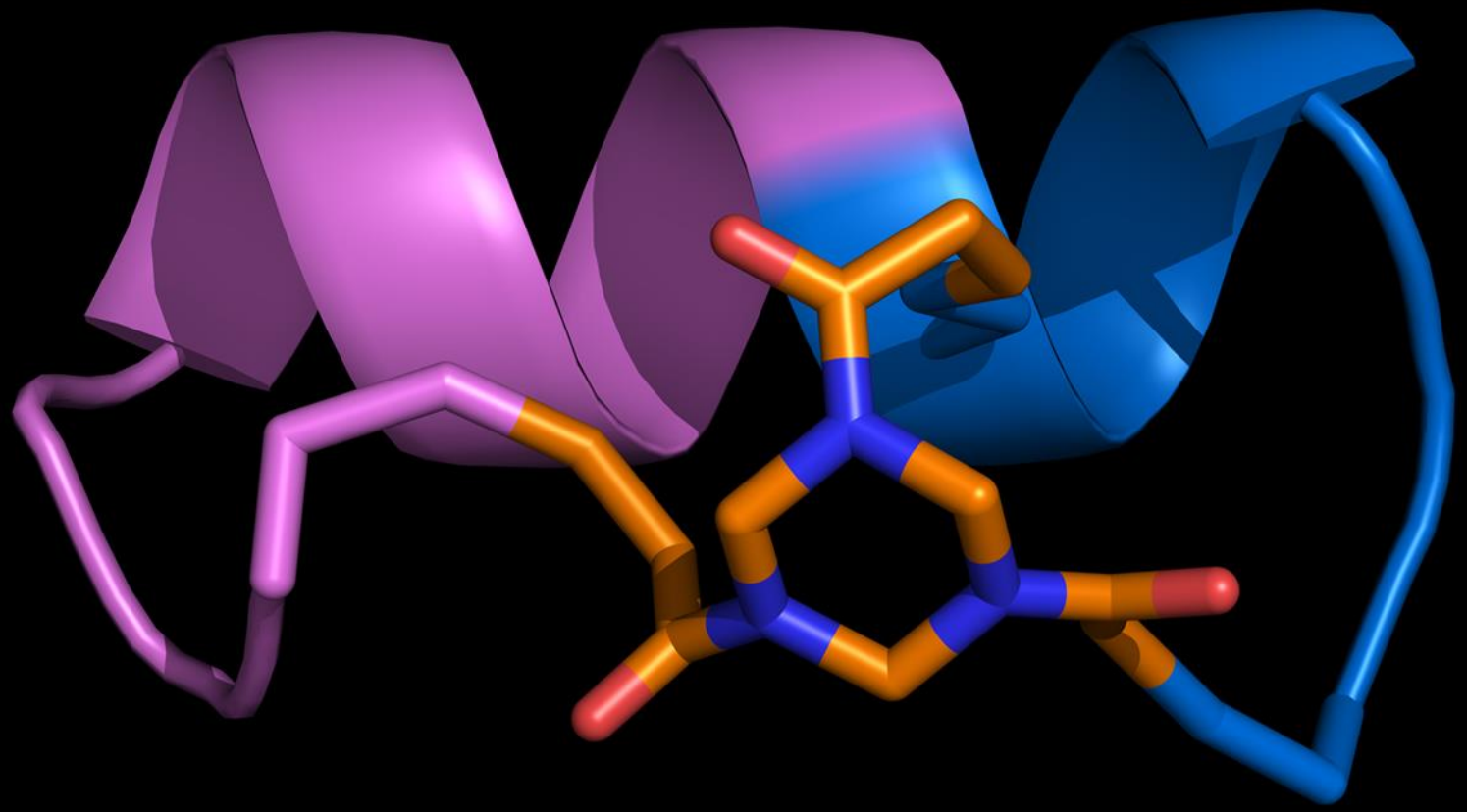
Bicycles – a new modality in the anti-viral armoury

Liuhong Chen
Vice President, Discovery
BicycleTx Ltd

TIDES Asia, March 2023



Bicycle®

Forward-looking statement

This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as “aims,” “anticipates,” “believes,” “could,” “estimates,” “expects,” “forecasts” , “goal,” “intends,” “may” “plans,” “possible,” “potential,” “seeks,” “will,” and variations of these words or similar expressions that are intended to identify forward-looking statements. All statements other than statements of historical facts contained in this presentation are forward-looking statements, including statements regarding: our future financial or business performance, conditions, plans, prospects, trends or strategies and other financial and business matters; our current and prospective product candidates, planned clinical trials and preclinical activities, current and prospective collaborations and the timing and success of our development of our anticipated product candidates.

Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results, our plans to initiate clinical trials and the designs of the planned trials and other future conditions, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, the risk that any one or more of our product candidates will not be successfully developed or commercialized, the risk that we may not realize the intended benefits of our technology, including that we may not identify and develop additional product candidates for our pipeline, the risk that our product candidates or procedures in connection with the administration thereof will not have the safety or efficacy profile that we anticipate, the risk that prior results will not be replicated or will not continue in ongoing or future studies or trials,, the risk that the size and potential of the market for our product candidates will not materialize as expected, risks associated with our dependence on third-parties, and risks relating to our ability to obtain and maintain intellectual property protection for our product candidates. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled “Risk Factors” in our Annual Report on Form 10-K, filed with the Securities and Exchange Commission on February 28, 2023, as well as in other filings we may make with the SEC in the future, as well as discussions of potential risks, uncertainties and other important factors in our subsequent filings with the Securities and Exchange Commission. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

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Developing novel antivirals to SARS-CoV-2 has been challenging

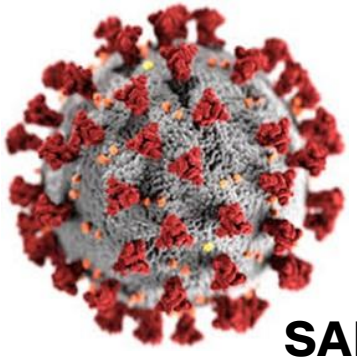
Emergent virus

↓

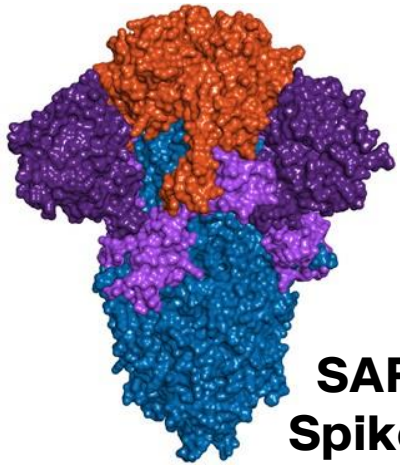
New to science

↓

Many unknowns

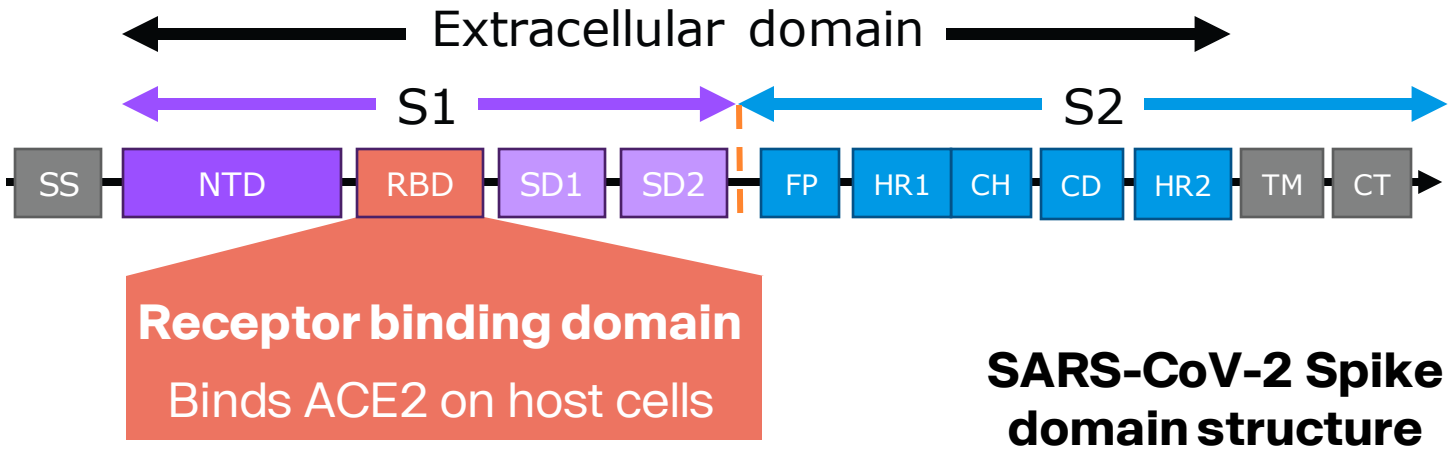


SARS-CoV-2 virion



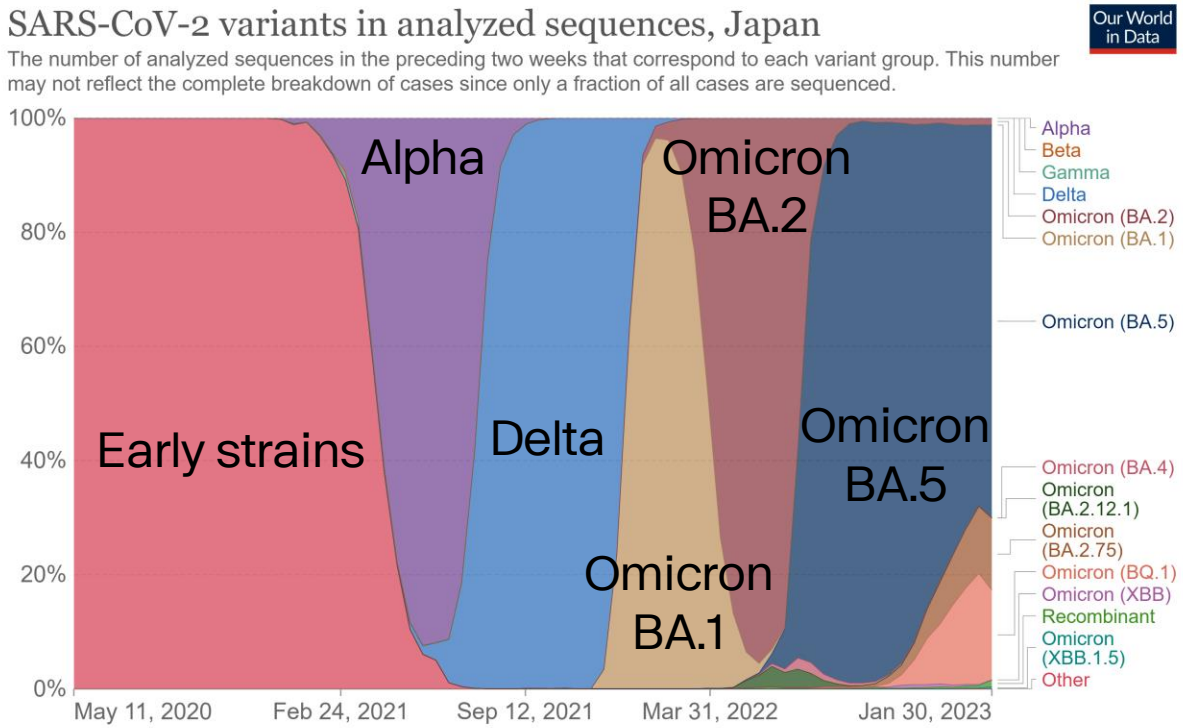
SARS-CoV-2 Spike (trimer)

