Bicycles – a new modality in the anti-viral armoury

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Forward-looking statement

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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. The emergence of this virus is new to science, and there are many unknowns. Here are some key areas of interest:

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

The SARS-CoV-2 virion and Spike (trimer) structures are shown alongside the receptor binding domain (RBD), which binds to ACE2 on host cells. The extracellular domain includes S1 and S2 subunits, with various domains such as NTD, RBD, SD1, SD2, FP, HR1, CH, CD, HR2, TM, and CT.
Constantly and rapidly evolving target presents a challenge for traditional drug discovery

SARS-CoV-2 variants in analyzed sequences, Japan
The number of analyzed sequences in the preceding two weeks that correspond to each variant group. This number may not reflect the complete breakdown of cases since only a fraction of all cases are sequenced.

- Early strains
- Delta
- Omicron BA.1
- Omicron BA.2
- Omicron BA.5

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

WHO living guideline on drugs for covid-19

- Convalescent plasma
- Colchicine
- Hydroxychloroquine
- Lopinavir-ritonavir
- Casirivimab and imdevimab
- Sotrovimab

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

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

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Megan Neary
Helen Box
Jo Herriott
Edyta Kijak
Lee Tatham

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**Bicycle®** a unique & disruptive therapeutic modality

- Biologically relevant 3D structures
  - Hairpins (β, γ)
  - Loops
  - Helices (α, 3₁₀)

- 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

Affinity and selectivity in a small, synthetic format
Bicycles are highly efficient ligands

Molecular weight: 2.3 kDa
Total surface area: 2,120 Å²
Binding area: 896 Å² = 42%
Size: 19aa + scaffold
Binding residues: 16aa + scaffold = 85%
Affinity: 1.9 nM

Bicycle®

Molecular weight: 47.9 kDa
Total surface area: 24,124 Å²
Binding area: 850 Å² = 4%
Size: 445aa
Binding residues: 19aa + scaffold = 85%
Affinity: 1.9 nM

Fab

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
- Diverse Bicycle phage libraries ($>10^{20}$)
- Natural Amino Acids

**Peptide & Medicinal Chemistry**

- Optimize Bicycle monomers
- Target binding Bicycles
- Non-natural Amino Acids

**Bicycle® Medicines**

- Build and Optimize Therapeutic Bicycle
- Targeted Drug Conjugates
- Multi-valent Bicycles
- Targeted ASO/siRNA delivery

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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*

- Monomer: >10,000 nM
- Dimer: ~500 nM
- Trimer: 3.4 nM
- Tetramer: 6.2 nM

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Combining *Bicycles* to different sites also makes potent inhibitors – potentially via alternative mechanisms of inhibition.
New combinations can be found quickly to respond to new VoC

Omicron mutations
E2 Bicycles
E4 Bicycles

Non-ACE2 competitive RBD binder E1 + E4 NTD binder

Alpha
0.67 nM

Beta
25 nM

Delta
61 nM

Omicron
44 nM

Bicycle M

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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)

Bicycle M

gN-RNA copies per 18S normalised %DMSO (log10)

E2 Trimer

E2E4

Convalescent serum

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Bicycles are effective at restricting viral spread in hACE2 mice

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**

**Subcutaneous treatment with Remdesivir (25mg/kg b.i.d.) for 5 days.**

- **Nose**
  - CxCL10, CxCL9, IL-6, IFN-γ, CCL2, CCL3, CCL4, CCL5, Mx1

- **Lung**
  - CxCL10, CxCL9, IL-6, IFN-γ, CCL2, CCL3, CCL4, CCL5, Mx1

- **Brain**
  - IHC SARS-CoV-2 N protein

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**Treatment group**

<table>
<thead>
<tr>
<th>Group</th>
<th>Animal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected</td>
<td>1</td>
</tr>
<tr>
<td>Infected</td>
<td>+</td>
</tr>
<tr>
<td>E2 Trimer</td>
<td>+</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>+</td>
</tr>
</tbody>
</table>

**Negative**

+ + + + +

---

**Side effects**

- **CCL2, CCL3, CCL4, CCL5, Mx1**

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**Negative**

+ + + + +

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**Notes**

- **Bicycles**
  - E2 x3
  - E2 Trimer
  - E2 E4
  - Biparatopic

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**TIDES Asia March 2023**
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)

Subcutaneous 300 mg/kg t.i.d. (x3 daily) for 4 days

1st dose 4 h before virus day -1 0 4

Dose (mg/kg)

Log_{10}(TCID_{50}/g) (Cytopathic Effect Assay)

Uninfected Infected E2E4 E2 Trimer Remdesivir

Vehicle 1 3 10 100

** ****

pfu/ml (log_{10})

Uninfected Infected E2E4 E2 Trimer Remdesivir

Vehicle 1 3 10 100

* ****

Subcutaneous t.i.d. (x3 daily) for 4 days

1st dose 4 h before virus day 0 4

K18 hACE2

E2 Trimer

Lung homogenate

Serial dilution

Monolayer of cells

E2

E4

E2 x3
Potent antiviral effect from intranasal dosing at 10mg/kg t.i.d.

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

Nasal

Lung

Vehicle Control
E2 Trimer
E2E4 Biparatopic
Untreated

Log_{10}(TCID_{50}/g)

Log_{10}(TCID_{50}/g)

LoQ

LoQ

0
1
2
3
4
5
6
7
8
9
10

17

Beyond injectables

E2 Trimer

E2E4 Biparatopic

Intranasal 10mg/kg t.i.d. (x3 daily) for 4 days
1st dose 1 h before virus
day 0 4

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**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

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