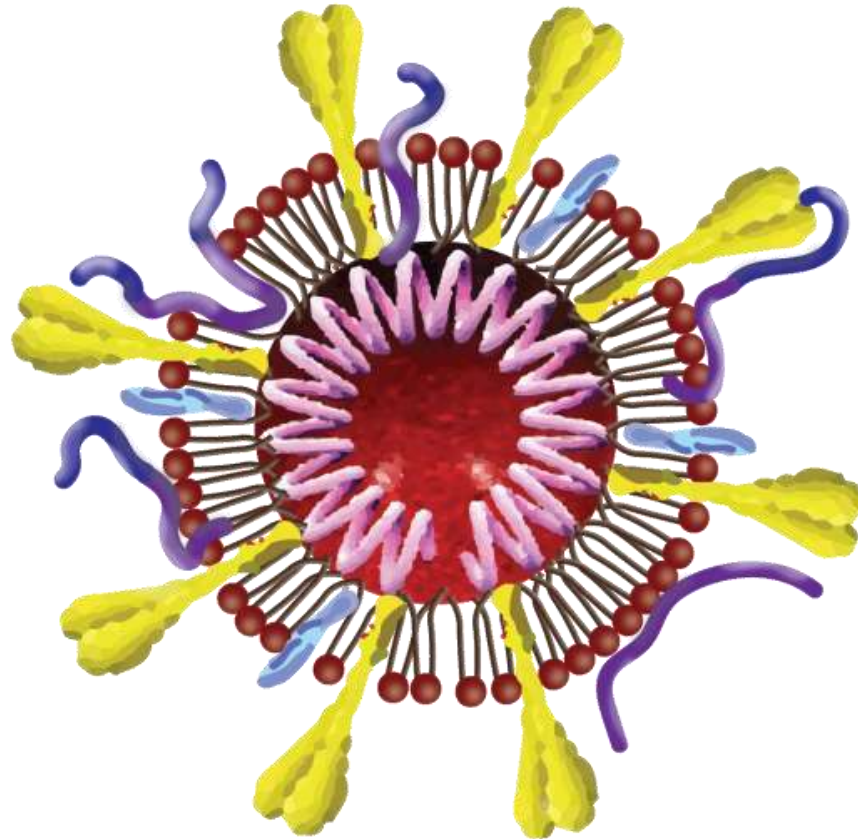
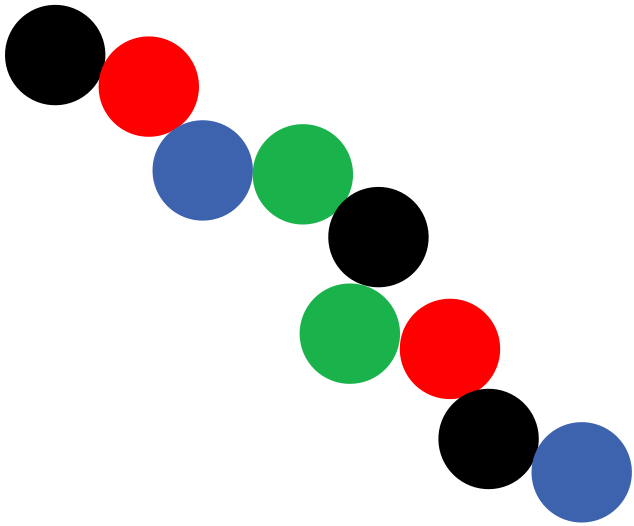


Polymer-membrane interactions at non-equilibrium conditions



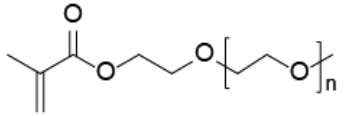
Project Aims

- Design amphipathic copolymers with high affinity for viral envelope that can inhibit viral infection
- Study physicochemical factors that drive interaction and inhibition

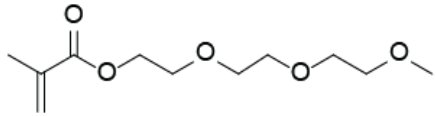


Polymer Design

Biocompatible Monomers

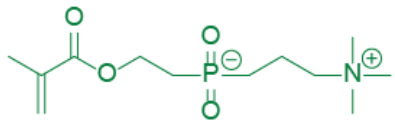


Poly(ethylene Glycol) Methyl Ether Methacrylate, Mn 300 (PEGMA300)

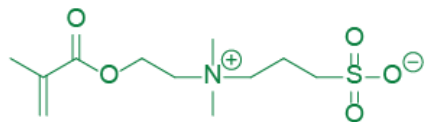


Tri(ethylene Glycol) Methyl Ether Methacrylate (TEGMA)

Zwitterionic Monomers

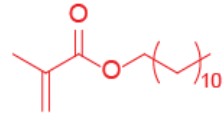


2-(Dimethylamino)ethyl Methacrylate (MPC)

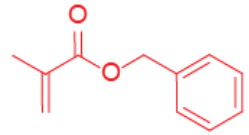


2-(Dimethylamino)ethyl Methacrylate (SBMA)

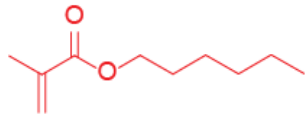
Hydrophobic Monomers



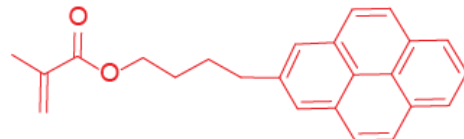
Lauryl Methacrylate (LMA)



Benzyl Methacrylate (BMA)

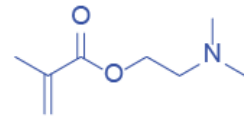


N-Hexyl Methacrylate (HMA)

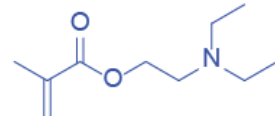


1-Pyrene Butyl Methacrylate (1PBMA)

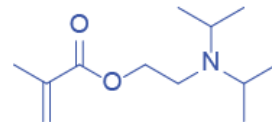
Charge Shifting Monomers



2-(Dimethylamino)ethyl Methacrylate (DMAEMA)