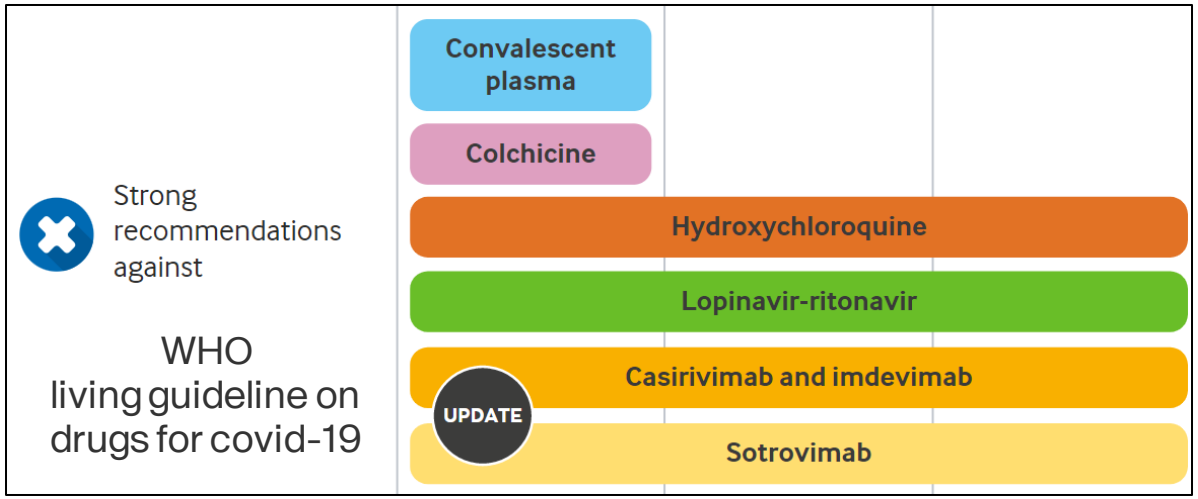
- Viral biology?
- Host infection mechanisms?
- Viral structure?
- *In vitro* and *in vivo* models?
- Resistance mechanisms?



SARS-CoV-2 Spike domain structure

Constantly and rapidly evolving target presents a challenge for traditional drug discovery

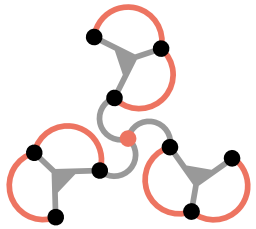




- Biologics rapidly lose efficacy against variants
- Small molecules slow to develop
- Can alternative modalities give us additional options?

https://ourworldindata.org/
WHO-2019-nCoV-clinical-2023.1

Collaborating to develop *Bicycle*® treatments to SARS-CoV-2



Bicycle®

Michael Skynner

Katherine Gaynor

Maximilian Harman

Katerine van Rietschoten

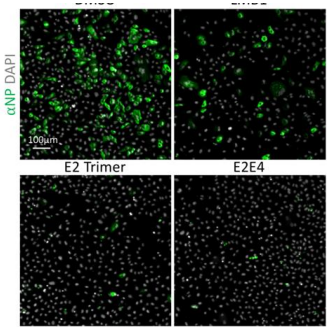
Paul Beswick

Brian McGuiness

Gustavo Bezerra

Phillip Jeffrey

Steven Stanway



UKRI MRC Laboratory of Molecular Biology

Leo James

Marina Vaysburd

Anna Albecka-Moreau

Guido Papa

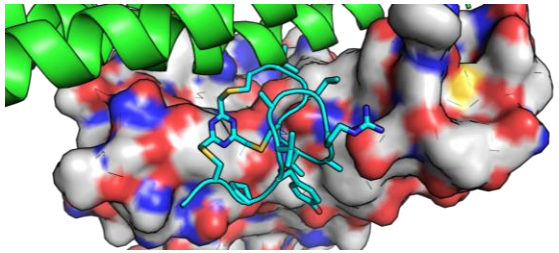
Donna Mallery

Veronica T Chang

John Briggs

(now at Max Planck Institute of Biochemistry)

