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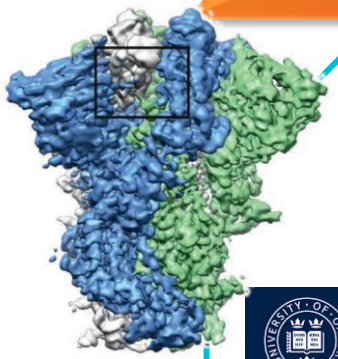
bicycle therapeutics

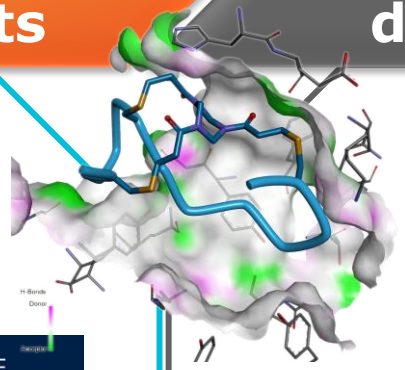
Bicycle®: A novel therapeutic modality for SARS-CoV-2

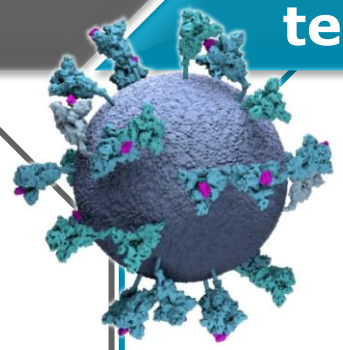
Leo James
MRC Laboratory of Molecular Biology
Cambridge

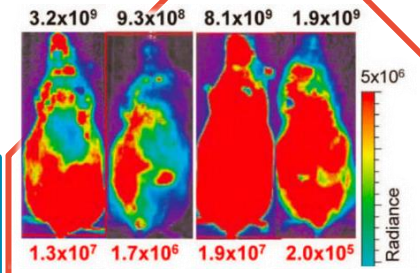
Industry - Academia Partnership

Protein & reagents → **Structural data** → ***In vitro* testing** → ***In vivo* testing**









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How do we make new antivirals quickly?

Small molecules

- Require extensive R&D infrastructure.
- Hit-to-drug success rate is low due to low chemical diversity, slow to develop
- Off target activity often leads to associated toxicities
- Not suited to drugging protein-protein interactions to block viral infection
- Good stability, long shelf-life

Antibodies

- Quick to identify, but costly to manufacture.
- High dose & requires intravenous injection in clinic by HCP.
- Rapid variant escape.
- Blocks generation of de novo B cell responses.
- Poor stability, requires cold chain distribution

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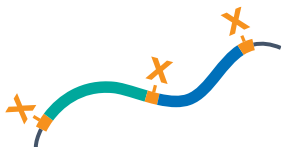
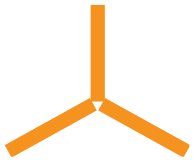
Bicycles - Drugs but not as we know them

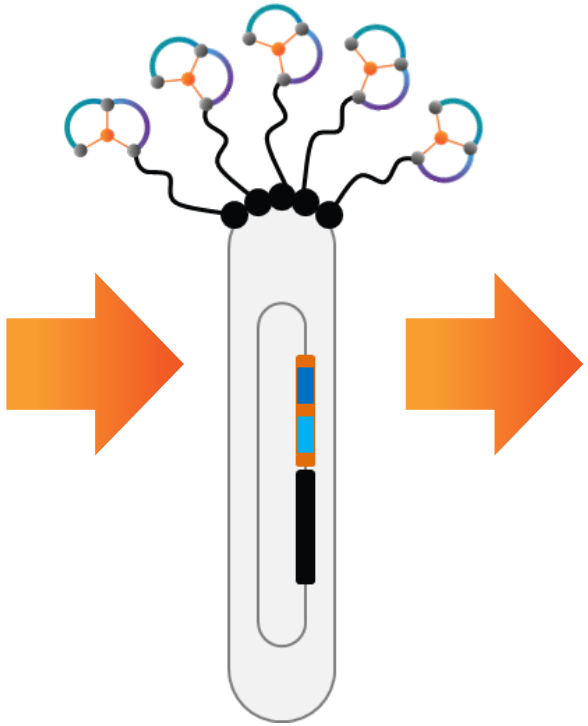


Short linear peptide

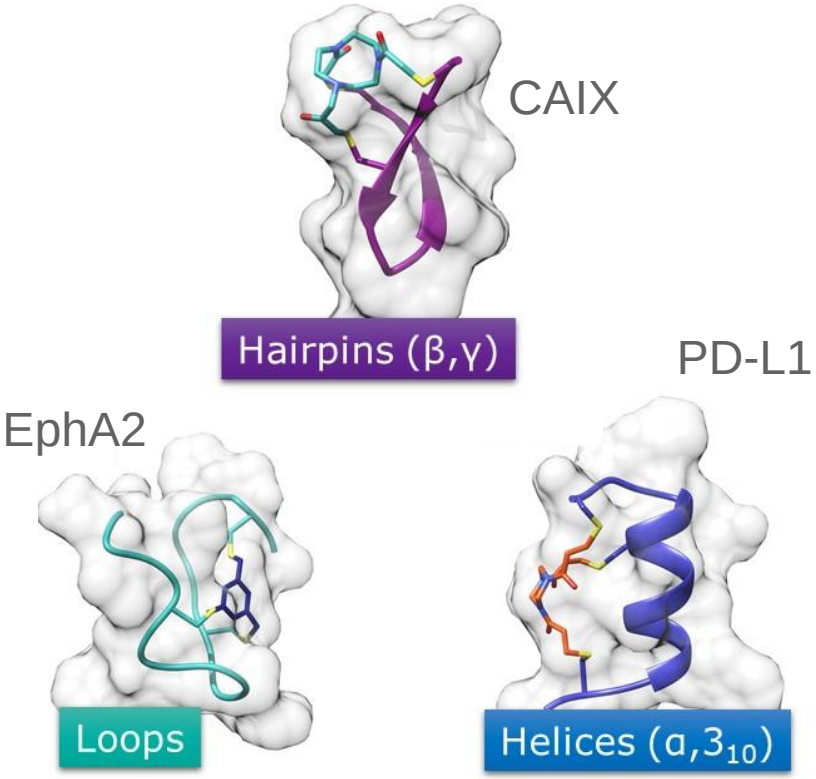
+



Scaffold



Diverse *Bicycle* phage library (>10^{20})