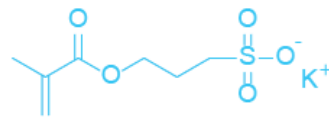


2-(Diethylamino)ethyl Methacrylate (DEAEMA)



2-(Diisopropylamino)ethyl Methacrylate (DiPAEMA)

Anionic Monomers



3-Sulfopropyl methacrylate potassium salt (3-SPM)

Statistical copolymer

1.1 million unique combinations

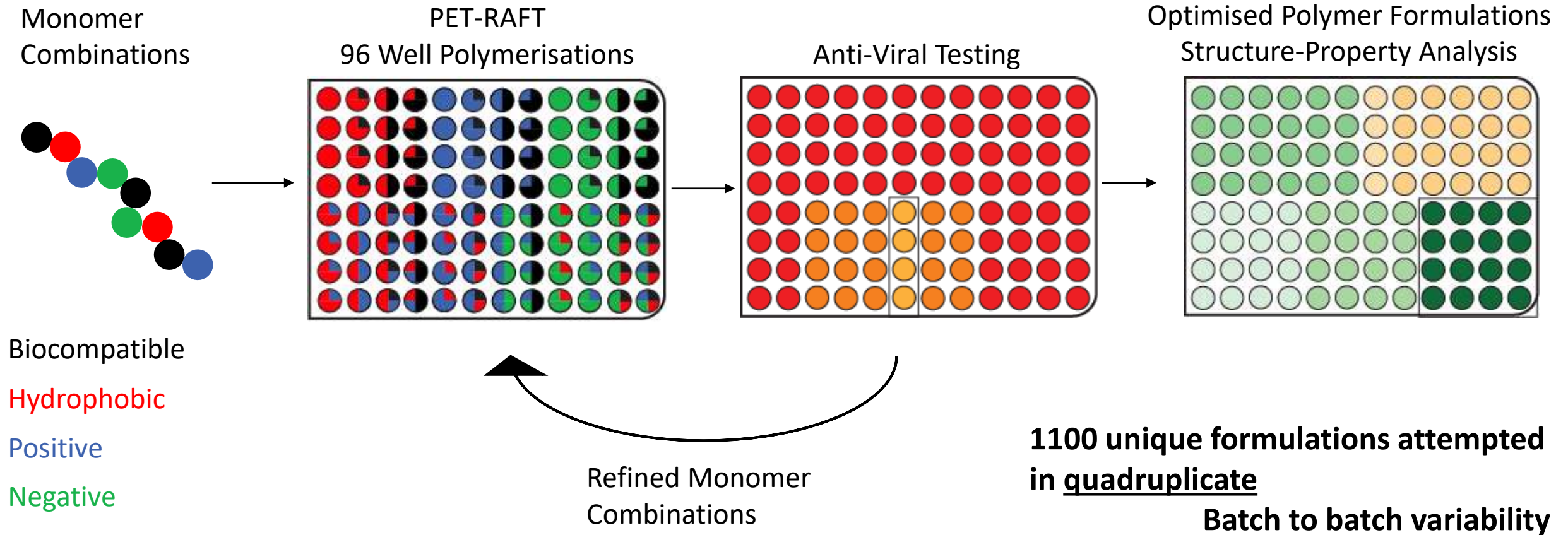
Traditional synthetic methods – 20 - 50 polymers...



Rapid polymer antiviral development



Dr Paul Denman



Antiviral Screening



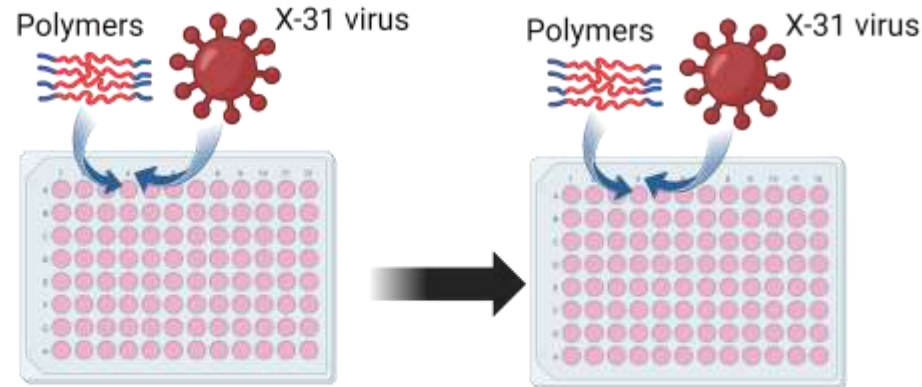
Hyle Mengist
(UQ)



A/Prof Kirsty
Short (UQ)

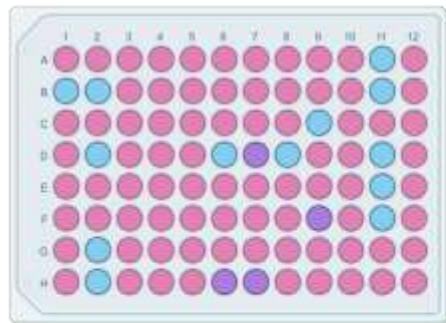


1) Seed MDCK cells the day prior to infection. In the second day, they should be confluent

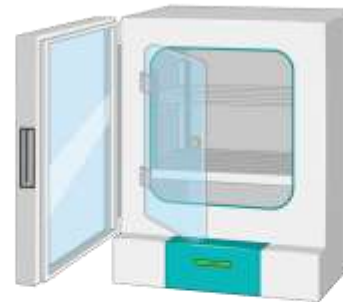


2) Mix X-31 virus and polymers in round bottomed 96 well plate

3) Incubate the virus-polymer mixture at 37 for 1 hour



4) Infect cells (in step 1) for 1 hour at 37 with virus-polymer mix from step 3. Remove infection media after 1 hour