Katarzyna Ciazynska



UNIVERSITY OF CAMBRIDGE

Marko Hyvönen Lab

Paul Brear

Aleksei Lulla

Nicola Coker Gordon

UNIVERSITY OF LIVERPOOL

James Stewart

Eleanor G Bentley

Parul Sharma

Adam Kirby

Ximeng Han

Andrew Owen

Jo Sharp

Megan Neary

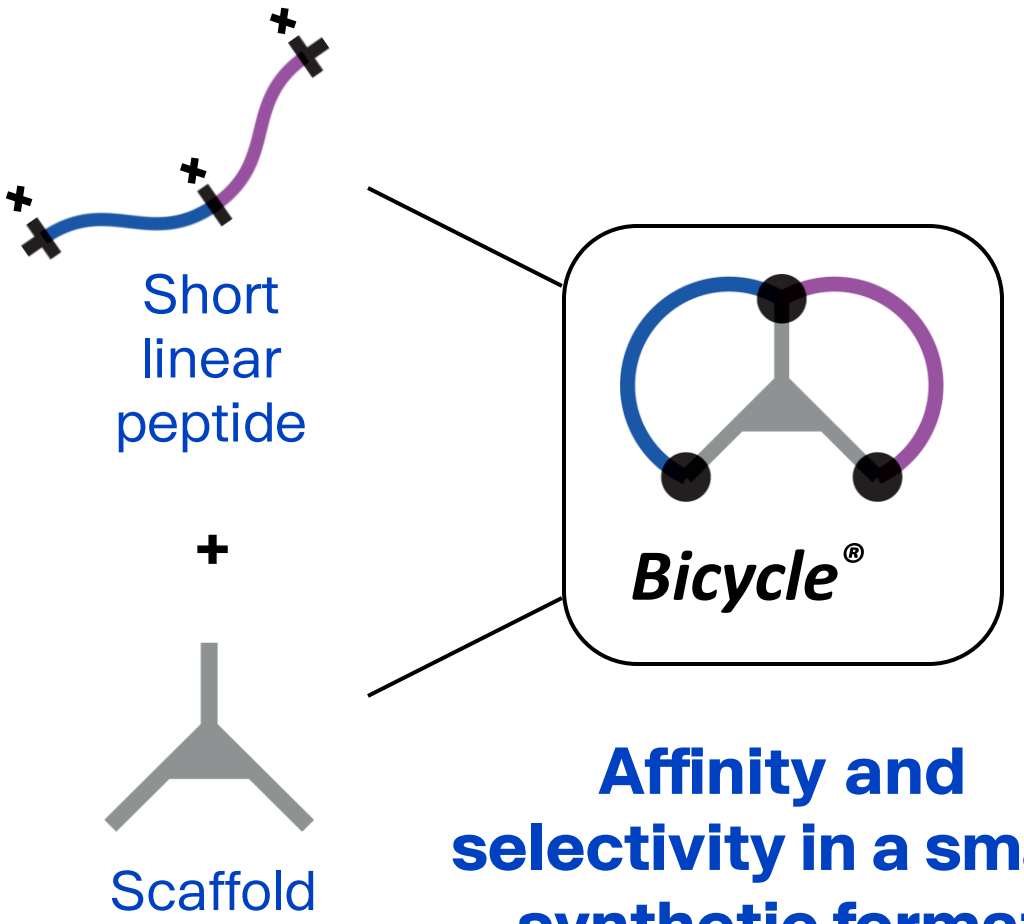
Helen Box

Jo Herriott

Edyta Kijak

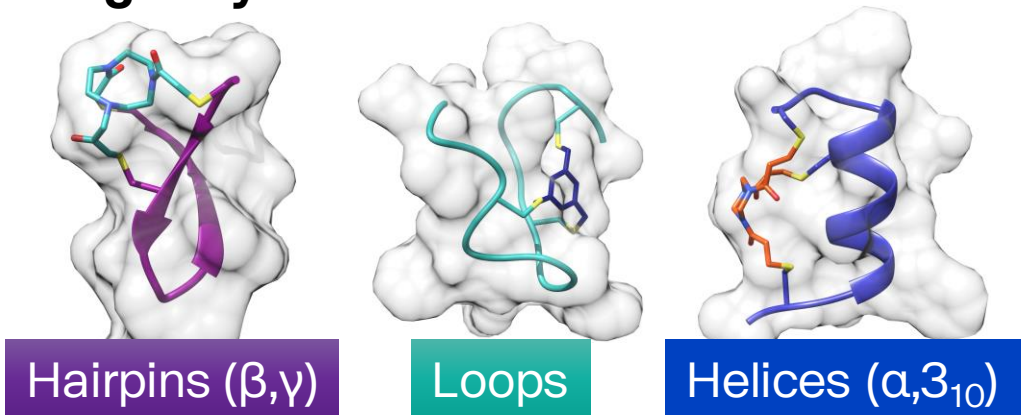
Lee Tatham

Bicycle® a unique & disruptive therapeutic modality



Affinity and selectivity in a small, synthetic format

- **Biologically relevant 3D structures**

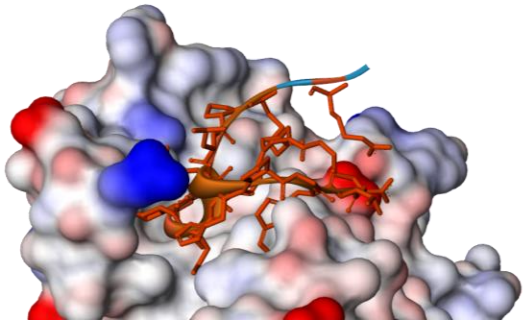


- **Favourable drug-like properties**

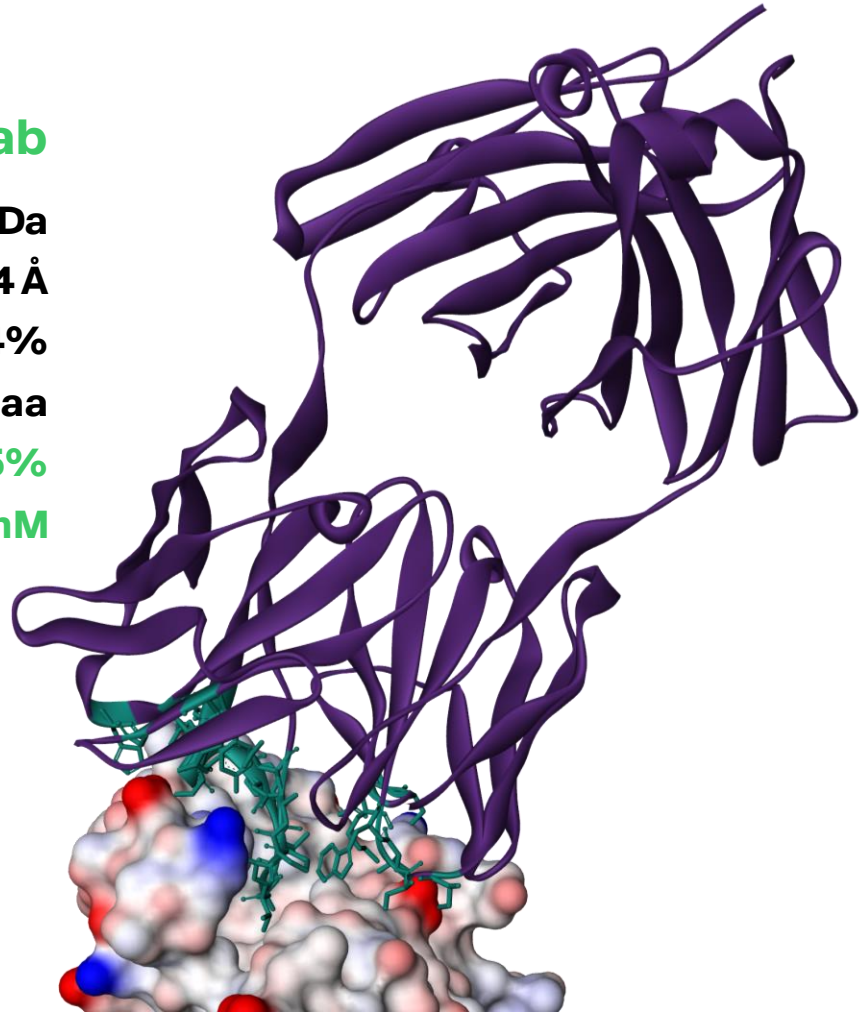
Small size (1.5-2 kDa)
High specificity
Chemical synthesis (NCEs)
Rapid tissue penetration
Complex protein targets druggable
Multiple routes of administration
Renal route of elimination
Not immunogenic

Bicycles are highly efficient ligands

	Bicycle®	Fab
Molecular weight:	**2.3 kDa**	**47.9 kDa**
Total surface area:	**2,120 Å²**	**24,124 Å**
Binding area:	**896 Å² = 42%**	**850 Å² = 4%**
Size:	**19aa + scaffold**	**445aa**
Binding residues:	**16aa + scaffold = 85%**	**24aa = 5%**
Affinity:	**1.9 nM**	**140 nM**



EphA2-binding
Bicycle®
(from BTC BT5528)



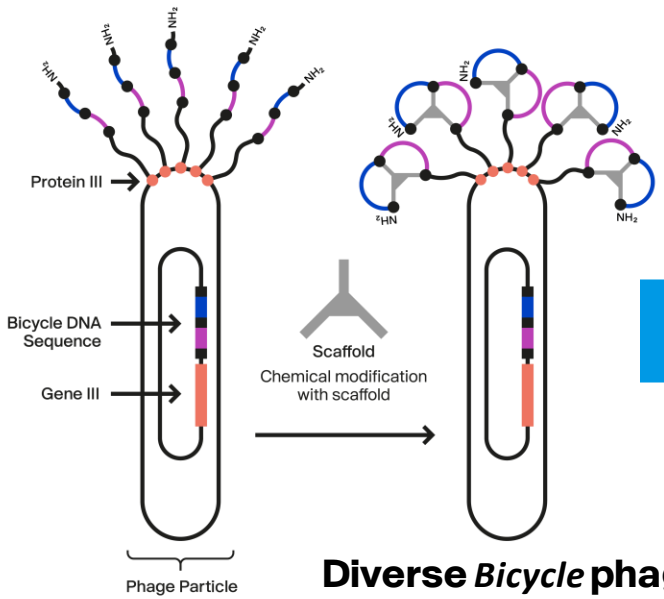
EphA2-binding
Fab
(from ADC MEDI-547)

Bicycle® platform: a marriage of phage display and peptide /medicinal chemistry creating novel potential medicines

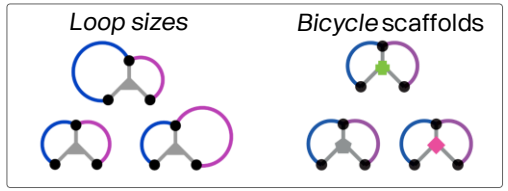
Bicycle® Phage Display

Linear peptide

Bicycle®



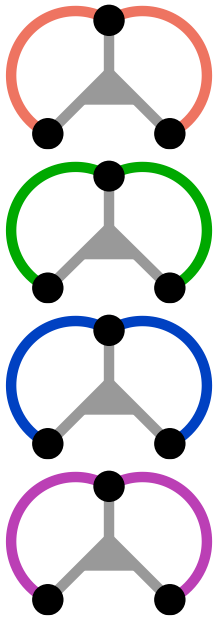
Diverse *Bicycle* phage libraries (>10^{20})



Natural Amino Acids

Optimize Bicycle monomers

Peptide & Medicinal Chemistry



Target binding *Bicycles*

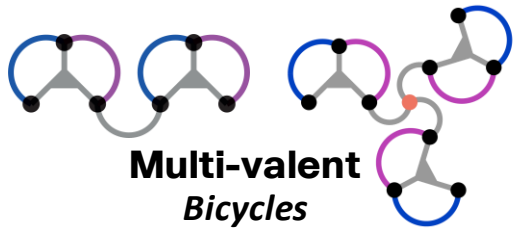
Non-natural Amino Acids

Build and Optimize Therapeutic Bicycle

Bicycle® Medicines

Monomeric *Bicycles*

Targeted Drug Conjugates

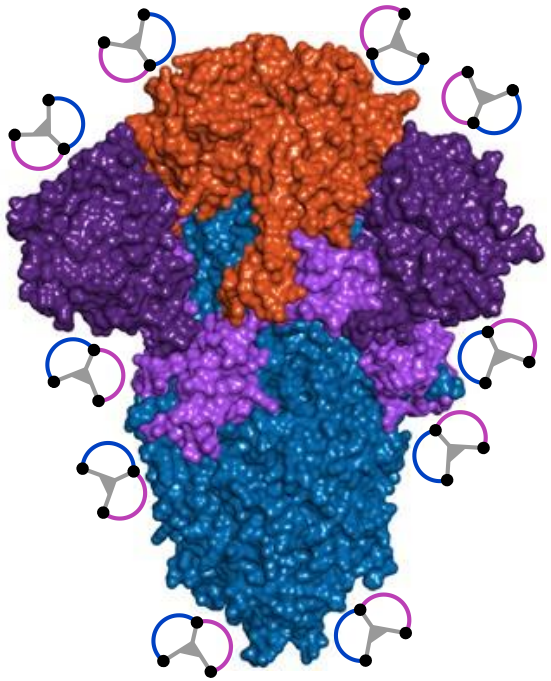


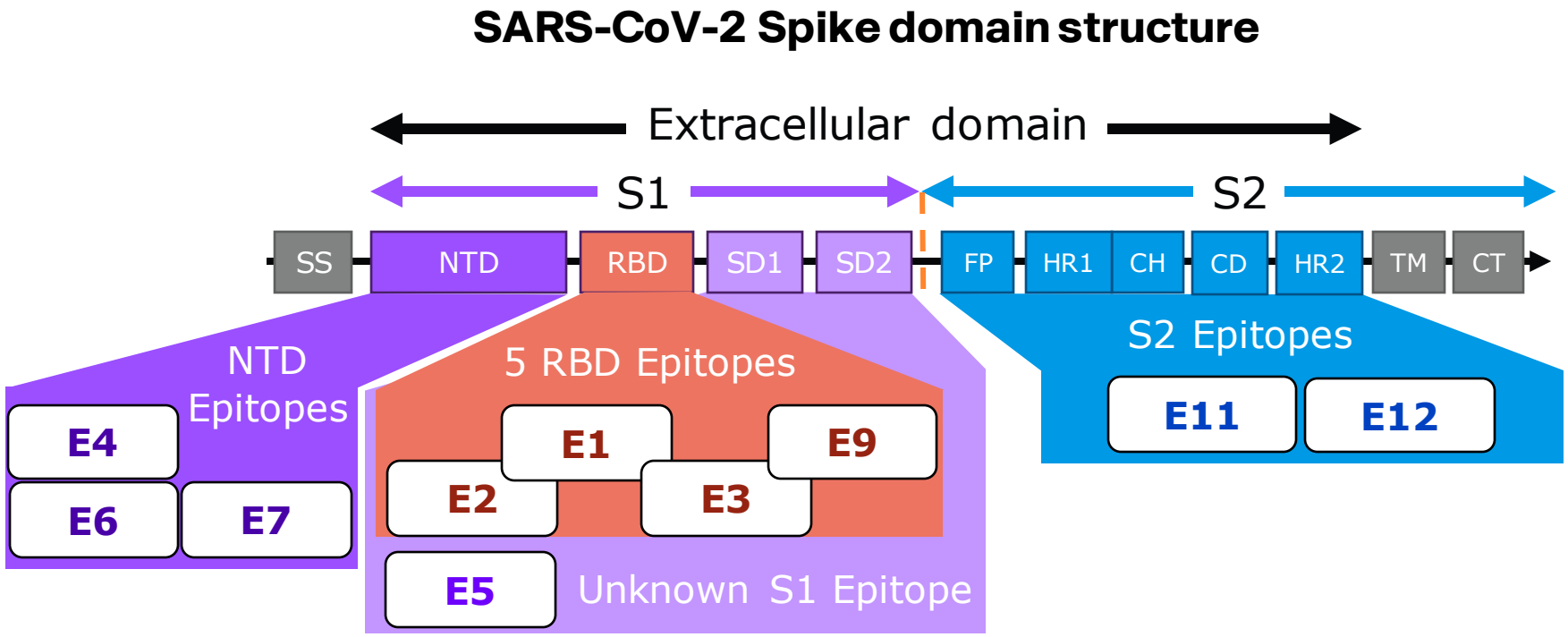
Multi-valent *Bicycles*

Targeted ASO/siRNA delivery

IONIS

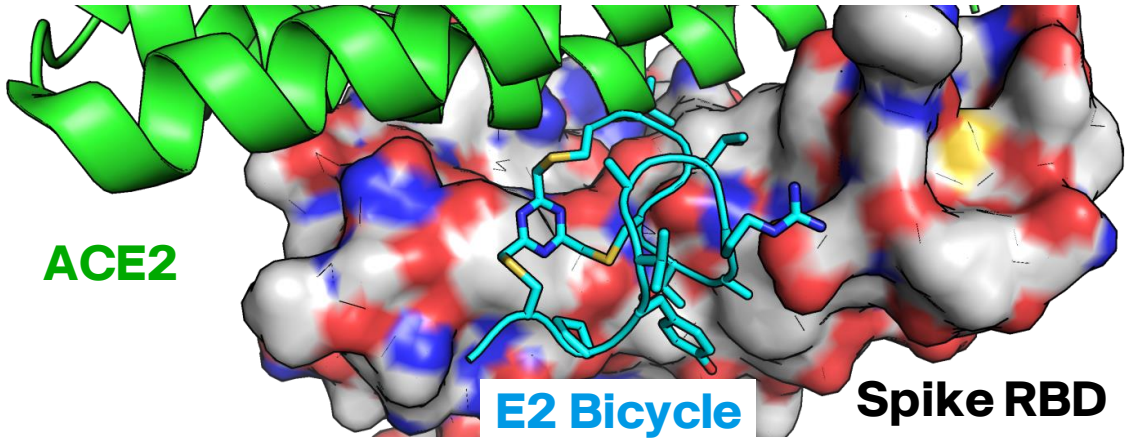
Many *Bicycles* generated against different epitopes on SARS-CoV-2 Spike protein

