Bicycle Therapeutics Announces Significant Progress Across Multiple Therapeutic Programs Beyond Oncology

March 30, 2021

- First milestone achieved in neuroscience collaboration with Dementia Discovery Fund and the Alzheimer's Research UK Oxford Drug Discovery Institute

- Significant advances made in the application of Bicycle *technology against emerging antimicrobial and antiviral targets*

- Additional Bicycles *identified through multiple development partnerships*

CAMBRIDGE, England & BOSTON--(BUSINESS WIRE)--Mar. 30, 2021-- Bicycle Therapeutics plc (NASDAQ: BCYC), a biotechnology company pioneering a new and differentiated class of therapeutics based on its proprietary bicyclic peptide (*Bicycle*®) technology, today announced progress updates for its *Bicycle*-based partnered programs outside of oncology.

"Over the last five years, Bicycle's strategy has been to use our novel technology to discover and develop a pipeline of innovative assets in oncology while additionally using non-dilutive funding and collaborations to explore the therapeutic potential of *Bicycles* in disease areas outside of oncology. Today, for the first time, we are providing an overview on our progress in demonstrating the broad utility of this platform to create molecules with the potential to treat some of the most serious diseases and address future healthcare challenges," said Kevin Lee, Ph.D., Chief Executive Officer of Bicycle Therapeutics. "It's incredibly exciting to see how the Company has worked innovatively and highly collaboratively with many diverse institutions to address these challenges and, at the same time, generated significant revenues to offset the costs of developing and progressing our internal oncology pipeline. I would like to thank all of our collaborators for their enthusiasm in this endeavor and look forward to continuing our work to advance these important molecules."

Bicycle has achieved the first milestone in its collaboration with Dementia Discovery Fund (DDF) and the University of Oxford's ARUK Oxford Drug Discovery Institute (ODDI)

- **The Company identified and optimized nM affinity *Bicycles* to TREM2, a genetically validated target for the treatment of dementia, and nM affinity *Bicycles* to transferrin receptor 1 (TfR1), a molecular shuttle.** In 2019, Bicycle established a collaboration with DDF, later expanded to include ODDI, to use *Bicycle* technology for the discovery and development of potential novel therapeutics for the treatment of dementia. The three parties are collaborating to identify and characterize *Bicycles* that bind to and activate TREM2, a genetically validated dementia target. As part of the collaboration, Bicycle is also using its technology to identify binders to TfR1, a blood brain barrier transporter, that could potentially enable delivery of *Bicycles*, or any other molecular payload, into the central nervous system (CNS), or other organ systems, expressing TfR1. Under the terms of the collaboration with DDF, Bicycle retains all rights to the TfR1 molecules outside of the license granted for use with targets defined within the DDF collaboration.

Bicycle advances platform in multiple anti-infective areas, including antimicrobials and antivirals

- **Innovate UK's Biomedical Catalyst (BMC) awarded the Company funding to advance a *Bicycle* inhibitor for a key cell wall biosynthesis target in *Enterobacterales,* Penicillin Binding Protein 3 (PBP3).** Bicycle is using its proprietary platform to try to address the significant healthcare challenge of antimicrobial resistance and has identified several potential *Bicycle* PBP3 inhibitors. Through grants awarded by the UK government and in collaboration with investigators at the University of Warwick, Bicycle intends to progress these PBP3 inhibitors, potentially representing the first novel class of antibiotics identified in decades, to candidate and initial toxicology testing.
- **Innovate UK, under a specific program targeting key technologies to rapidly respond to the challenge of COVID-19 (UKRI Ideas to Address COVID-19 – Innovate UK Article 25), provided funding to support Bicycle's efforts to discover new healthcare solutions to the SARS-CoV-2 pandemic.** Bicycle has identified numerous discrete families of *Bicycles* which bind to at least 10 different epitopes on the SARS-CoV-2 spike protein, binders to the Nucleocapsid protein and the viral attachment site on the host ACE2 human receptor. Through Bicycle's partnership with researchers at the MRC Laboratory of Molecular Biology, *Bicycles* identified by these screens have demonstrated nanomolar activity in inhibiting SARS-CoV-2 infection of human lung cells. These monomeric *Bicycles* have been conjugated together to make a diverse range of bi-paratopic and multi-valent small molecules (less than 10kD), some of which are active in the picomolar range in viral entry assays and may be resistant to the current SARS-CoV-2 variants of concern. Bicycle continues to advance these novel compounds in pre-clinical evaluation. Bicycle has also formed partnerships with diagnostic experts to evaluate its novel SARS-CoV-2 binding *Bicycles* in Lateral Flow Tests and other diagnostic screening formats.

