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

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Protein & reagents

Structural data

In vitro testing

In vivo testing
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.
*Bicycles*- Drugs but not as we know them

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

Biologically relevant 3D structures
Bicycles against SARS-CoV-2 Spike

- Rapid discovery of binders to every part of Spike
Multimerising *Bicycles* makes potent inhibitors

![Diagram showing the multimerisation of bicycles](image)

**Pseudovirus**
- **Monomer**
- **Dimer**
- **Trimer**
- **Tetramer**

**SARS-CoV-2**
- **DMSO**
- **Trimer**

**Cartoon images and graphs**
- Bicycle M vs. % Infection
- Bicycle M vs. Normalised gN-RNA copies (log10)

**Legend**
- Bicycle
- Spike
- RBD
- PEG linker
- MRC Laboratory of Molecular Biology
- bicycle therapeutics
Biparatopic **Bicycles** are also potent inhibitors

Bicycles are also potent inhibitors of SARS-CoV-2.

Multimerising **Bicycles** against different epitopes allows binding to multiple domains simultaneously.
A combinatorial toolbox for bespoke inhibitors

Epitope E1 E2 E3 E9 E4 E5 E6 E7 E11 E12

Competitive

S1-RBD
S1-NTD
S1
S-Trimer
S2

Stem
NTD
RBD
Spike
SD1
SD2

S1
S2

Competitive

Bicycle M

% Infection

E2E3 E2E4 E2E5

E1E4 E1E5 E3E5

E3E4 E4E5
Multimer and Biparatopic Bicycles inhibit VOC
Non-ACE2-competitive *Bicycles* are inhibitors

ACE2 Competition

Pseudovirus Infection

ACE2 Competition

Pseudovirus Infection
**Bicycles inhibit SARS-CoV-2 in hACE2 mice**

- **Bicycle (100mg/kg)**
- **CoV2 Challenge**
- **Bicycle (100mg/kg)**

Endpoint

Day

-1 0 3/Day 5

**Infected**

**E2 Trimer**

**E2E4**

**James Stewart**

**University of Liverpool**

**MRC Laboratory of Molecular Biology**

**bicycle therapeutics**
Bicycles inhibit SARS-CoV-2 in mice and hamsters

**Lung Plaque Assay**

**Lung Cytokine Transcripts**

**Cytopathic Assay**

![Image of plaque assay results](image)

![Image of cytokine transcript levels](image)

![Image of cytopathic effect assay](image)
**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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