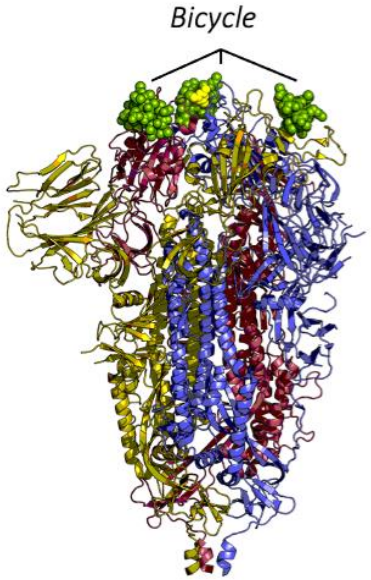


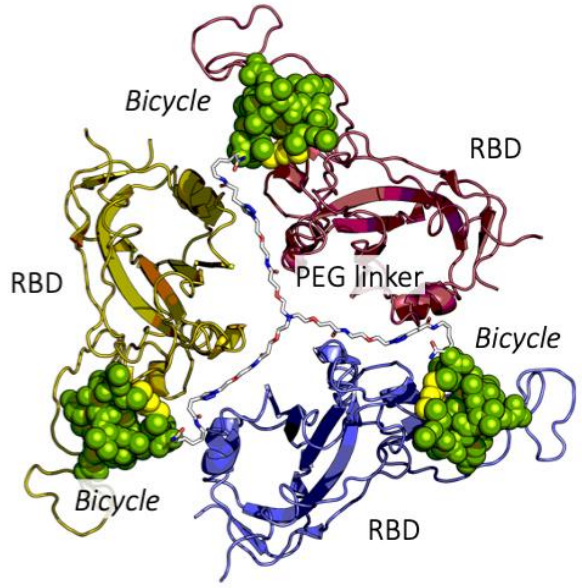


- *Bicycle*® binders found to **all parts of the Spike** protein
- **12 distinct binding sites** (epitopes) identified

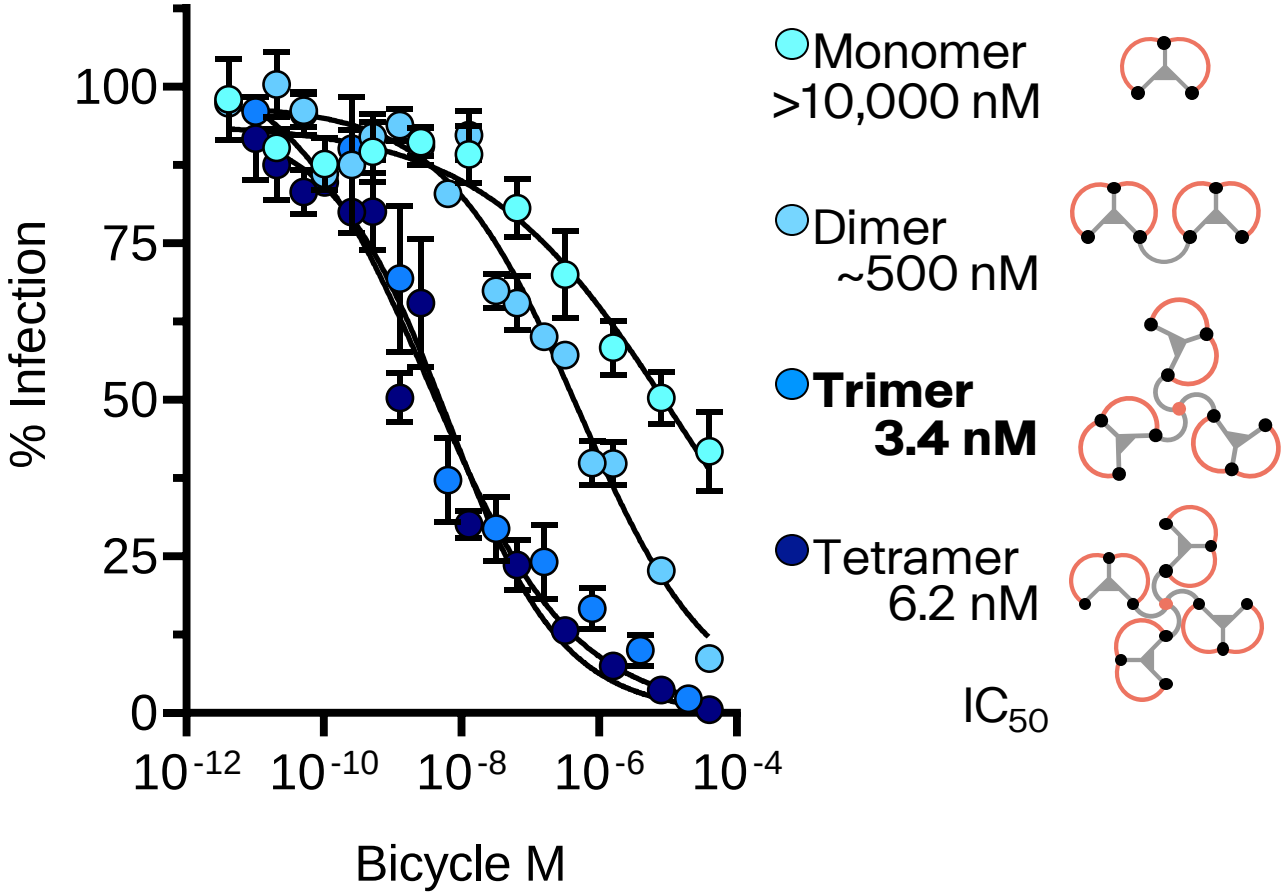
Multimeric *Bicycles* – a rapid route to potent inhibitors