Biologically relevant 3D structures

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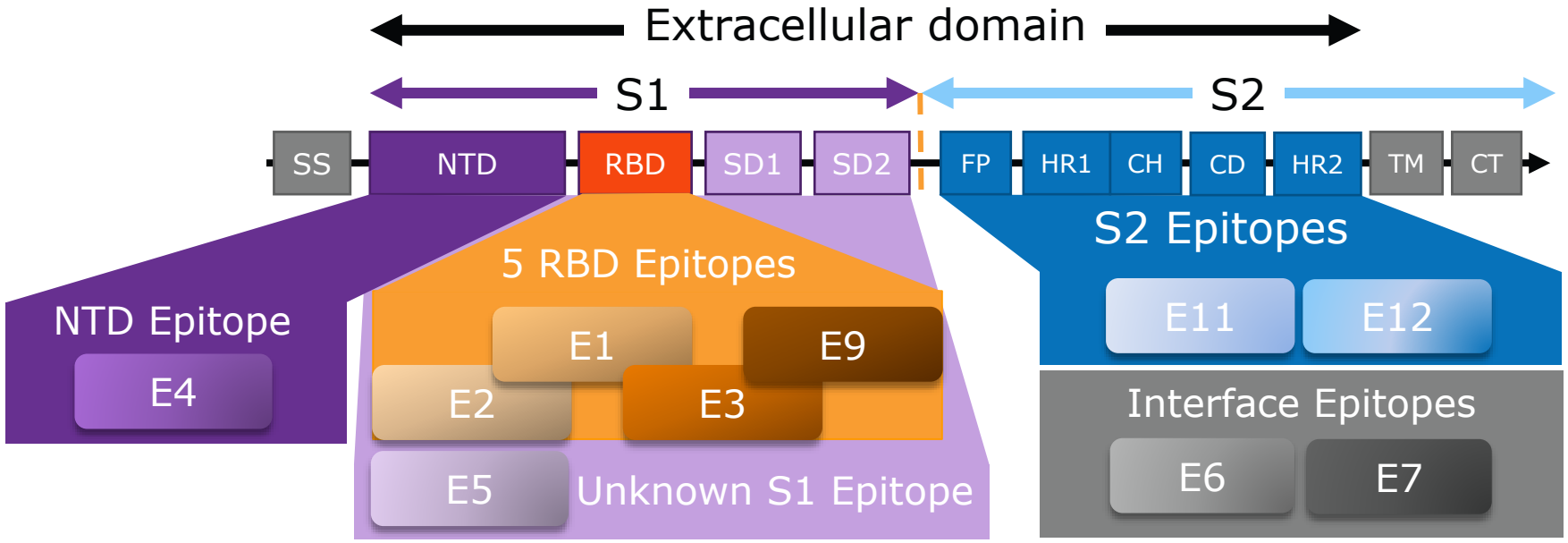
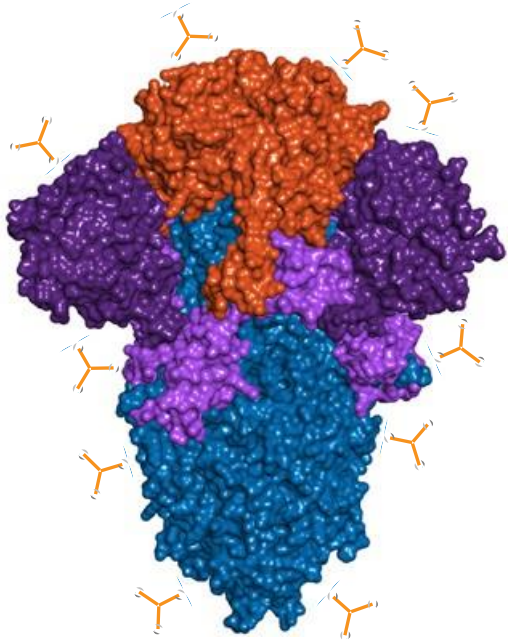
Bicycles against SARS-CoV-2 Spike

- Rapid discovery of binders to every part of Spike





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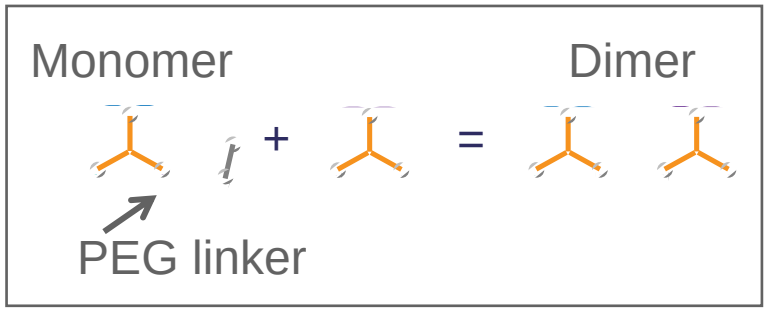
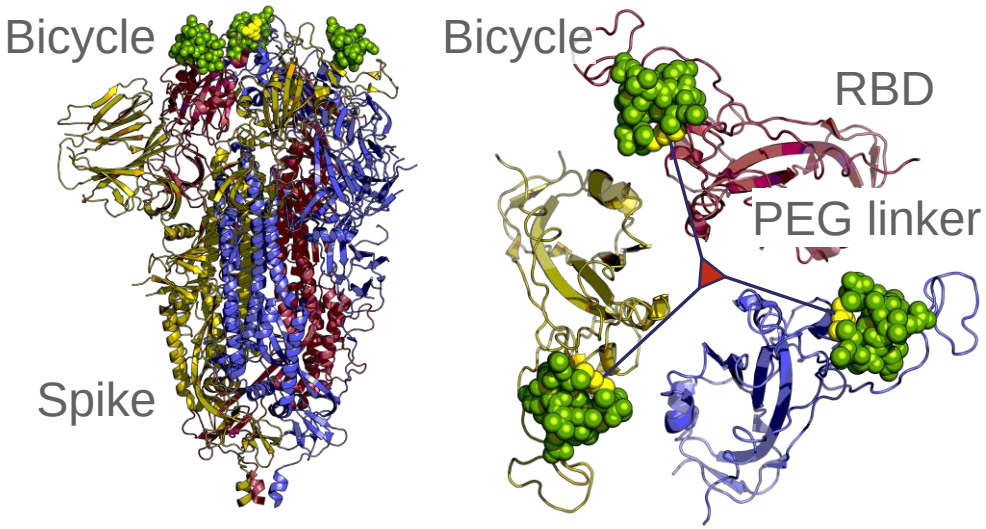
Multimerising *Bicycles* makes potent inhibitors