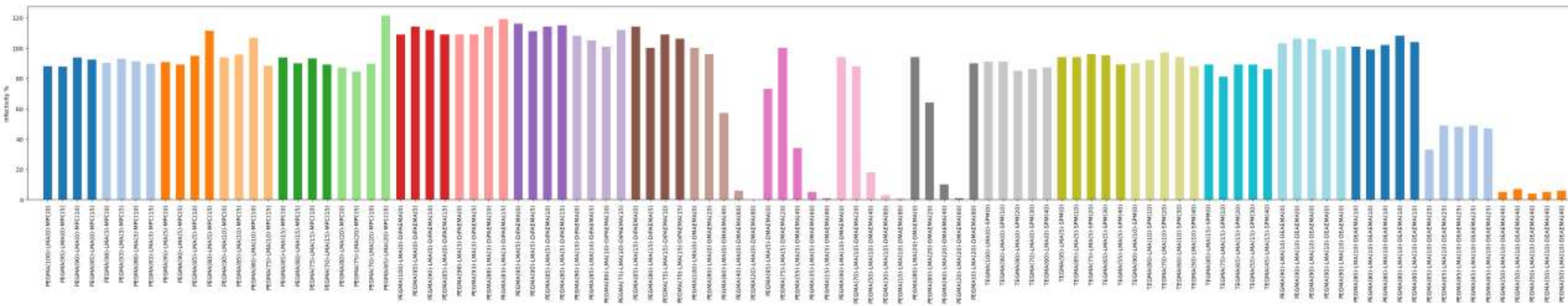
5) Add overlay media and incubate plates at 37 for 72 hours



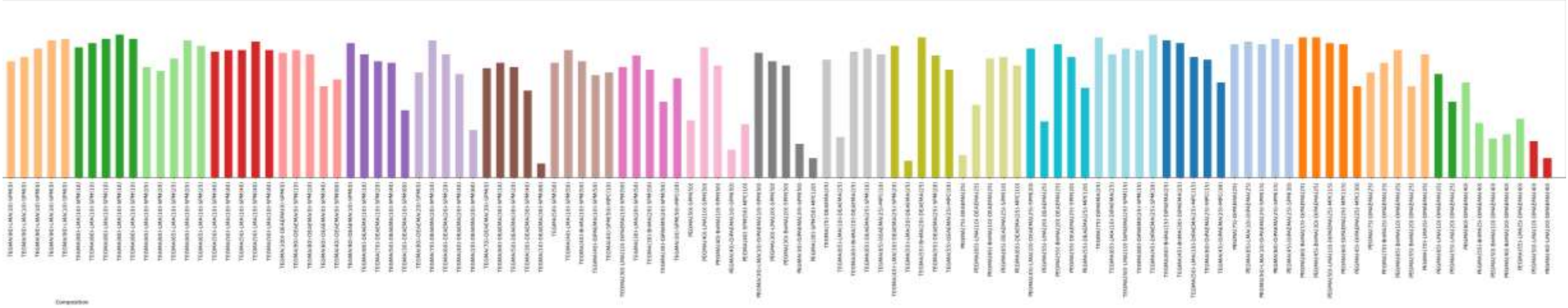
6) Fix cells, stain with Abs and read fluorescence

Antiviral (virucidal) screening

A lot of screening, a lot of misses...