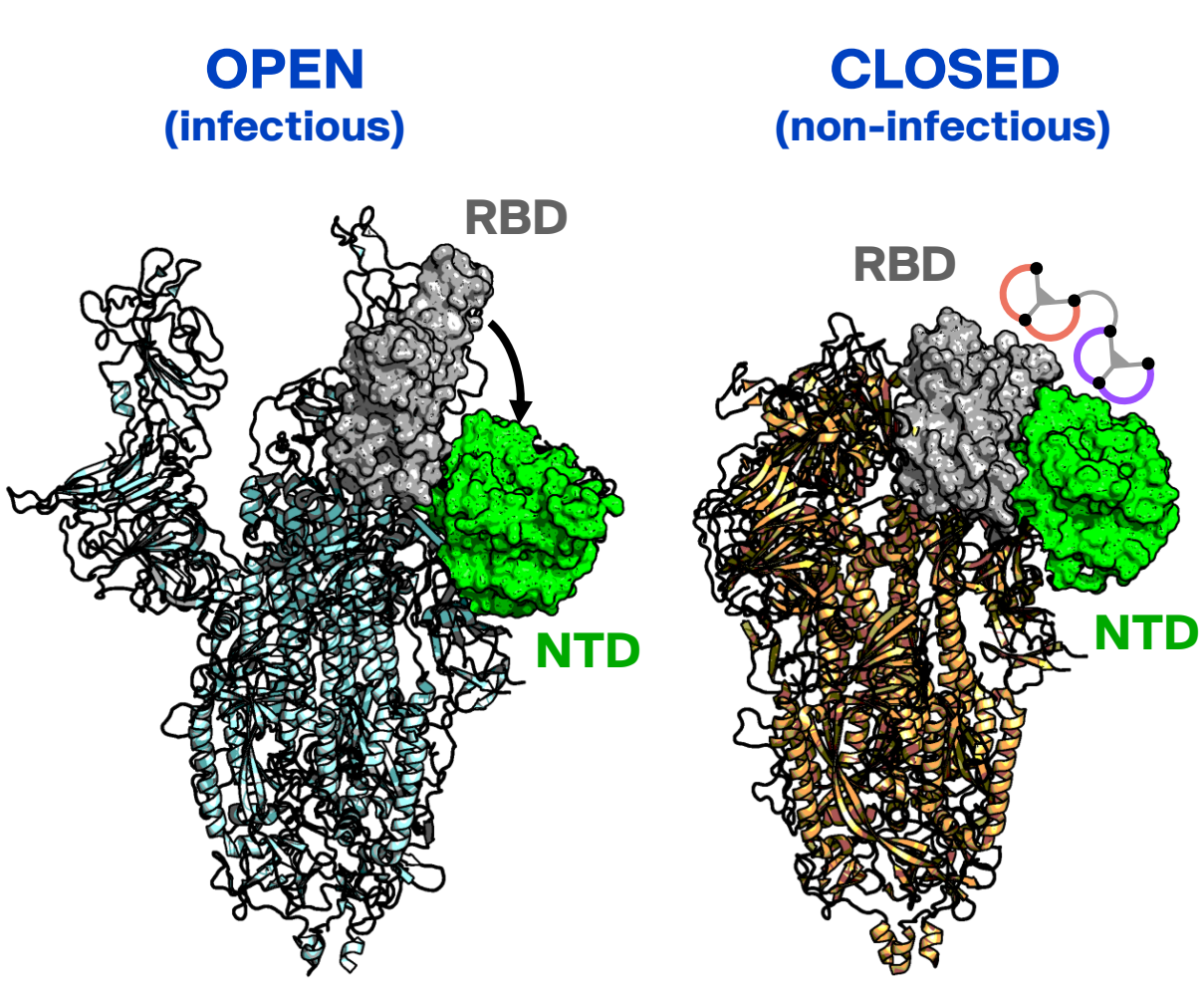


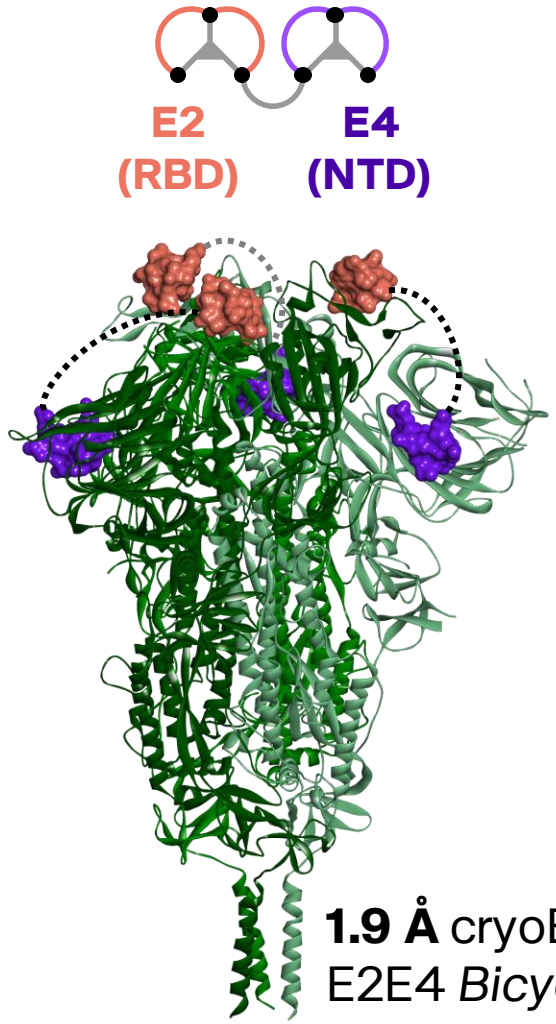


Inhibition of pseudovirus infection by RBD-binding (E2) *Bicycles*



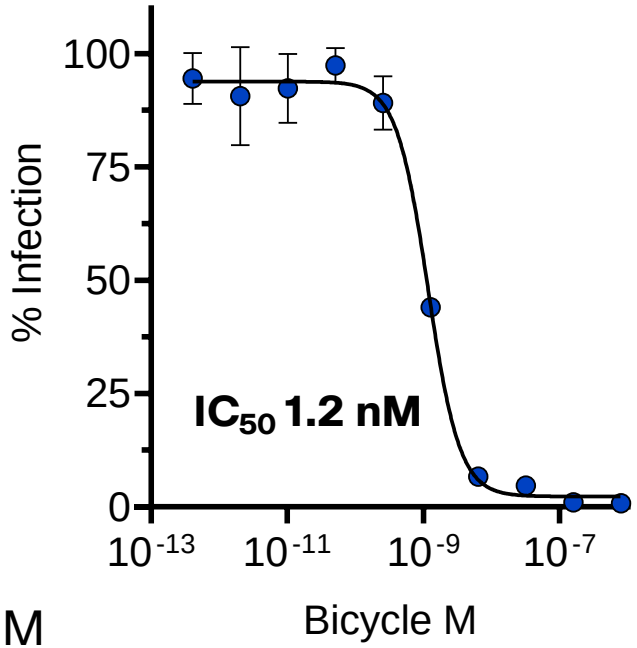
Combining *Bicycles* to different sites also makes potent inhibitors – potentially via alternative mechanisms of inhibition



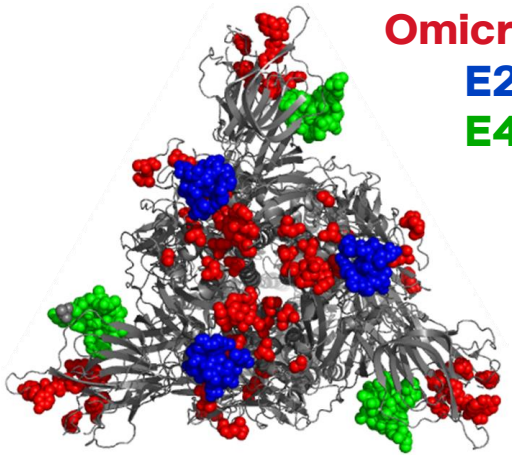


1.9 Å cryoEM
E2E4 *Bicycle*

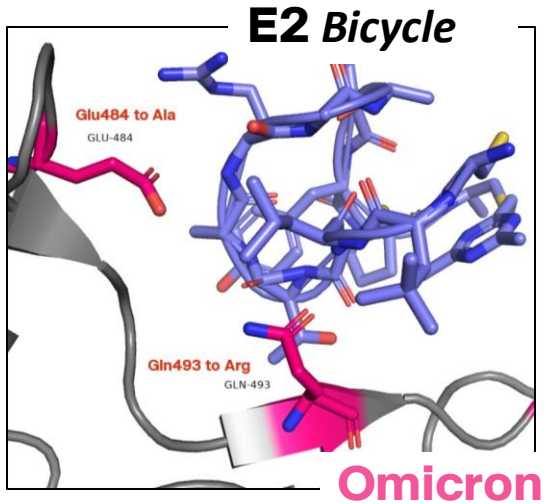
Inhibition of pseudovirus infection by biparatopic E2E4 *Bicycle*