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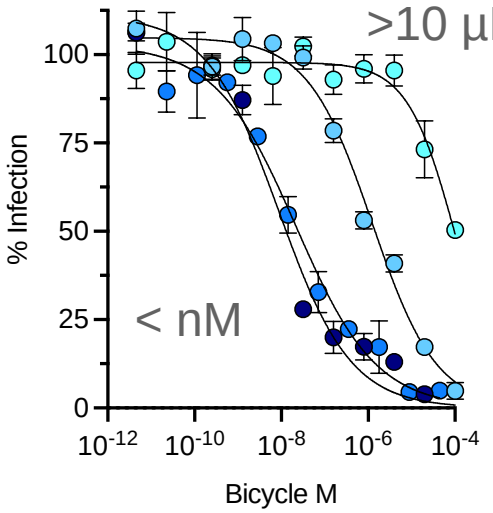
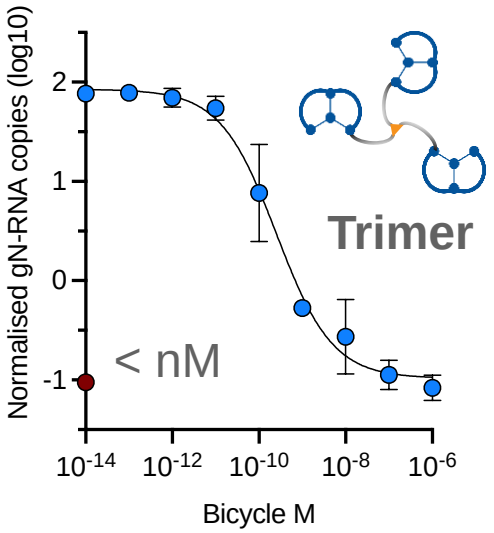
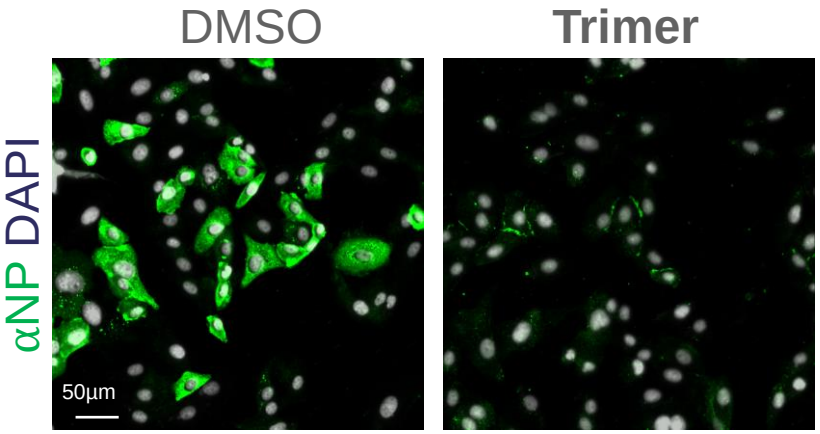




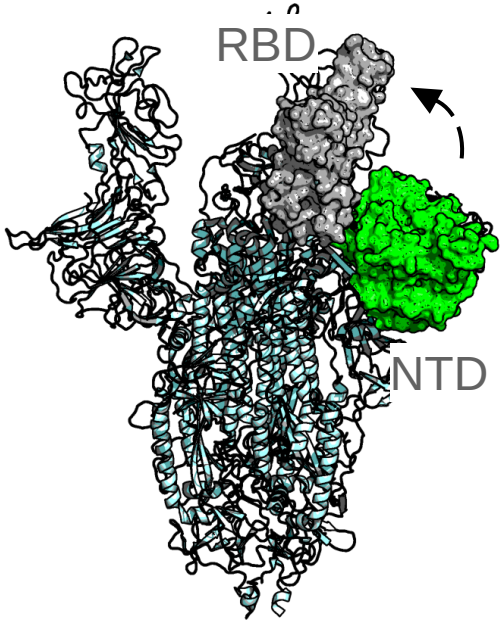
Pseudovirus

SARS-CoV-2



Biparatopic *Bicycles* are also potent inhibitors

'Open'



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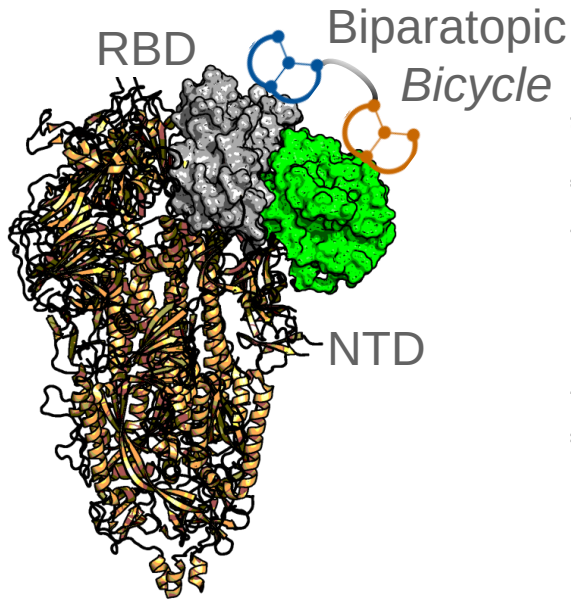
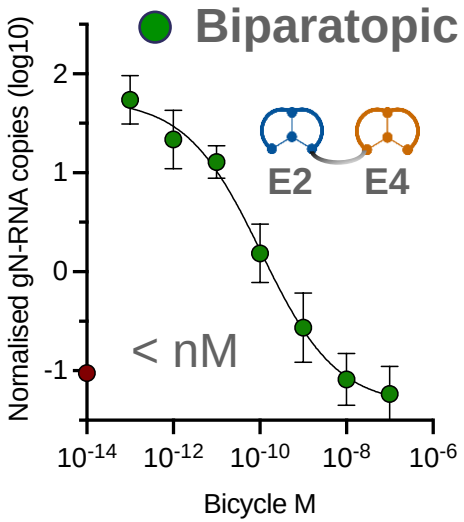
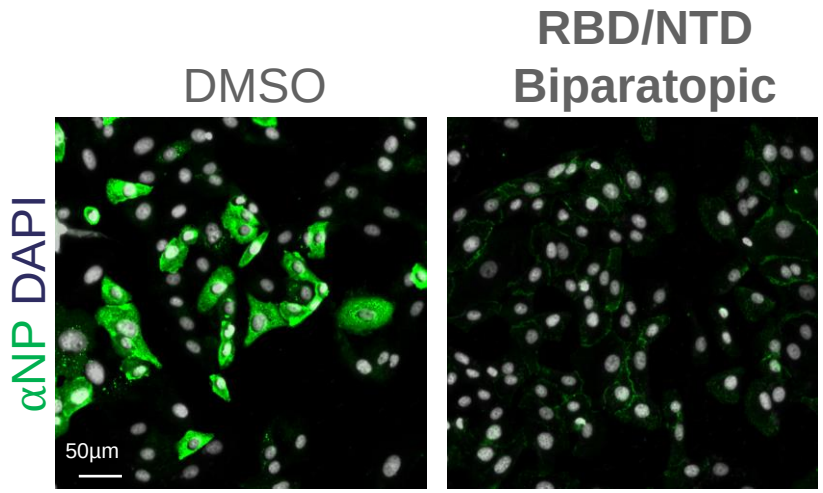