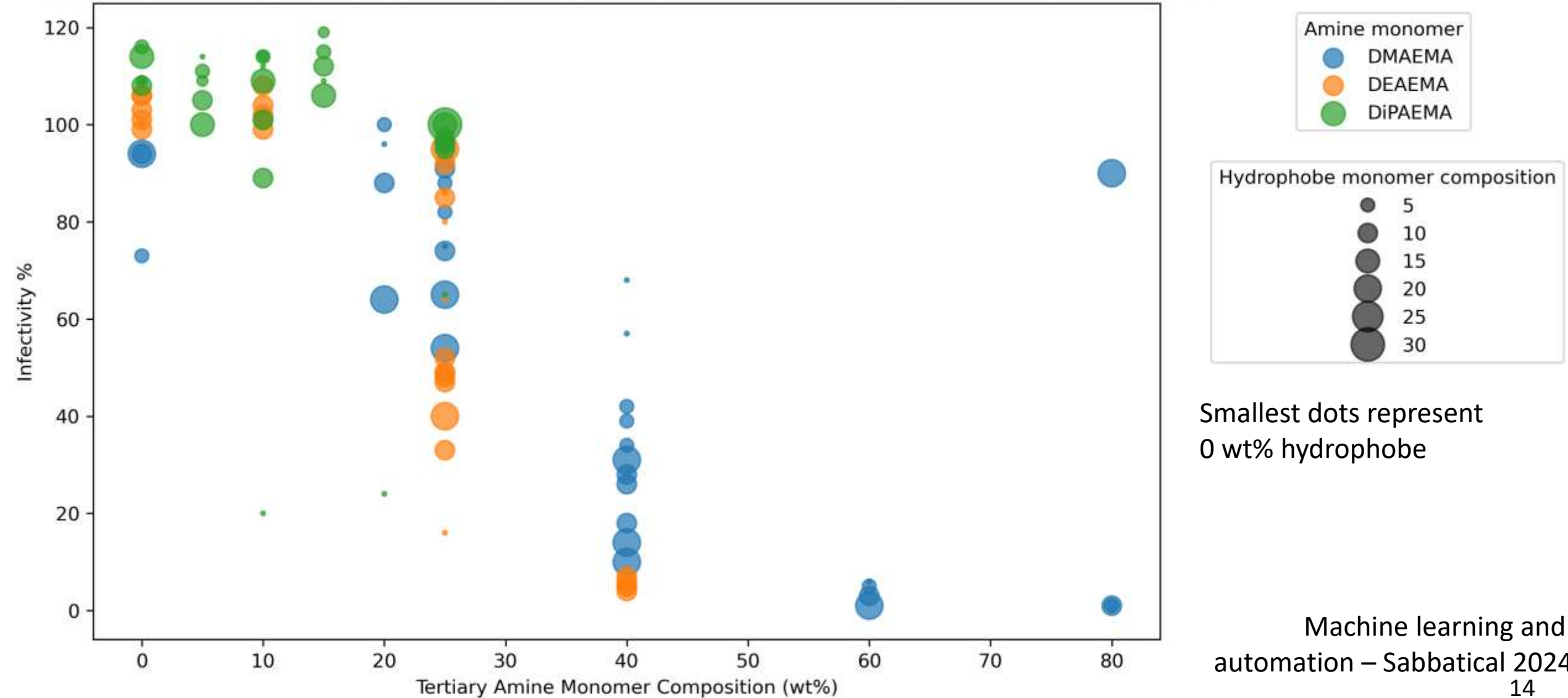


Antiviral Assay results for all polystyrenes



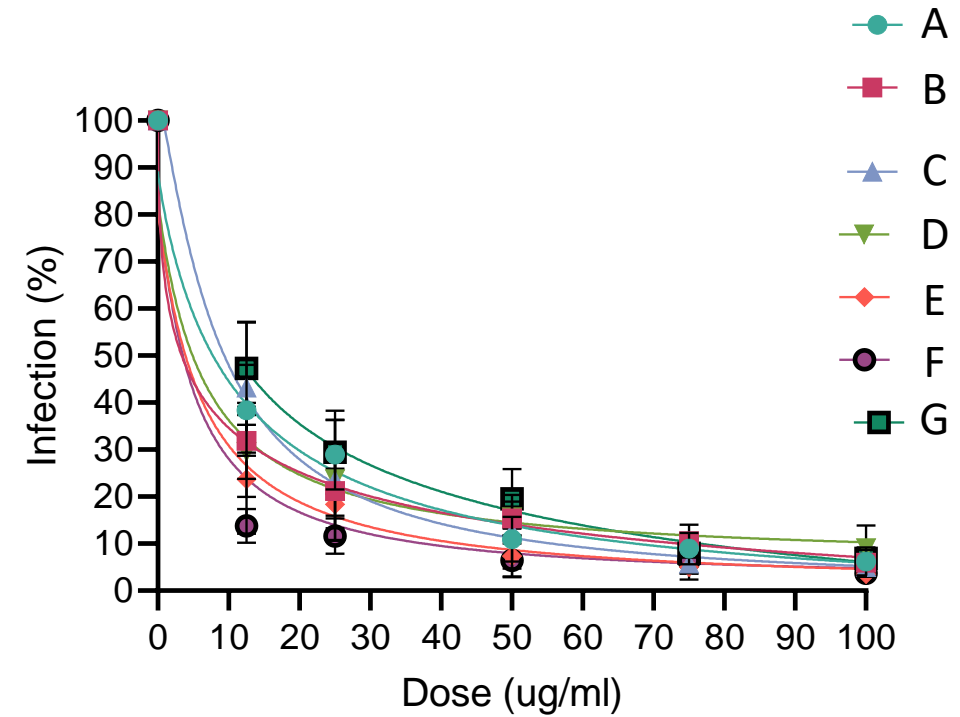
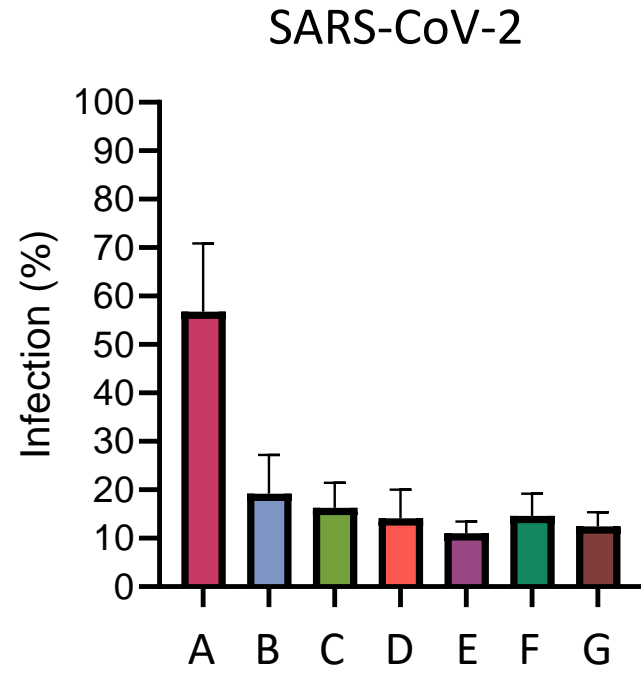
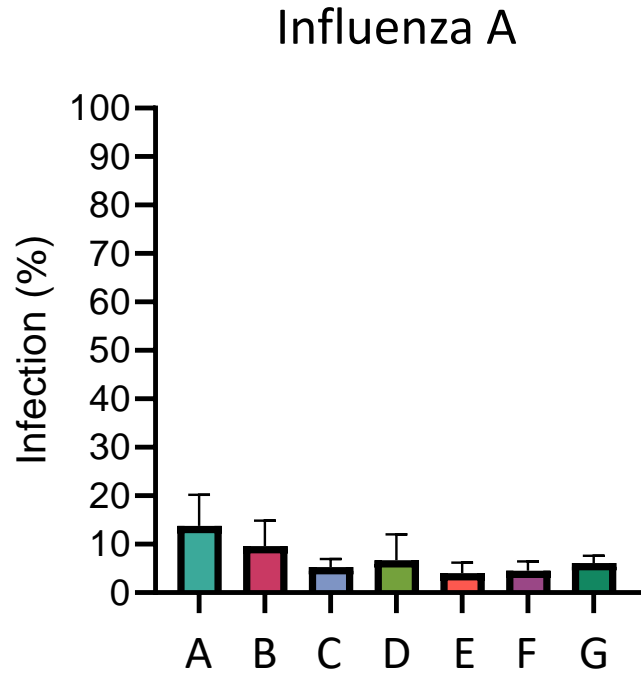
Learning from the complexity

Viral infectivity as a function of tertiary amine and hydrophobic monomer composition of copolymers



Smallest dots represent 0 wt% hydrophobe

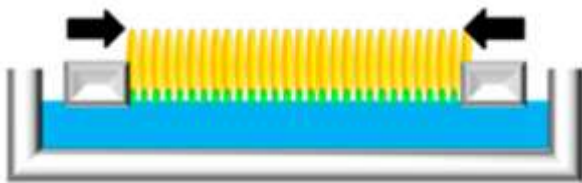
Early evidence of broad-spectrum efficacy