Bicycle has made significant progress through partnerships with biopharmaceutical therapeutic area leaders in indications outside of oncology

- **The Company has successfully discovered and advanced targets outside of oncology through the ongoing collaboration with AstraZeneca, a global biopharmaceutical company, to discover novel agents for the treatment of respiratory and cardiometabolic diseases.** Two assets have been transitioned to AstraZeneca for further development and are currently being progressed in their discovery pipeline. Two additional assets achieved transition criteria and were transitioned to AstraZeneca but were returned to Bicycle by AstraZeneca.
- **Bicycle has also identified targets in its collaboration with Bioverativ (acquired by Sanofi in 2018) for the treatment of rare hematological diseases.** The Bioverativ collaboration successfully identified nM multi-valent inhibitors to P-Selectin, which inhibited human neutrophil binding and rolling, with potential applications in sickle cell disease and other inflammatory diseases. The Bioverativ collaboration also identified the first small molecule Factor VIII mimetic for the potential treatment of Hemophilia A. This mimetic is comprised of a multivalent *Bicycle* binding to both Factor IX and Factor X, leading to the production of activated Factor X (FXa), which successfully activated thrombin in plasma from Hemophilia A patients *ex vivo*. In 2019, Sanofi elected not to pursue further development, and the collaboration agreement was terminated. These "lead stage" assets have now been returned to Bicycle.

Kevin Lee commented, “With four *Bicycle* molecules now in clinical trials for both oncology and non-oncology indications, the technology has shown initial evidence of clinical tolerability and suitability for pharmaceutical development, and I look forward to seeing how *Bicycles* may bring important new treatment opportunities to poorly served patients in additional therapeutic areas.”

About Bicycle Therapeutics

Bicycle Therapeutics (NASDAQ: BCYC) is a clinical-stage biopharmaceutical company developing a novel class of medicines, referred to as *Bicycles*, for diseases that are underserved by existing therapeutics. *Bicycles* are fully synthetic short peptides constrained with small molecule scaffolds to form two loops that stabilize their structural geometry. This constraint facilitates target binding with high affinity and selectivity, making *Bicycles* attractive candidates for drug development. Bicycle’s lead product candidate, BT1718, a *Bicycle* Toxin Conjugate (BTC) that targets MT1-MMP, is being investigated in an ongoing Phase I/IIa clinical trial in collaboration with the Centre for Drug Development of Cancer Research UK. Bicycle is also evaluating BT5528, a second-generation BTC targeting EphA2, in a company-sponsored Phase I/II trial. BT8009 is a BTC targeting Nectin-4, a well-validated tumor antigen, and is also currently being evaluated in a Company-sponsored Phase I/II trial. Bicycle is headquartered in Cambridge, UK with many key functions and members of its leadership team located in Lexington, MA. For more information, visit bicycletherapeutics.com.

Forward-Looking Statements

This press release 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, although not all forward-looking statements contain these words. Forward-looking statements in this press release include, but are not limited to, statements regarding anticipated advancement of preclinical development efforts and initiation of clinical trials; the availability of data from preclinical studies and clinical trials; Bicycle’s ability to generate shareholder value; the therapeutic potential of Bicycle’s and its collaborators’ pre-clinical targets and product candidates; Bicycle’s and its’ collaborators’ ability to achieve planned milestones; and the availability of future funding. Bicycle may not actually achieve the plans, intentions or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various factors, including: risks to Bicycle’s and its collaboration partners’ abilities to meet anticipated deadlines and milestones presented by the ongoing COVID-19 pandemic; uncertainties inherent in the initiation and completion of preclinical studies and clinical trials and clinical development of Bicycle’s product candidates by Bicycle or its collaboration partners; the risk that Bicycle or its collaboration partners may not realize the intended benefits of Bicycle’s technology; availability and timing of results from preclinical studies and clinical trials; whether the outcomes of preclinical studies will be predictive of clinical trial results; whether initial or interim results from a clinical trial will be predictive of the final results of the trial or the results of future trials; the risk that studies and trials may be delayed and may not have satisfactory outcomes; potential adverse effects arising from the testing or use of Bicycle’s product candidates; risks related to Bicycle’s ability to maintain existing collaborations and realize the benefits thereof; expectations for regulatory approvals to conduct trials or to market products; and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, are described in greater detail in the section entitled “Risk Factors” in our Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on March 11, 2021, as well as in other filings Bicycle may make with the SEC in the future. Any forward-looking statements contained in this press release speak only as of the date hereof, and Bicycle expressly disclaims any obligation to update any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise, except as otherwise required by law.

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Investor and Media Contact:
Argot Partners
Maeve Conneighton
bicycle@argotpartners.com
+1-212-600-1902

Source: Bicycle Therapeutics plc