SARS-CoV-2



- Multimerising *Bicycles* against different epitopes allows binding to multiple domains simultaneously

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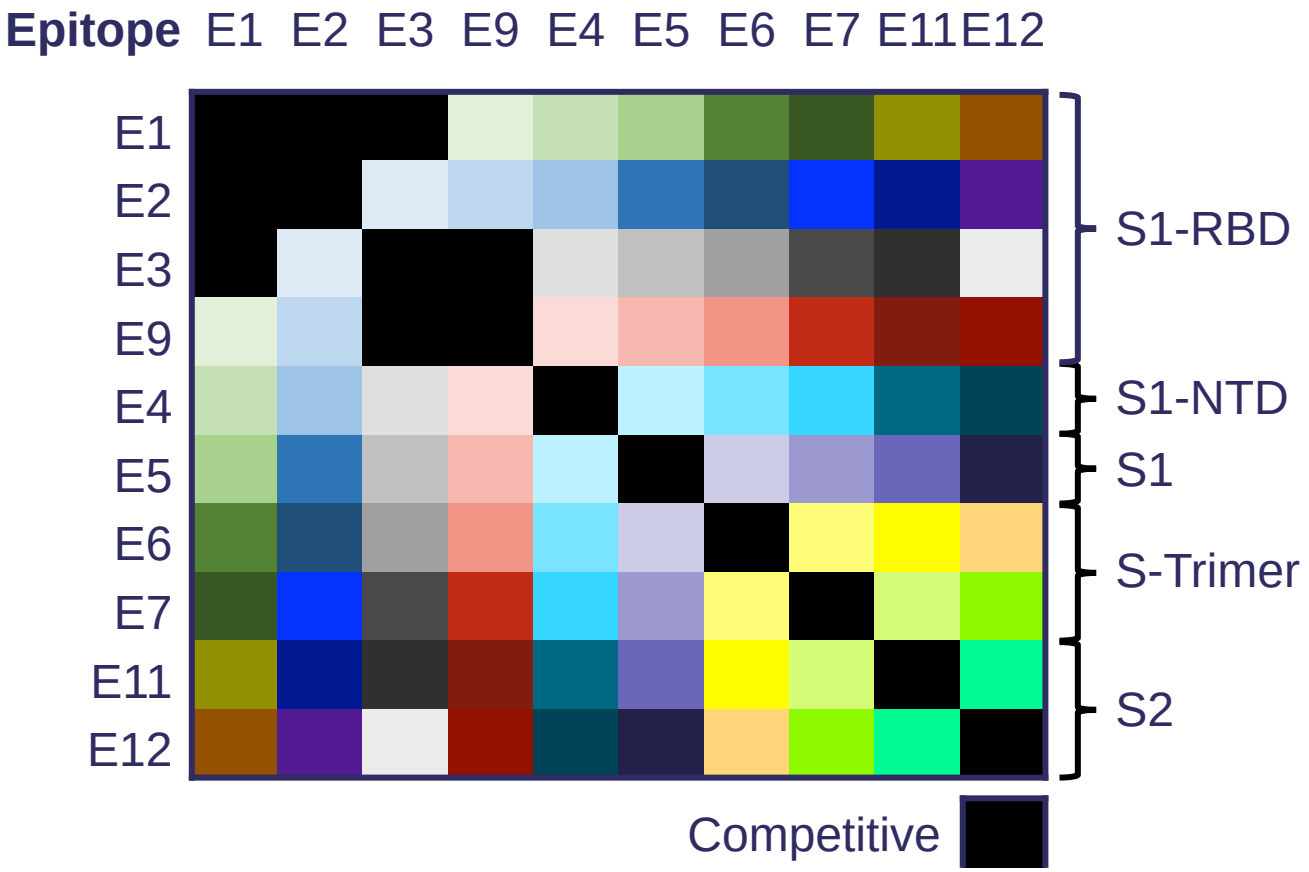
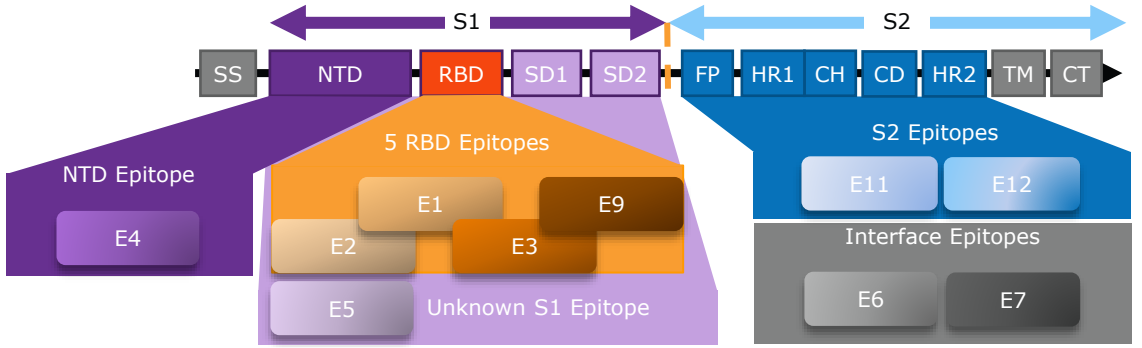
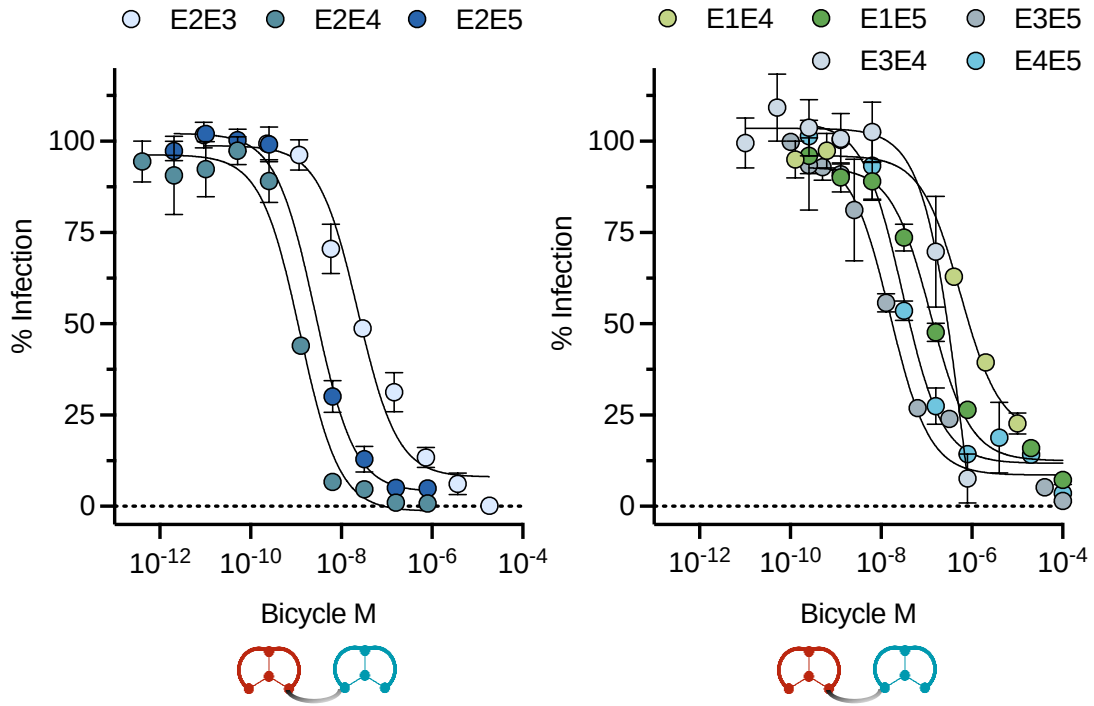
A combinatorial toolbox for bespoke inhibitors