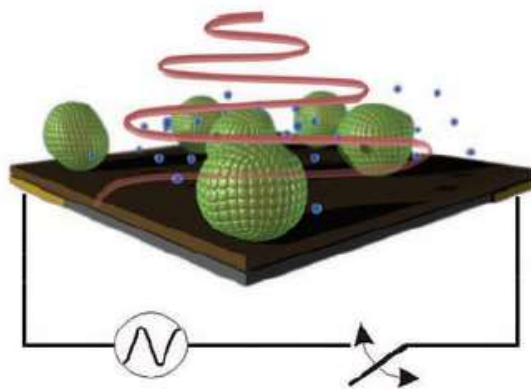
Conclusions

Viral membrane is a new target for polymers \longrightarrow Amphipathic polymer-membrane interactions

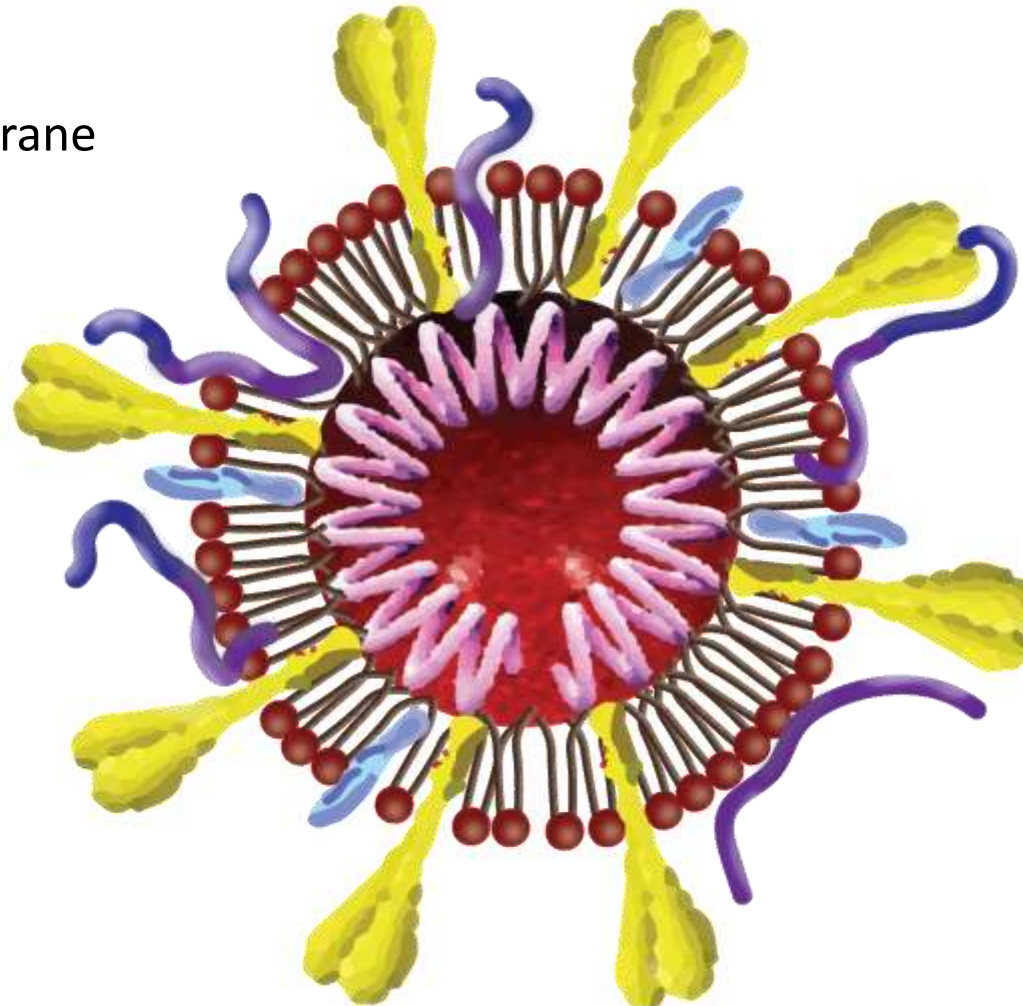
Tools for studying polymer-membrane interactions



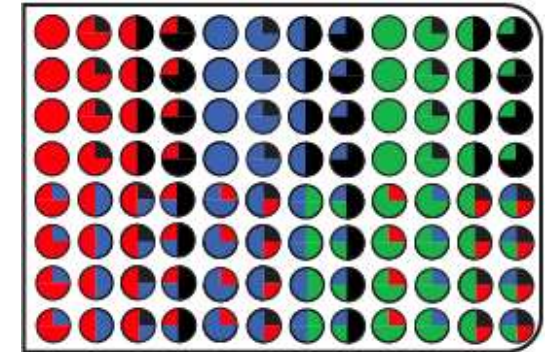
Langmuir Blodgett Films



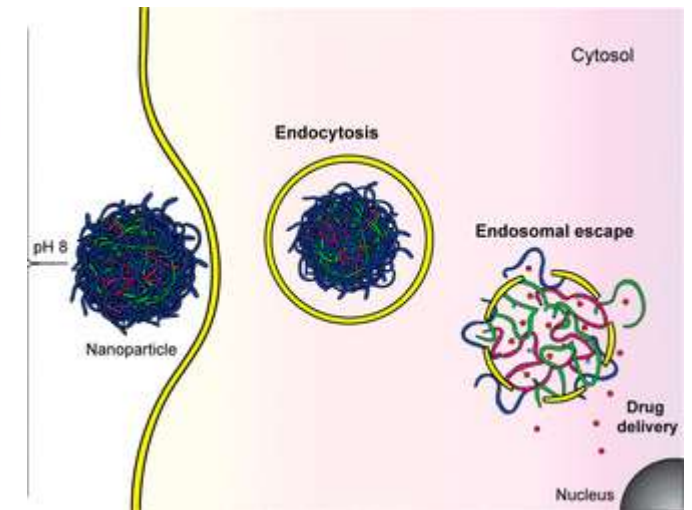
QCM-D



High-throughput polymer design



Applications beyond viruses...



