Revitalising the antiviral arsenal: *Bicycles* as a new therapeutic modality

International School of Crystallography
58th Course - Structural Drug Design: Biology, Chemistry and Computers

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Gustavo Bezerra
Associate Director – Structural Biology
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; the therapeutic potential for Bicycles in oncology; 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 of cessation or delay of any ongoing or planned clinical trials; 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 we may not maintain our current collaborations or enter into new collaborations in the future; or that we may not realize the intended benefits of these collaborations; 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 we will be unable to obtain and maintain regulatory approval for our product candidates; risks associated with our dependence on third-parties, risks regarding the accuracy of our estimates of expenses, risks relating to our capital requirements and needs for additional financing; 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 Quarterly Report on Form 10-Q, filed with the Securities and Exchange Commission on May 4, 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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Clinical stage biopharma company pioneering Bicycles – a new differentiated class of innovative medicines

**Unique Platform**
Generating Bicycles – a novel synthetic peptide modality that enables complex previously undruggable targets to be drugged
Bicycle® modular format platform based on Nobel Prize science
Strong intellectual property portfolio

**Internal Programs**
Focused on oncology and immuno-oncology with multiple Phase I/II clinical assets (BT5528, BT8009 and BT7480)
BT5528 and BT8009 have shown signs of anti-tumor activity
Trial updates for BT5528, BT8009 and BT7480 in 2023

**Validating Partnerships**
Extending the clinical utility of Bicycle® platform into diverse range of therapeutic areas

**Ambitious Company**
Deeply experienced team
Located in Cambridge, UK and Cambridge, MA
NASDAQ: BCYC
Robust patent portfolio

*As of March 31, 2023*
Bicycle® platform: a marriage of phage display and peptide/medicinal chemistry creating novel potential medicines

Diverse Bicycle phage libraries (>10^20)

Optimize Bicycle monomers

Build and Optimize Therapeutic Bicycle

Target binding Bicycles

Monomeric Bicycles

Targeted Drug Conjugates

Multi-valent Bicycles

Targeted ASO/SiRNA delivery

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*Bicycles* are highly efficient ligands

**Favourable drug-like properties**

- Antibodies
  - MWT 150kDa
  - Poor/Slow extravasation
  - Limited tissue penetration
  - Hepatic/catabolic clearance
  - Long half life

- Fragments
  - MWT 50-60kDa
  - Poor/Slow extravasation
  - Limited tissue penetration
  - Hepatic/catabolic/renal clearance
  - Medium half life

- Domains
  - MWT 10-15kDa
  - Poor/Slow extravasation
  - Limited tissue penetration
  - Renal clearance
  - Medium half life

- Bicycles
  - MWT 1-3kDa
  - Rapid extravasation
  - Extensive tissue penetration
  - Renal clearance
  - Tuneable half life

Target-Bicycle

Target-antibody

Erice, June 2023
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

Spike open conformation

Bicycle
ACE2
2.3 Å cryo-EM reconstruction of SARS-CoV-2 Spike in complex with a trimeric *Bicycle*
Biparatopic *Bicycles* are potent inhibitors, with proposed alternative mechanisms of inhibition.
1.9 Å cryo-EM reconstruction of SARS-CoV-2 Spike in complex with a biparatopic Bicycle

Collaboration with ThermoFisher
Ieva Drulyte

Erice, June 2023
New combinations can be found quickly to respond to new VoC

Omicron mutations
E2 Bicycles
E4 Bicycles

90°

Omicron mutations
E484 A
Q493R
A67V
HV69-70del
G142D
VVY143-145del
N211del
L212I
ins214EPE

Erice, June 2023
**Bicycles** can potentially inhibit infection by live SARS-CoV-2

**Reduction of viral genomic RNA**

- E2 Trimer
- E2E4
- Convalescent serum

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

- SARS-CoV-2 Spike
- Bicycle
- hACE2
- Vero GFP 1-10
- Vero GFP 11
- Multinucleated GFP+ cell

**DMSO**

- Spike-hACE2 Interaction
- Syncytia formation
- Membrane Fusion

- NO Spike-hACE2 Interaction

**E2 Trimer**

**E2E4**

**Erice, June 2023**

**NO Syncytia formation**
Potent antiviral effect from intranasal dosing at 10mg/kg t.i.d.

Nasal turbinates or lung homogenate, cytopathic effect on Vero E6 cells
Antivirals for SARS-CoV-2 and beyond

Opens a gateway to other respiratory viruses and
- emerging pathogens in the developing world
- stable (no cold chain)
- non parenteral delivery

Influenza

Global Examples of Emerging and Re-Emerging Infectious Diseases

New therapeutic anti-viral modality

- Fully synthetic
- Scalable
- Low cost of goods
- Heat stable no cold chain for low income countries

- Multiple roles available
  - Subcutaneous
  - Intranasal
  - Inhalation
  - GI lumen restricted

- Payload enabled
  - Can be coupled to other Bicycle to create high affinity medicine which resists mutational escape

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

Michael Skynner
Katherine Gaynor
Maximilian Harman
Katerine van Rietschoten
Paul Beswick
Brian McGuiness
Gustavo Bezerra
Phillip Jeffrey
Steven Stanway
Simone Pellegrino

Leo James
Marina Vaysburo
Anna Albecka-Moreau
Guido Papa
Donna Mallery
Veronica T Chang

Marko Hyvönen Lab
Paul Brear
Aleksei Lulla
Nicola Coker Gordon

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

Erice, June 2023
Thank you

Bicycle®