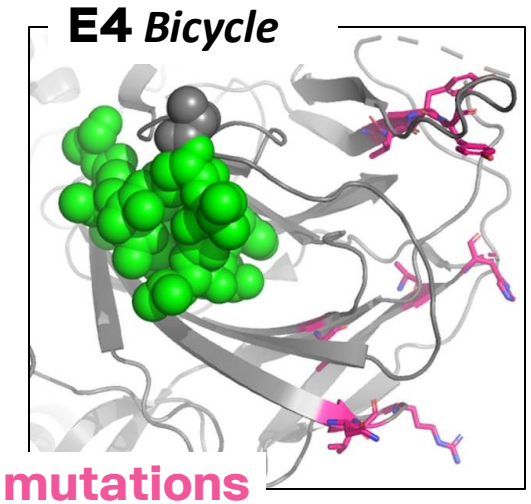


New combinations can be found quickly to respond to new VoC



Omicron mutations
E2 Bicycles
E4 Bicycles

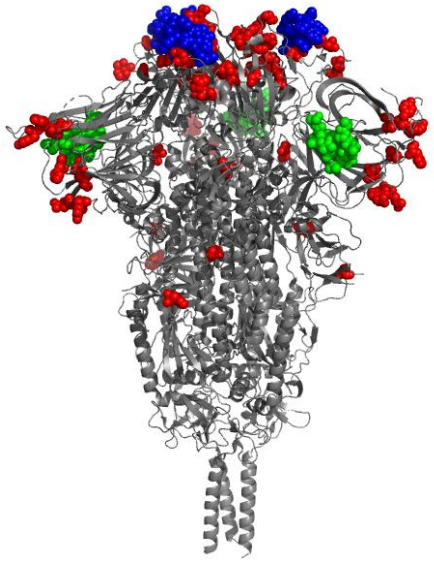


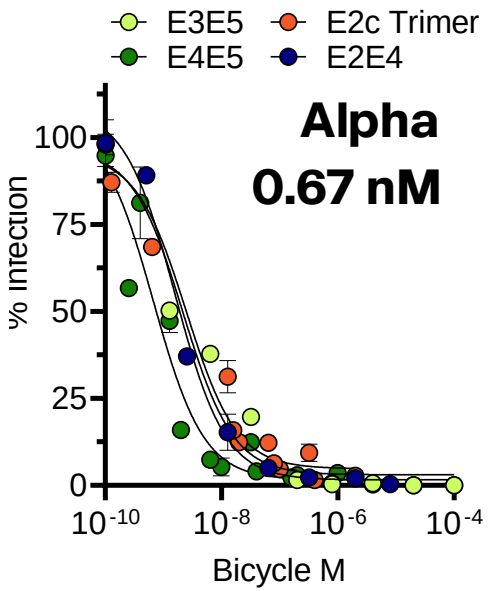


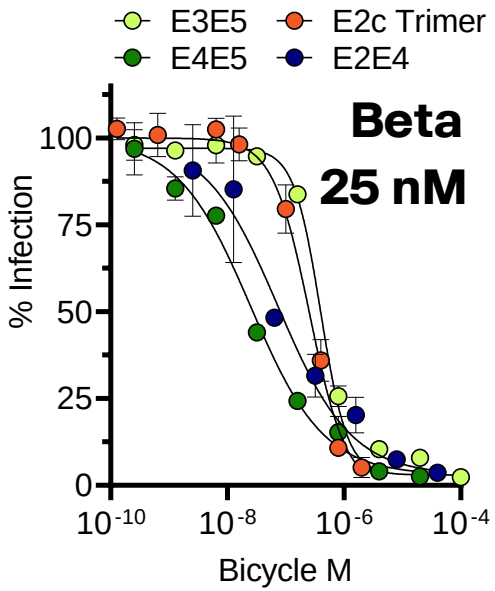
Omicron mutations

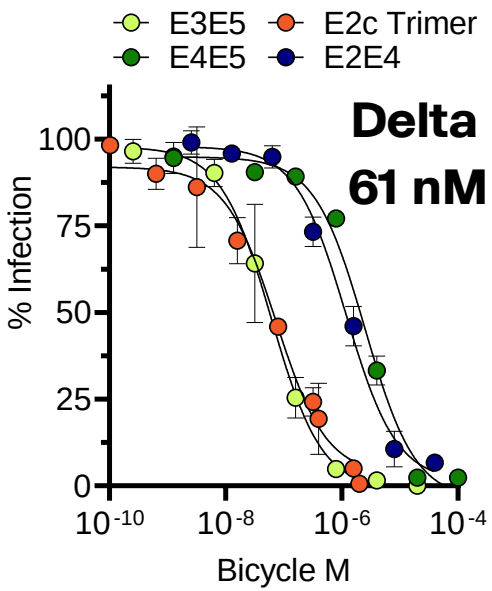
Non-ACE2 competitive RBD binder E1

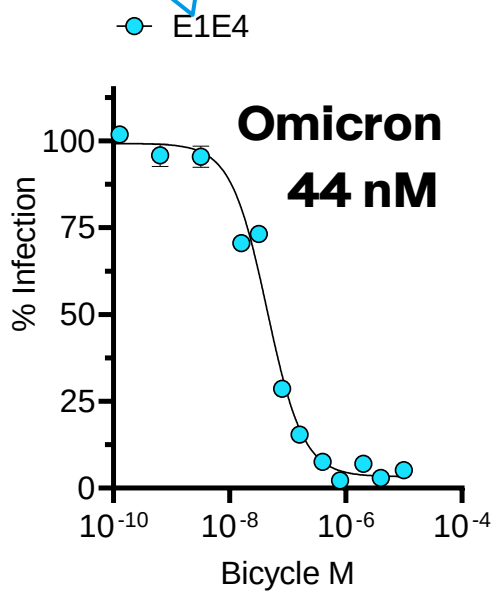
+ E4 NTD binder





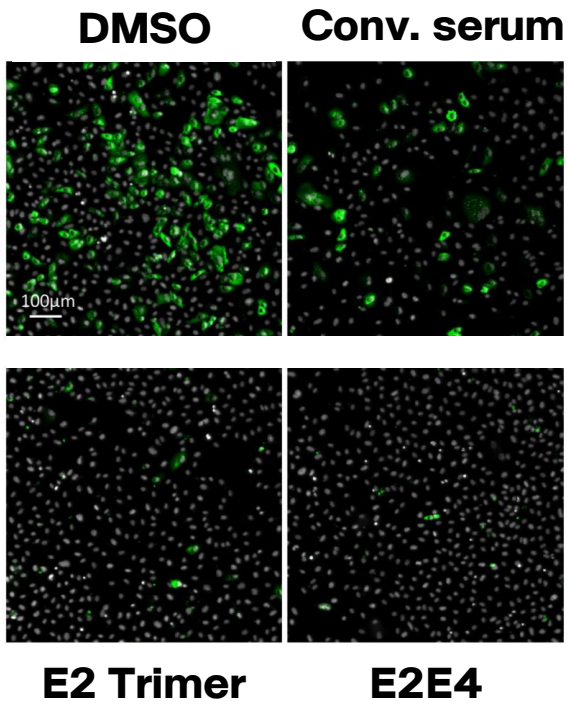




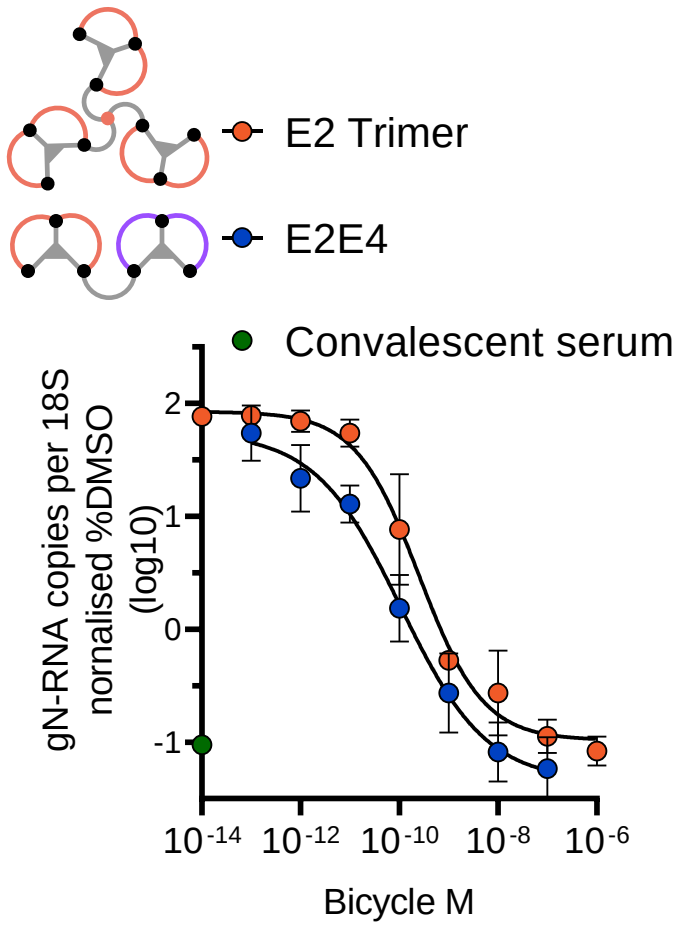


Bicycles can inhibit infection by live SARS-CoV-2 virus

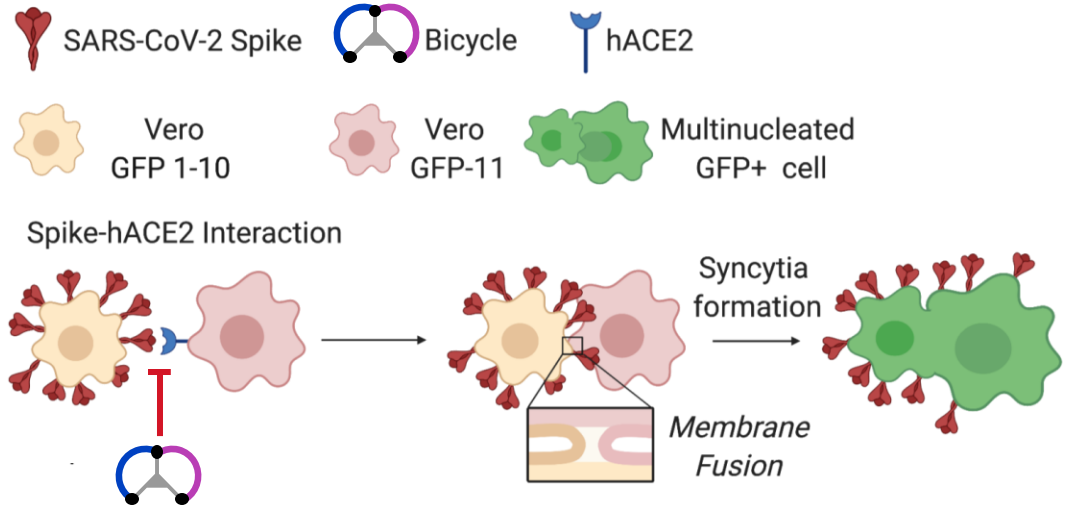
Reduction of viral Nucleocapsid protein

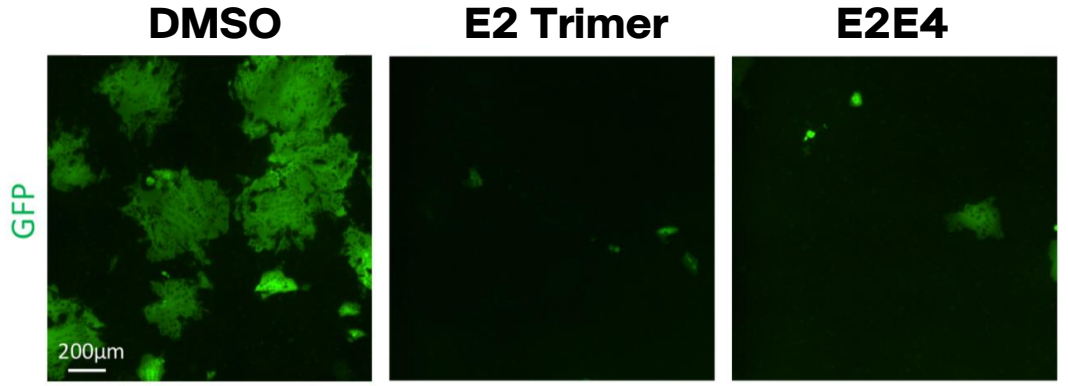


Reduction of viral genomic RNA

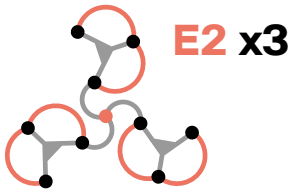


Reduction of Spike protein mediated cell-cell fusion (syncytia formation)

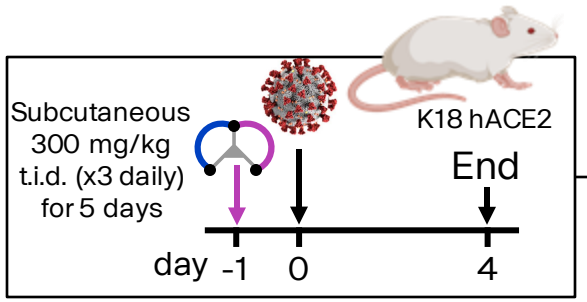


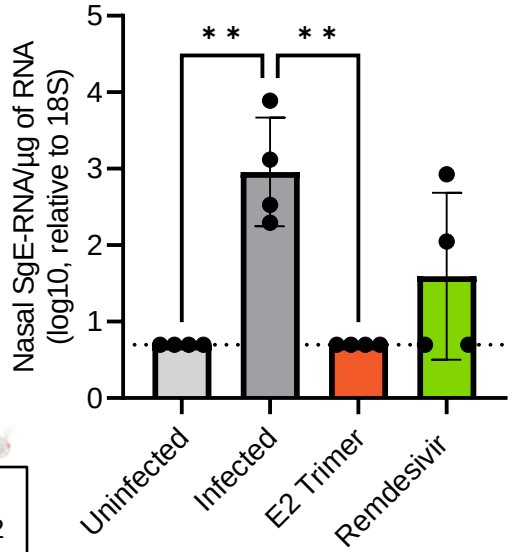


Bicycles are effective at restricting viral spread in hACE2 mice

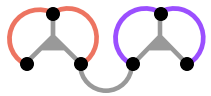


E2 Trimer

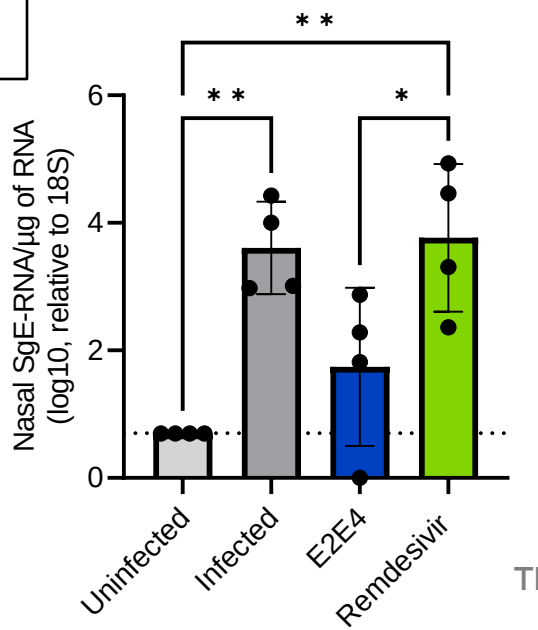




Nose — Lung — Brain

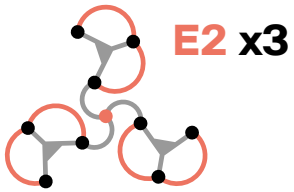


E2E4 Biparatopic

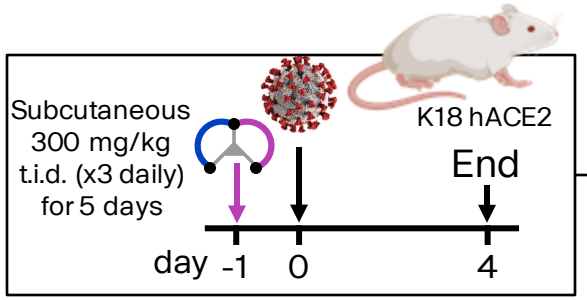


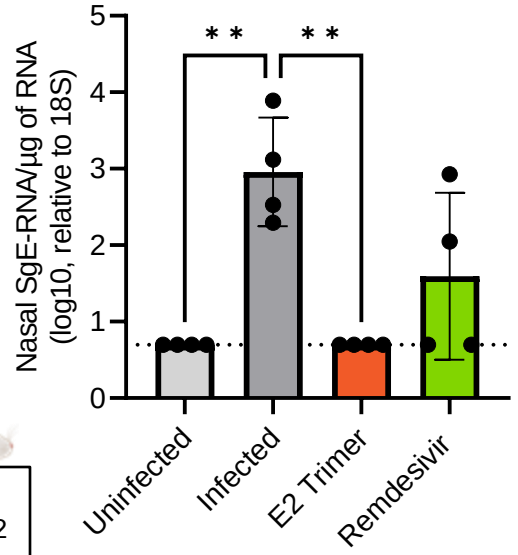
Nose – qPCR SARS-CoV-2 subgenomic E transcripts
Lung – qPCR cytokine transcripts
Brain – IHC SARS-CoV-2 N protein
Remdesivir 25mg/kg b.i.d. (x2 daily)