Acknowledgements



Medicinal Molecules and Materials Group

Dr Paul Denman

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Dr Sandra Wiedbrauk

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Dr Venkat Narreddula

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Prof Christopher Barner-Kowollik

Prof Deepak Dubal

A/Prof James Blinco

Dr Aaron Micallef

Dr Levi Swann

Dr Heather McKinnon

Prof Kristofer Thurecht (UQ)

Dr Nick Fletcher (UQ)

Mr Hylemariam Mengist (UQ)

Dr Julian Sng (UQ)

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Dr Andrew Nelson (ANSTO)

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Dr Gishan Ratnayake (Metro South Health)



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Centre for Material Science

AINSE and ACNS

US DoD Peer Reviewed Medical Research Program

Korea Evaluation Institute of Industrial Technology (KEIT)



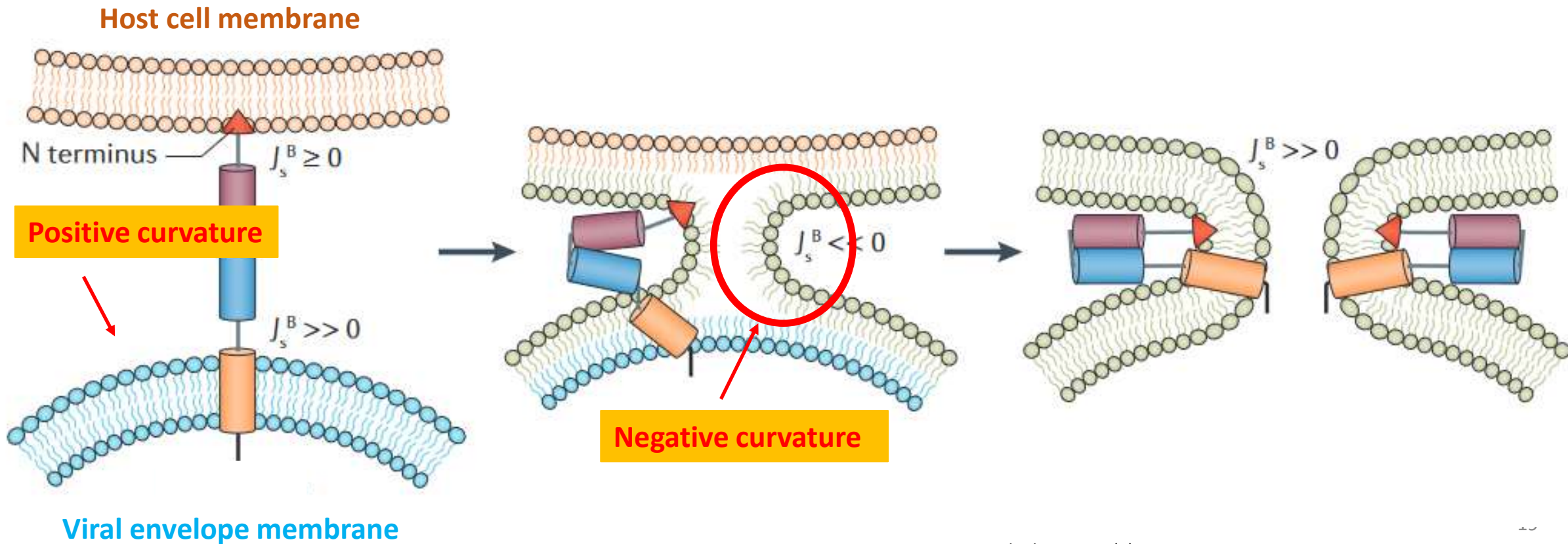
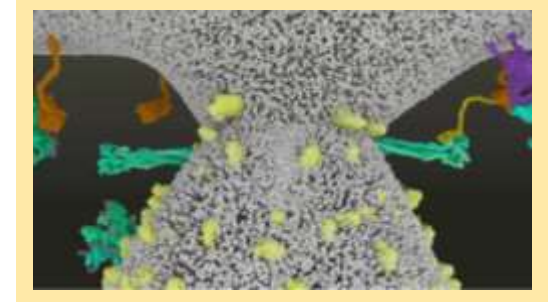
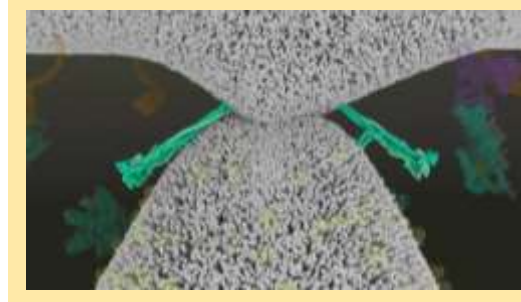
Centre for Materials Science