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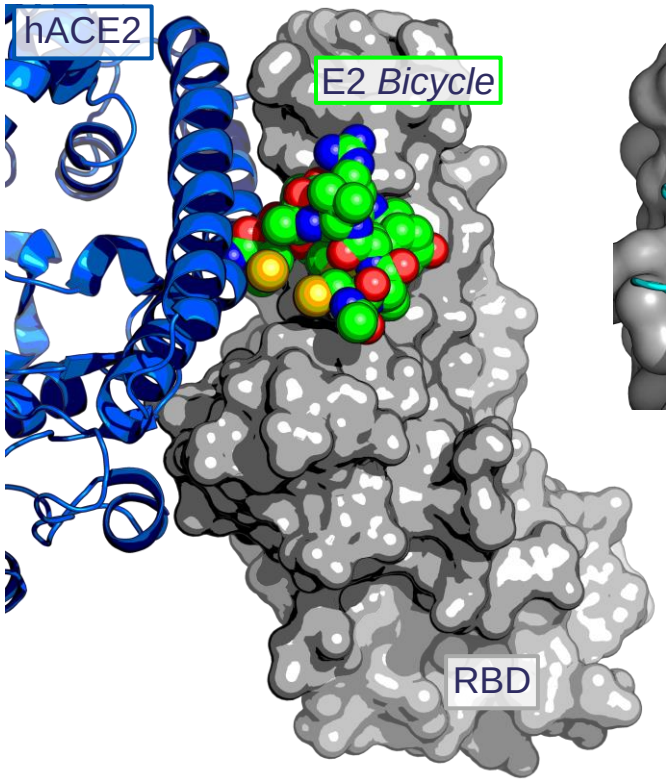
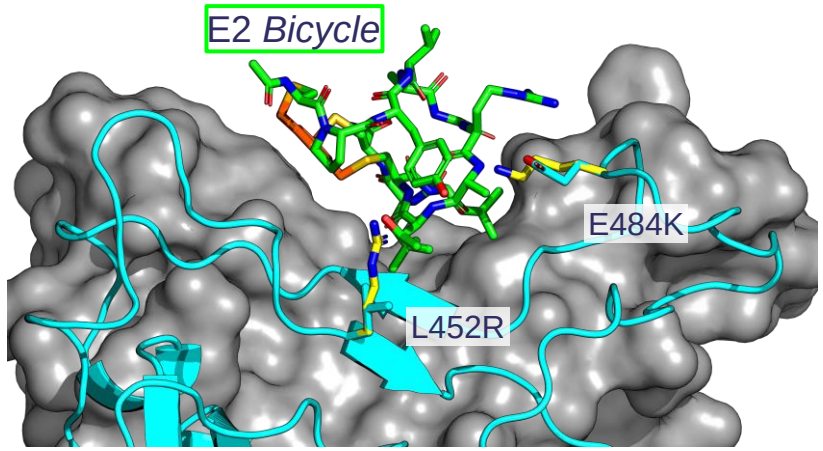
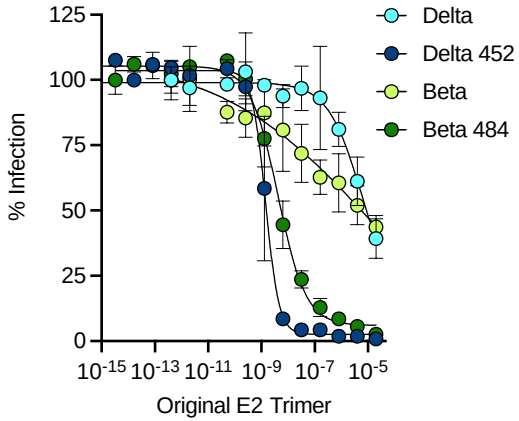
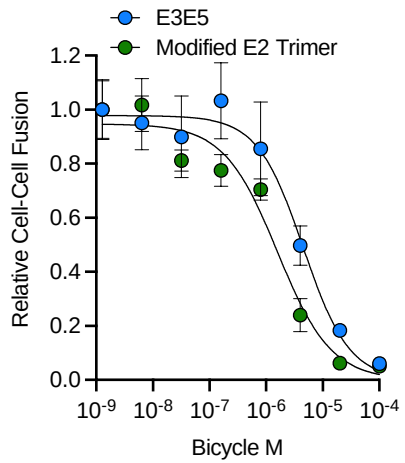
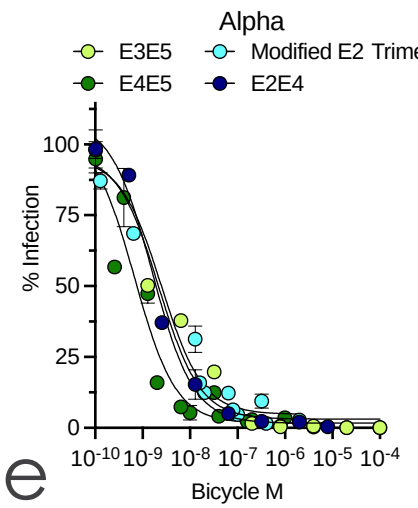
Multimer and Biparatopic *Bicycles* inhibit VOC