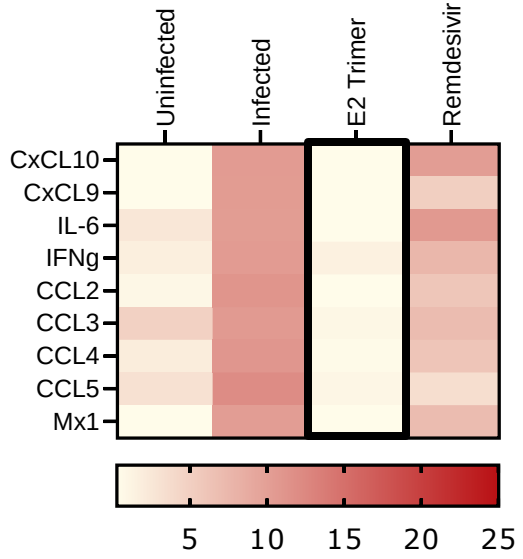
Bicycles are effective at restricting viral spread in hACE2 mice



E2 Trimer

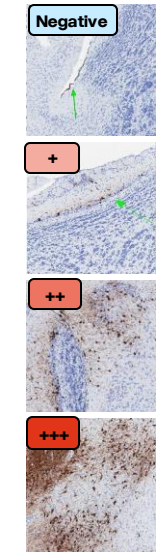


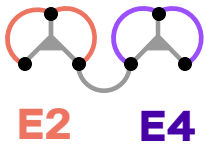




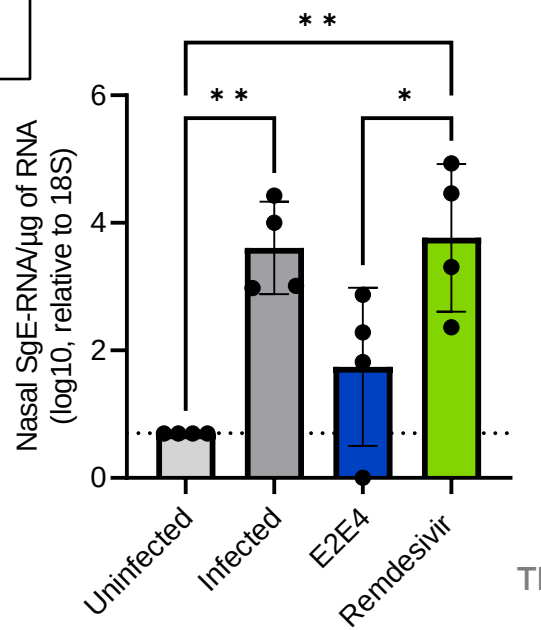
Treatment group	Animal			
	1	2	3	4
Uninfected				
Infected	+	++	++	+++
E2 Trimer				
Remdesivir		+	+	+++

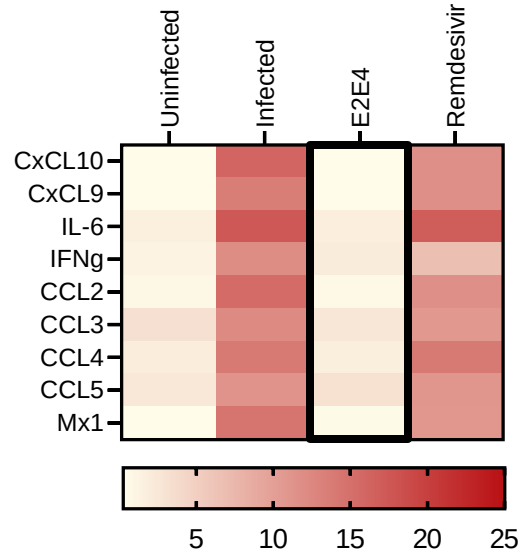
Nose Lung Brain





E2E4 Biparatopic





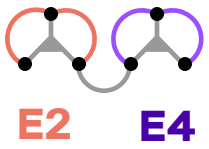
Treatment group	Animal			
	1	2	3	4
Uninfected				
Infected			+	+
E2E4				
Remdesivir				+

Nose – qPCR SARS-CoV-2 subgenomic E transcripts
Lung – qPCR cytokine transcripts
Brain – IHC SARS-CoV-2 N protein
Remdesivir 25mg/kg b.i.d. (x2 daily)

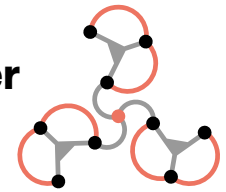
Bicycle®

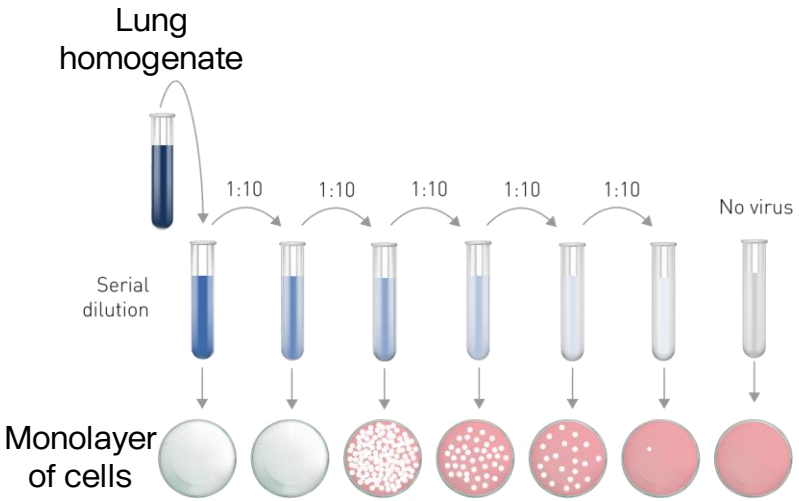
No replication competent virus detectable after *Bicycle®* treatment

E2E4 Biparatopic

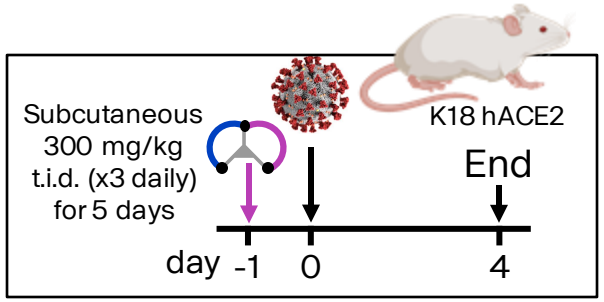


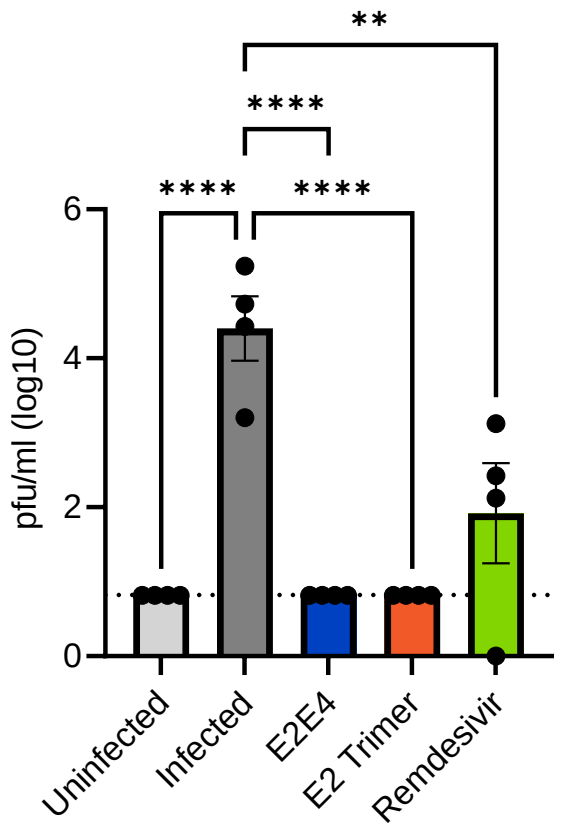
E2 Trimer



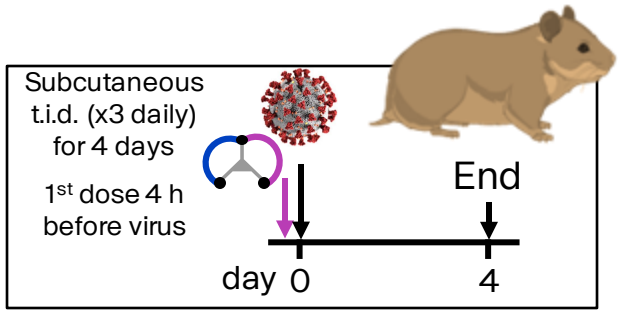


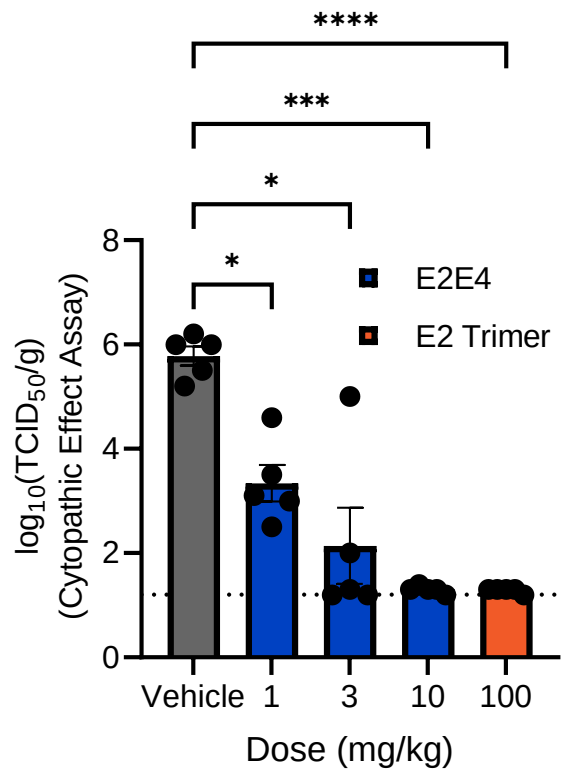
Mouse - Plaque assay (lung homogenate; Vero-hACE2-hTMPRSS2)
Hamster - Cytopathic assay (lung homogenate; Vero E6)