CRICOS No. 00213J



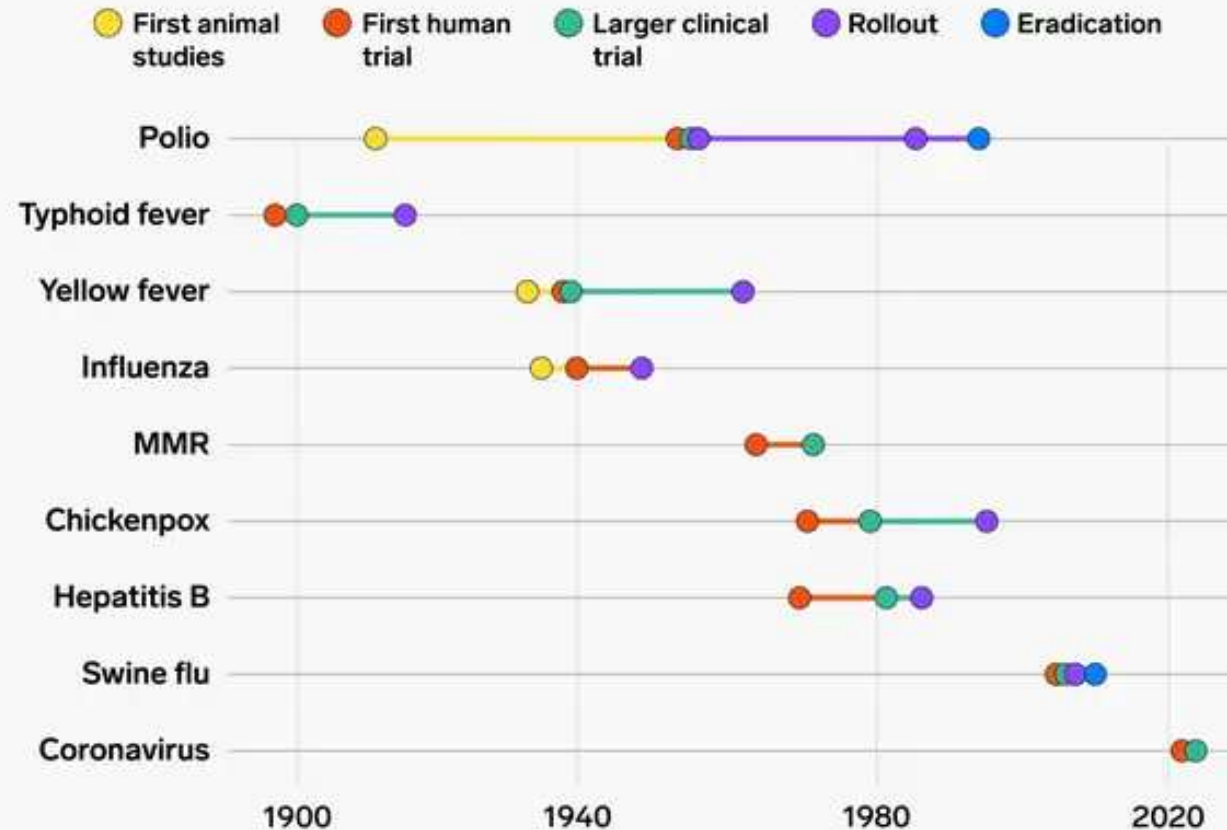


Membrane fusion energetics

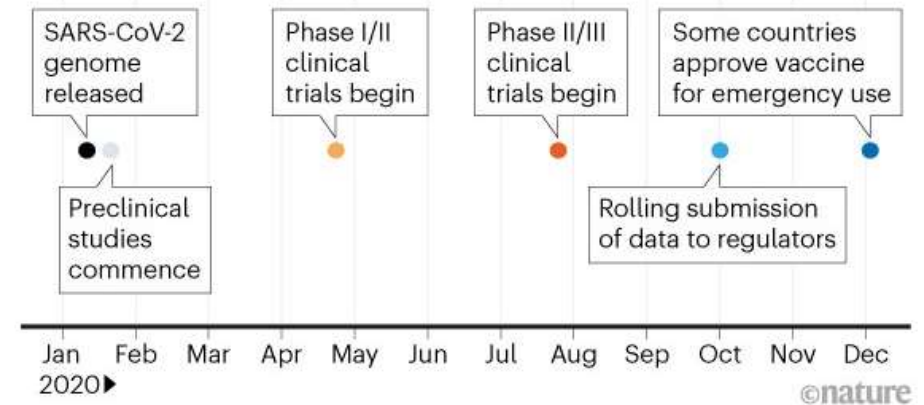


Why polymer antivirals?

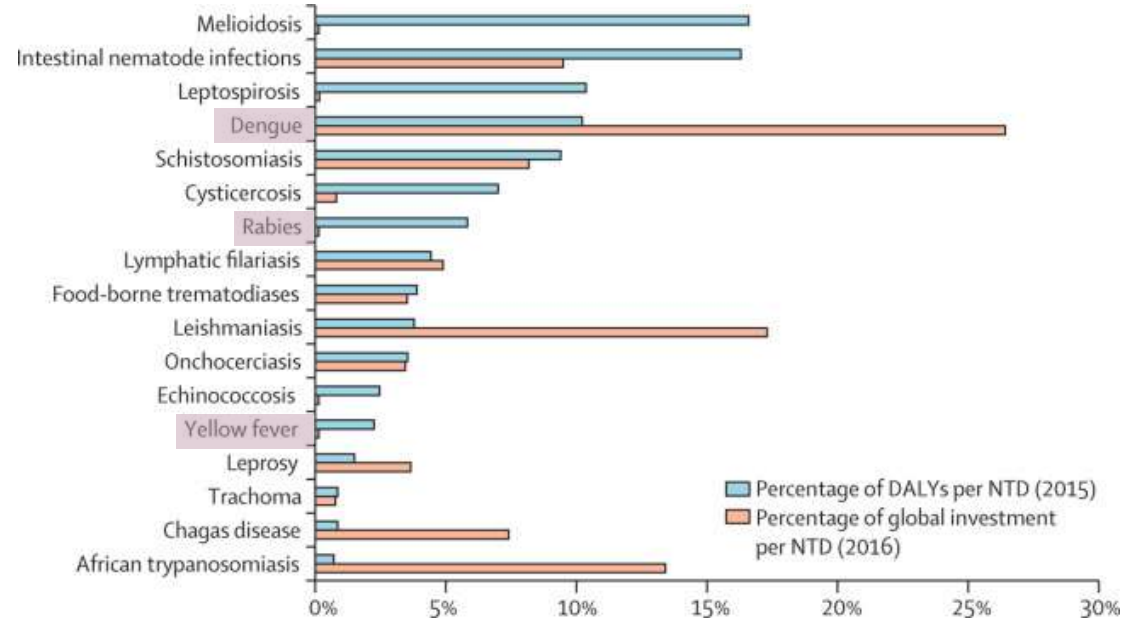
Comparing vaccine development throughout history



Sources: The College of Physicians of Philadelphia; WHO; CDC; National Institutes of Health; Business Insider