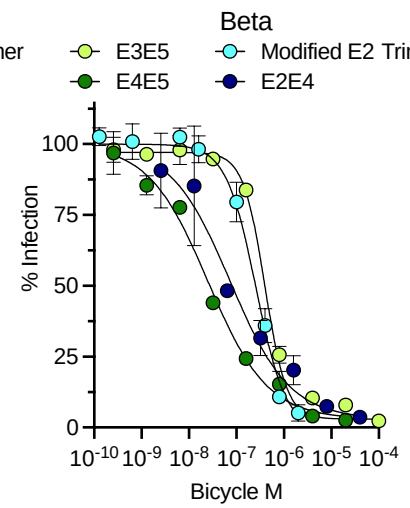


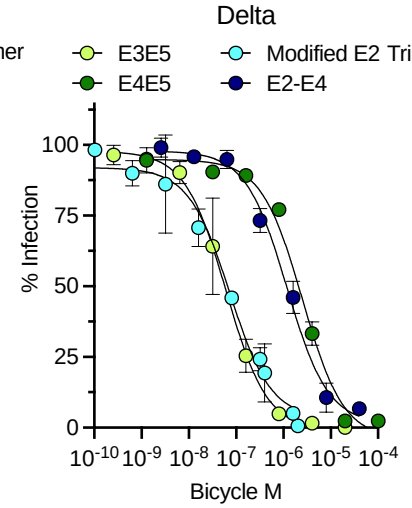


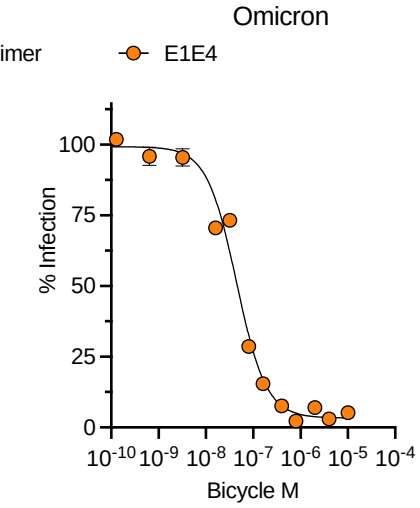












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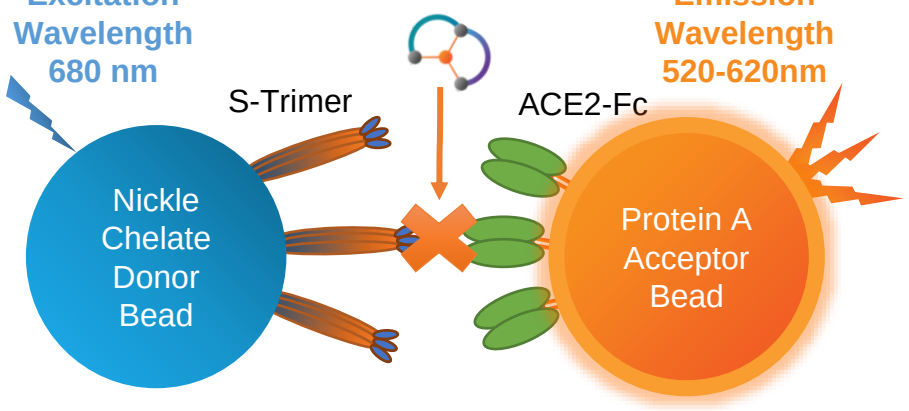
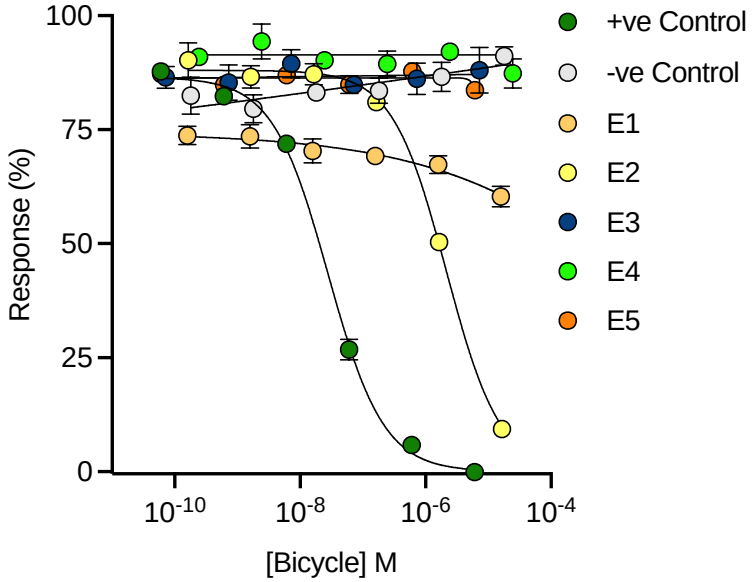
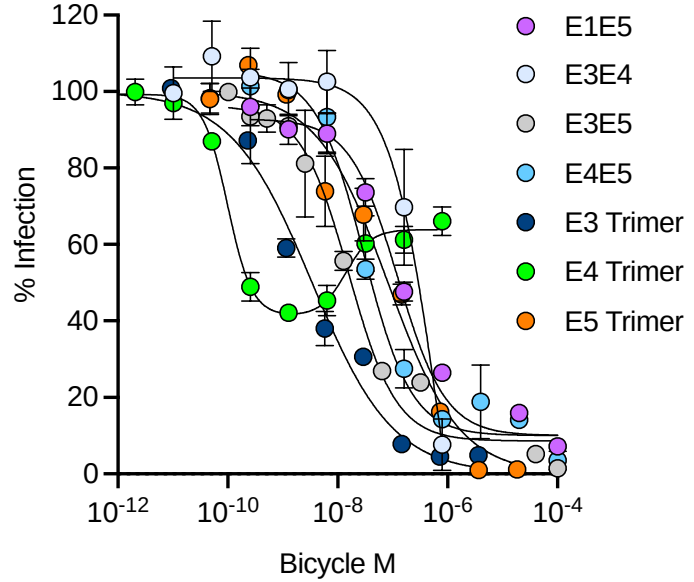
Non-ACE2-competitive *Bicycles* are inhibitors