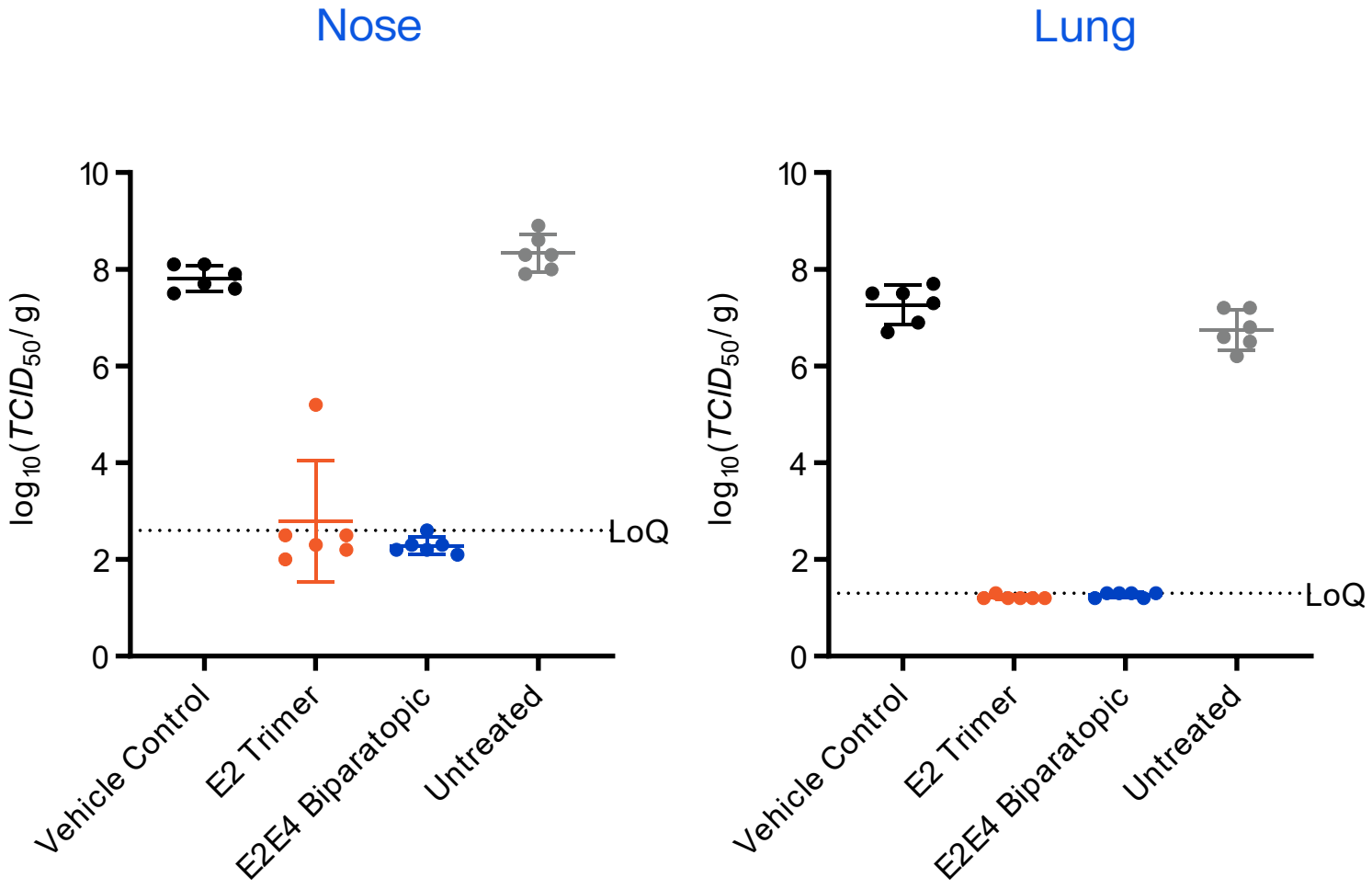


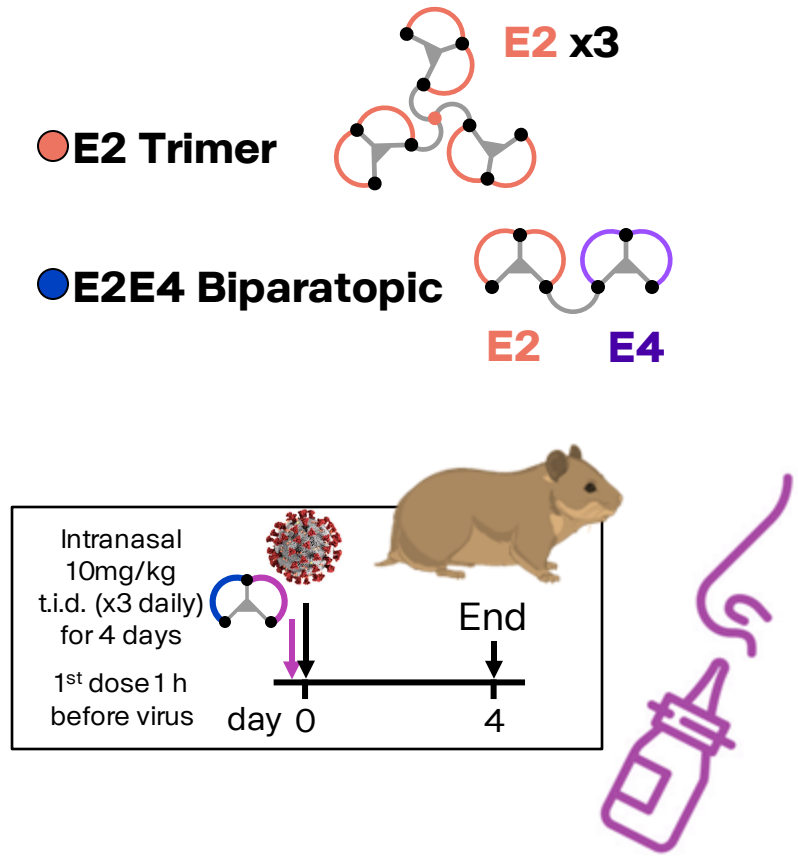
Lung





Potent antiviral effect from intranasal dosing at 10mg/kg t.i.d.





- Beyond injectables

Nasal turbinates or lung homogenate, cytopathic effect on Vero E6 cells

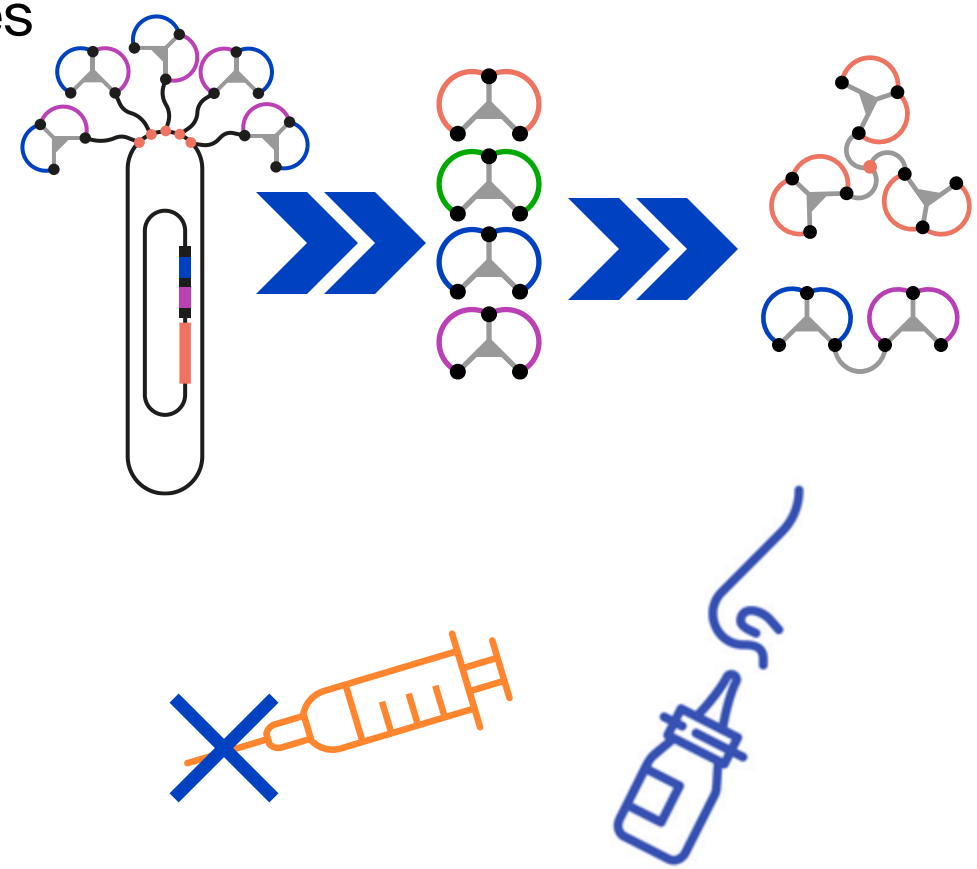
Bicycles – a new modality that could provide a rapid response in the defense against emergent viral threats

Proven platform

- Effective at preventing SARS-CoV-2 viral spread and pathologies
- Fast to identify new high potency potential medicines
- Conjugation ready for combinability
- Multiple potential mechanisms to inhibit infection
- High potential to resist mutational escape
- Key expertise and collaborations in place

Differentiated drug class with unique benefits

- Multiple convenient routes of administration
- Non-parenteral (intranasal) route
- Fully synthetic and scalable
- Heat stable, no cold chain



Thank you

Bicycle Therapeutics, Inc.
35 Cambridgepark Dr
Cambridge, MA
02140, USA
T. +1 617-945-8155

Bicycle Therapeutics plc
Portway Building
Granta Park, Cambridge
CB21 6GS, UK
T. +44 (0)1223 261503

BicycleRD Limited
Portway Building
Granta Park, Cambridge
CB21 6GS, UK
T. +44 (0)1223 261503

BicycleTx Limited
Portway Building
Granta Park, Cambridge
CB21 6GS, UK
T. +44 (0)1223 261503

Bicycletherapeutics.com

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