Neglected Tropical Diseases

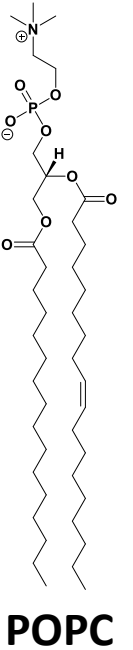
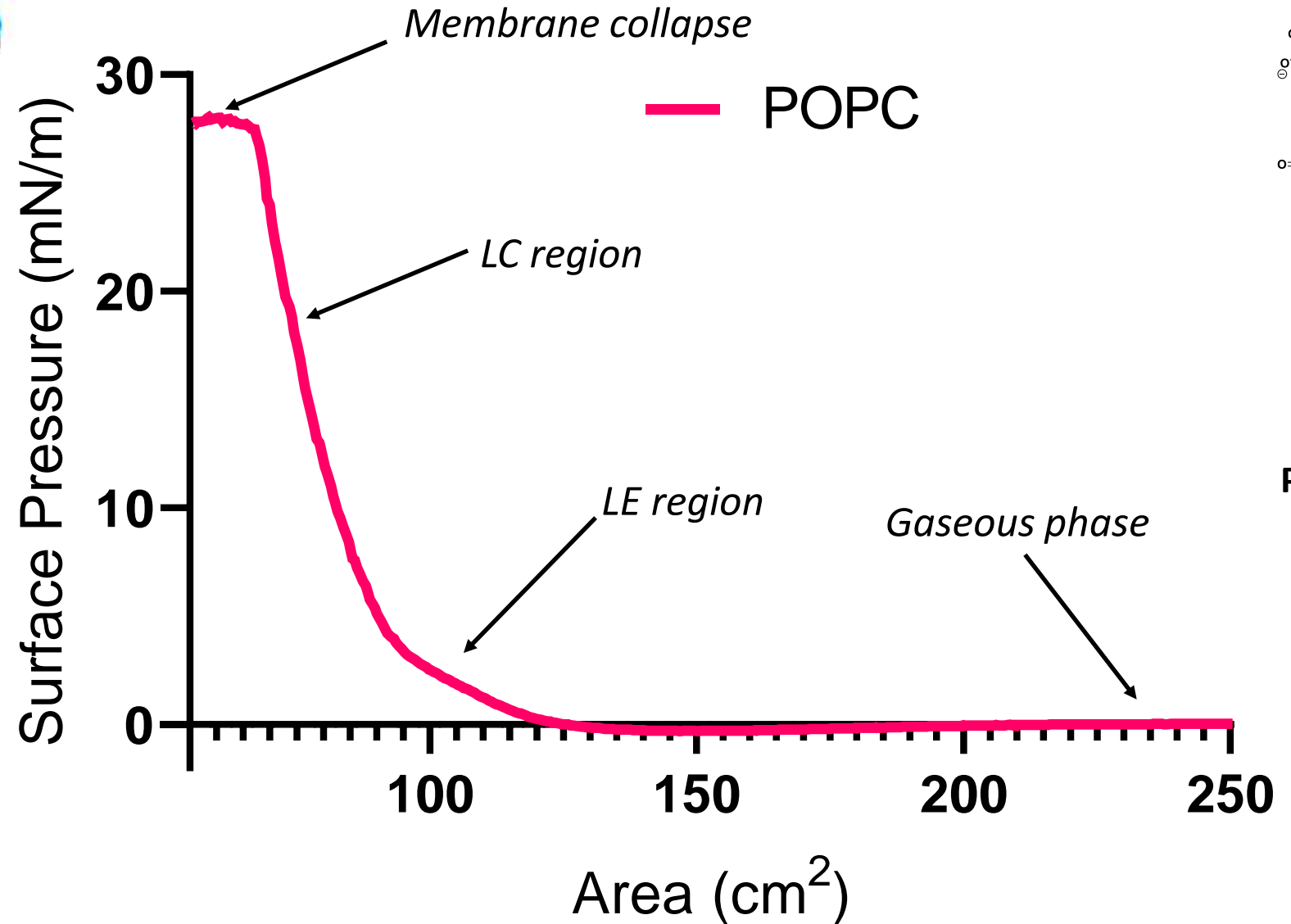
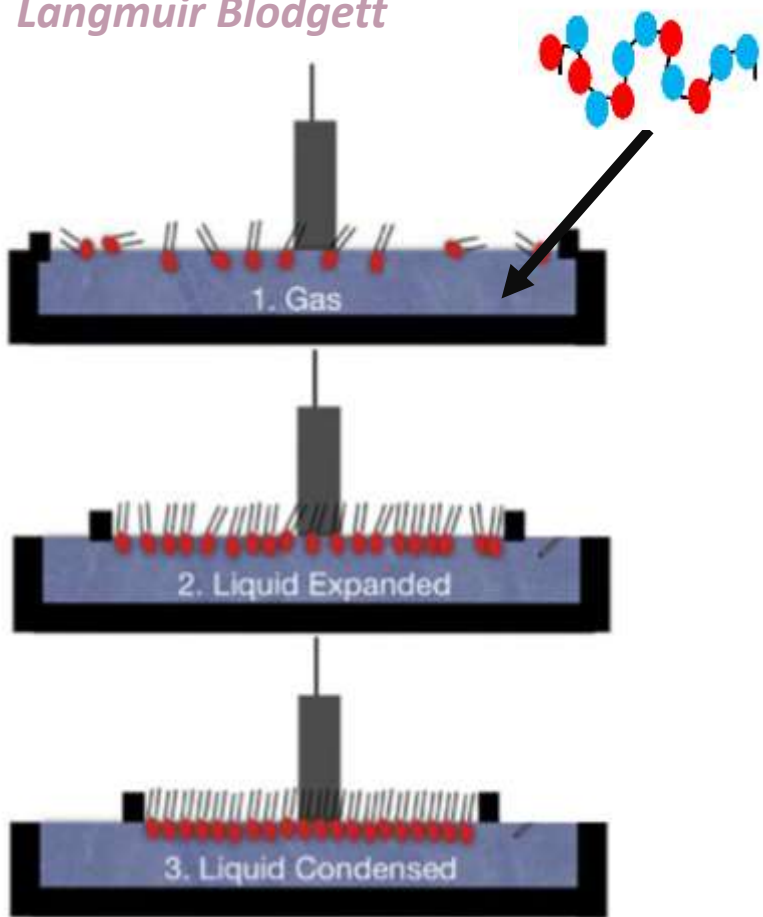


Ball, P., *Nature* **589**, 16-18 (2021)

Wiersinga, *The Lancet Infectious Diseases* **22**, e176-182, (2022)

Interactions with monolayer membranes

Langmuir Blodgett



Cytotoxicity Assay