ACE2 Competition





Pseudovirus Infection



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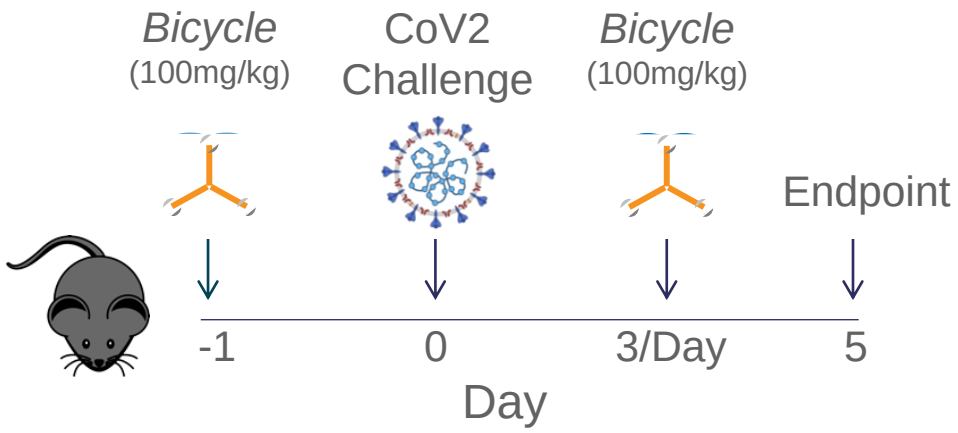
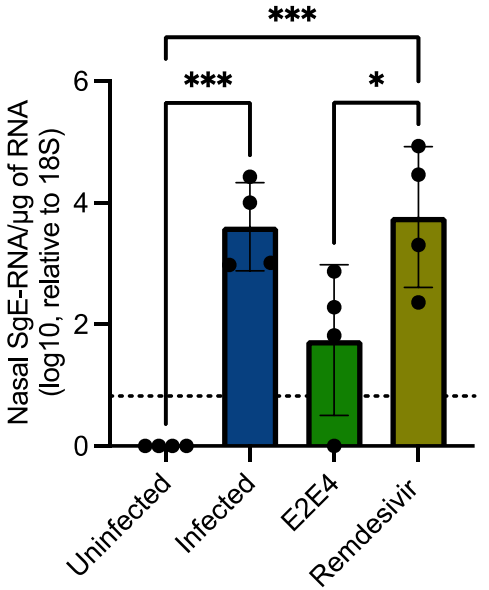
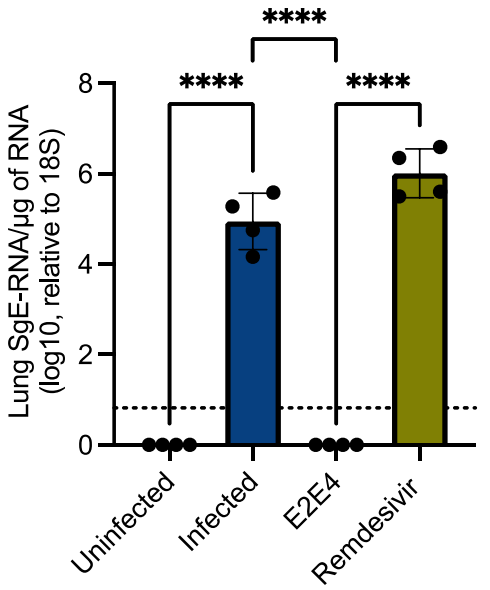
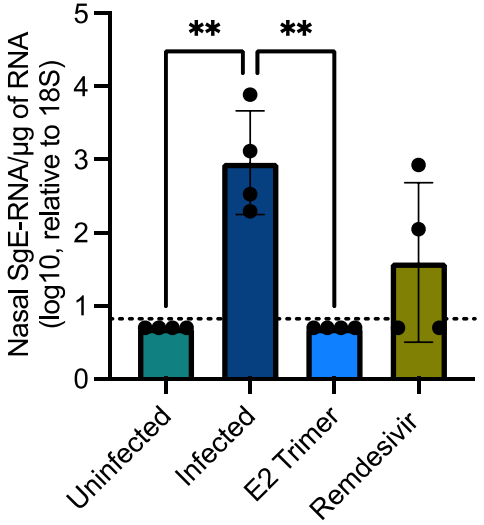
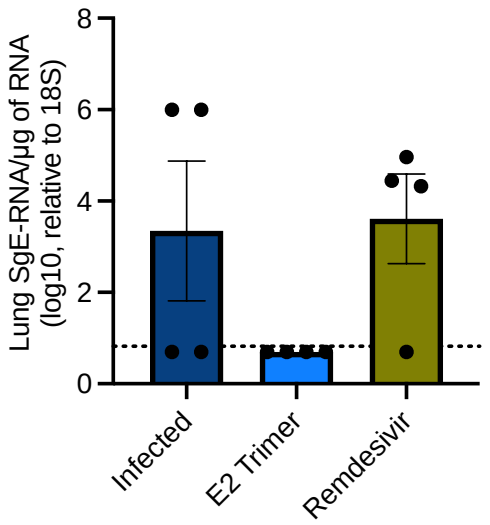
Bicycles inhibit SARS-CoV-2 in hACE2 mice

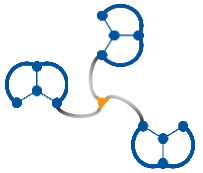












James Stewart

UNIVERSITY OF LIVERPOOL

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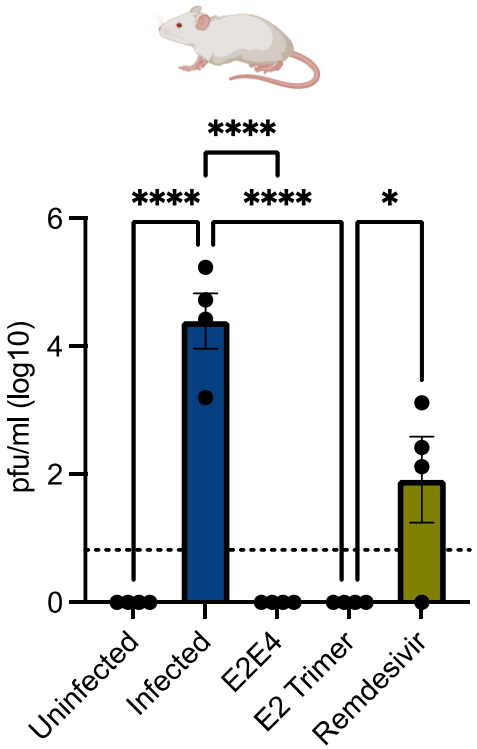
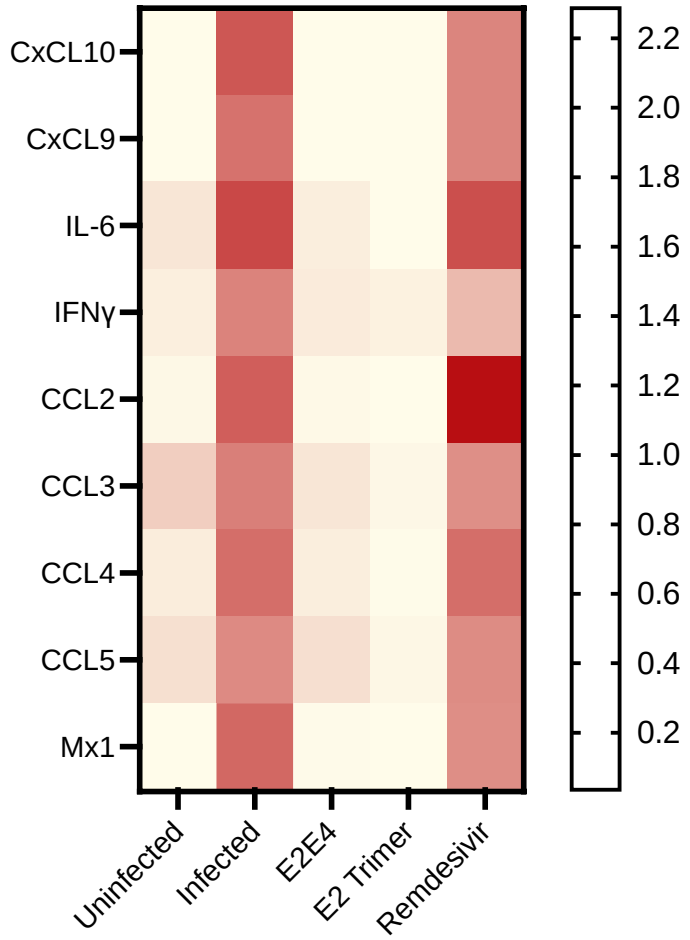
Bicycles inhibit SARS-CoV-2 in mice and hamsters

