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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Bicycle[°]

Clinical stage biopharma company pioneering Bicycles – a new differentiated class of innovative medicines

and			
Unique Distform	Internal Drograma	Validating	Ambitious
Platform	Programs	Partnerships	Company
Generating Bicycles – a novel synthetic peptide modality that enables complex	Focused on oncology and immuno-oncology with multiple	Extending the clinical utility of Bicycle® platform into diverse	Deeply experienced team
previously undruggable targets to be drugged	(BT5528, BT8009 and BT7480)	range of therapeutic areas	Located in Cambridge, UK and Cambridge, MA
Bicycle [®] modular format platform based on Nobel Prize	BT5528 and BT8009 have shown signs of anti-tumor activity		NASDAQ: BCYC
science		Dementia Discovery CANCER	Robust natent portfolio
Strong intellectual property portfolio	BT8009 and BT7480 in 2023	Evend Research	

*As of March 31, 2023 **Bicycle**®

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



Erice, June 2023

Bicycles are highly efficient ligands

Target-*Bicycle*

Favourable drug-like properties



Bicycle[®]



Target-antibody

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



▶7

2.3 Å cryo-EM reconstruction of SARS-CoV-2 Spike in complex with a trimeric *Bicycle*



Collaboration with ThermoFisher leva Drulyte

Thermo Fisher

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 leva Drulyte

Thermo Fisher

New combinations can be found quickly to respond to new VoC



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





Reduction of Spike protein mediated

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

Influenza

Influenza

Virus Anatomy

lemagglutinin

euraminidase (Sialidase)

Small hydrophobic protein (SH)

Attachment glycoprotein (G)

Fusion protein (F)

Matrix (M)

Nucleoprotein (RNA) Opens a gateway to other respiratory viruses and Lipid Envelop emerging pathogens in the developing world Figure stable (no cold chain) non parenteral delivery **RSV Global Examples of Emerging and Re-Emerging Infectious Diseases** Nucleoprotein (N) Antimicrobial West Nile virus Cryptosporidiosis Ebola virus disease Diphtheria _ MERS-CoV resistant threat - CRE - MRSA - C. difficile - N. gonorrhoe E. coli Akhmeta virus virus Rift Valley fever vphoid fever Phosphoprotein (P) SFTSV H3N2v influenz unvaviru E. coli 0157:H7 E. coli 0157:H7 Large RNA polymerase (L) Measle H10N8 Huma influenza H7N9 influenza Listeriosis Bourbon H5N1 influenza virus 2009 H1N1 SARS influenza Adenovirus 1 Nipah virus Anthrax Hendra virus Chikungunya Enterovirus 71 Human monkeypo: pulmonary Ebola virus diseas **Zika virus** Yellow fever Marburg Human African trypanosomiasis Cholera hemorrhagic fever MDR / XDR tuberculosis Zika virus Plaque New therapeutic anti-viral modality Fully synthetic Multiple rotes available Payload enabled Scalable Subcutaneous · Can be coupled to other ٠ Low cost of goods Intranasal Bicycles to create high · Heat stable no cold chain Inhalation affinity medicine which for low income countries · GI lumen restricted resists mutational escape

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 Simone Pellegrino



MRC Laboratory of Molecular Biology

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John Briggs (now at Max Planck Institute of Biochemistry) Katarzyna Ciazynska





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

Thank you