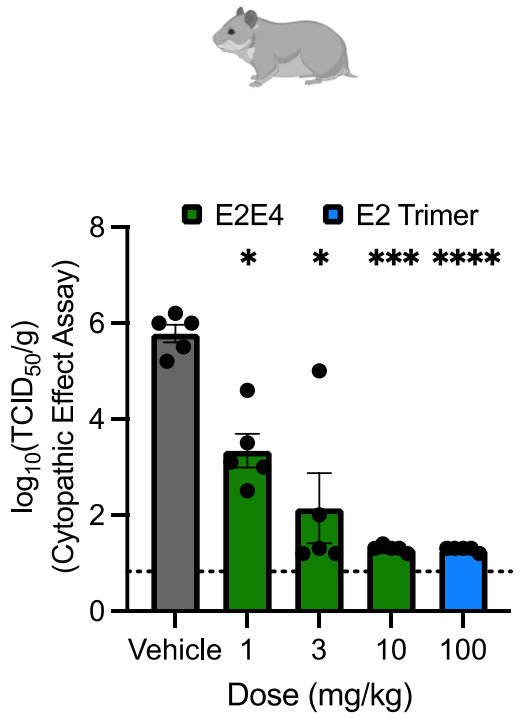
Lung Plaque Assay



Lung Cytokine Transcripts



Cytopathic Assay



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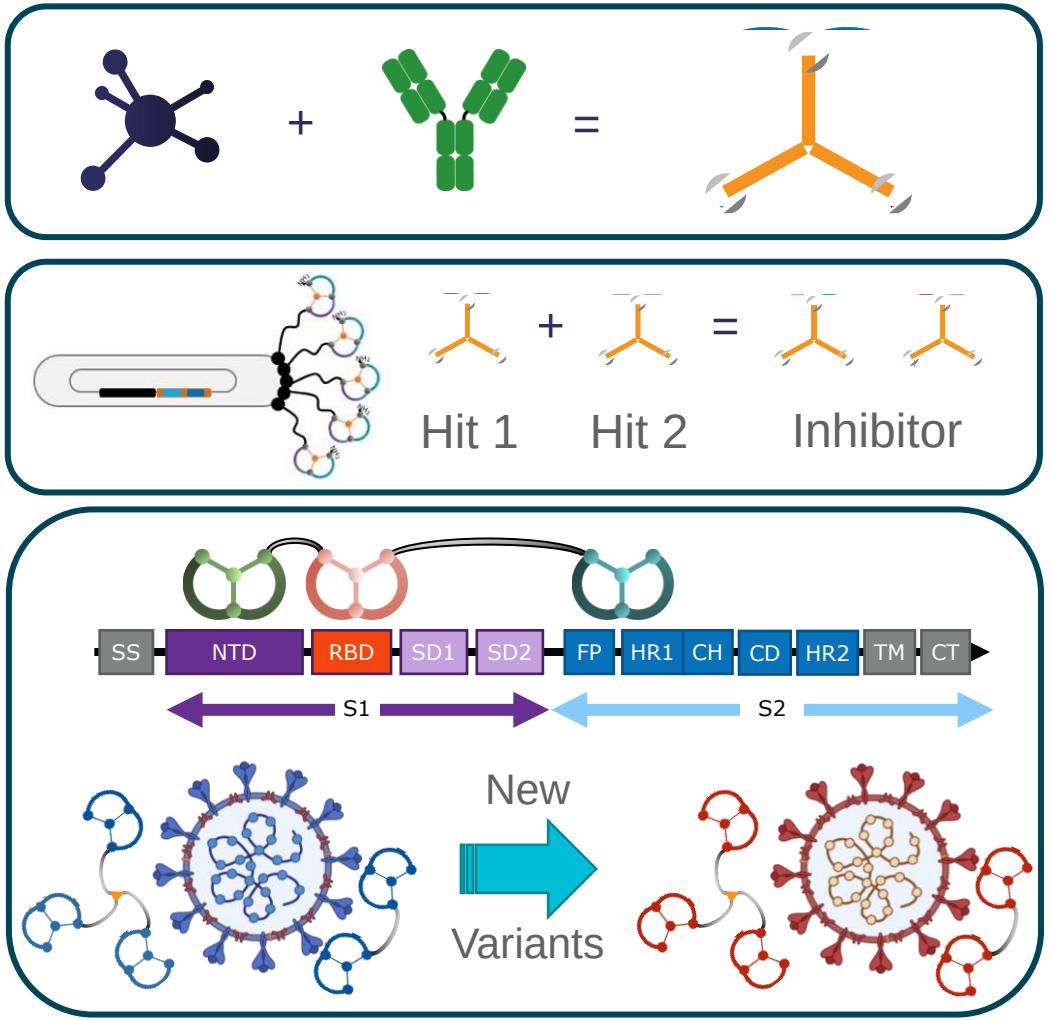
Viroclinics biosciences

Bicycles: potent antivirals made fast

- Bicycles combine the advantages of small molecules and antibodies

- Hits to new targets can be identified quickly
- Multimerising hits generates potent inhibitors

- Modular design:
  - Build inhibitors to specific domain(s)
  - Novel inhibitory mechanisms
  - Rapidly reconfigure to address new variants



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Acknowledgements

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