Press Release

FOR IMMEDIATE RELEASE

Contact: Gideon Bosker, MD
CEO, DarwinHealth, Inc.
Email: GBosker@DarwinHealth.com
Phone: (1) 503-880-2207

July 19, 2022

DarwinHealth Publishes Results of Novel, Viral Checkpoint-based Technology for Predicting Drugs that Inhibit SARS-CoV-2 Replication: Global Collaboration Highlights Generalizability of Reported ViroTreat Model for Host Cell-Directed Antiviral Drug Discovery, the Role of Master Regulator Proteins, and Application to other Viral Pathogens and Pandemic Response

New York, NY – (July 19, 2022) – DarwinHealth, Inc., a New York-based biotechnology and cancer drug discovery company announces the July 19, 2022 online publication in ***Communications Biology*** (a *Nature Portfolio* peer-reviewed journal) of a foundational paper focused on new approaches to antiviral drug discovery, "A model for network-based identification and pharmacological targeting of aberrant, replication-permissive transcriptional programs induced by viral infection." (https://www.nature.com/articles/s42003-022-03663-8)

With the Covid pandemic still a significant issue in many countries—a situation compounded by mounting concern about recurrent surges attributable to such highly transmissible Omicron variants as BA.5, BA.2.75 and others—there remains an unmet need for developing and deploying antiviral drug discovery models that can accurately and expeditiously predict, validate, and leverage the potential therapeutic effects of both established and investigational agents that inhibit viral replication. This is especially the case for identifying antiviral drugs that make infected host cells more resistant to viral infection—so-called "host-directed therapy" or HDT—and, thereby, have the potential to be effective as monotherapy or combination treatment to maximize the clinical effectiveness of FDA-approved drugs targeting the virus directly through alternate mechanisms.

Against this backdrop, DarwinHealth scientists and their international colleagues introduce and experimentally validate ViroTreat, a novel integrative, regulatory network-based experimental model that can be deployed for rapid identification of antiviral drugs targeting the host cell response to viral hijack within a cell system-wide context. Specifically, the model integrates both computational and experimental assays to: (a) identify regulatory network aberrations, at the transcriptional level (the Viral Checkpoint), induced by infecting viruses; and (b) predict drugs capable of inhibiting viral replication and infectivity by counteracting the hijacking of host cell regulatory mechanisms required for viral Infection.

In their report, the scientists noted that overall, *15 of the 18 drugs (83%) predicted to be effective by their methodology induced significant reduction of SARS-CoV-2 replication, without affecting cell viability*. In contrast, none of the 12 drugs selected as potential negative controls showed significant antiviral effect. Drugs were prioritized for evaluation based on their experimentally elucidated, context-specific mechanism of action determined by drug perturbations in appropriately matched cell lines. This model for host-directed pharmacological therapy is fully generalizable and can be deployed to identify drugs targeting host cell-based master regulator signatures induced by virtually any pathogen.

The publication is the result of a multi-institutional effort in search of an efficient, precision-focused methodology for pursuing treatments for both SARS-CoV-2 and a wide range of other viruses, and represents the outcome of an international collaboration among scientists from the Department of Systems Biology, Columbia University and the University of Florida (U.S.), the Department of Infectious Diseases, Molecular Virology, Heidelberg University (Germany), The Center for Precision Medicine, University of Bern (Switzerland), and DarwinHealth, Inc. (U.S), which conceived and lead this global project.

“Against a challenging backdrop in which traditional drug screening approaches and/or designing specific antivirals to address global pandemics are hampered by either lack of precision or unacceptably long development periods, respectively, the ViroTreat model we have developed can be seen as a chimeric method in which we specifically target the host with small molecules that render cells less permissive to viral infection and replication,” explained virologist Dr. Steeve Boulant, a lead author and Associate Professor, Department of Molecular Genetics & Microbiology, University of Florida College of Medicine. “Importantly, recent progress in organoid culture models, which are functional 'mini-organs in a dish,' made it possible to secure physiologically actionable data in the setting of SARS-CoV-2 infection, thereby permitting us to deploy ViroTreat to quickly and predictably identify agents that reduce infectivity. These advances make it possible to study both new and existing viral pathogens, including influenza, in relevant organoid models in a matter of only a couple of months, thereby expanding our toolkit with a critical, new technology that will be invaluable for emerging pathogens, as well as for existing viral diseases for which better and safer treatments represent an unmet need."

The application of single cell analysis to improve the precision of antiviral drug discovery was a key dimension of the model’s experimental design. “Because molecular analyses performed at the tissue level can easily produce distorted/mixed signals generated by both infected and non-infected cells, applying single-cell technology has been crucial for this work, explained lead author, Dr. Pasquale Laise, Senior Director of Single Cells Systems Pharmacology at DarwinHealth. “In this model, single cell technology permitted us to clearly distinguish infected from non-infected cells, thereby uniquely amplifying the transcriptional effects of SARS-CoV-2 on infected host cells. This allowed our team to identify—in fact, quantify, using protein activity levels assessed by our proprietary VIPER algorithm—the specific Viral Checkpoint signature induced in the host by the virus; and, by extension, reliably predict drugs that would inhibit replication during the viral hijack phase of infection."

The results of this global effort identified a new approach for targeting vulnerabilities of infective viruses that depart from conventional strategies aimed at antiviral drug discovery. “This work demonstrates that replication-permissive, viral hijacking of host cells is not limited to exploiting the machinery required for ribonucleotide and protein synthesis—or interference with innate antiviral immune responses—but goes deeper into the mechanisms that regulate host cell transcriptional identity; in particular, those inducing a host cell phenotypic state compatible with virus replication,” explains Dr. Mariano Alvarez, CSO DarwinHealth. “Importantly, we show the mechanisms regulating the hijacked cell transcriptional identity can be dissected with precision. Moreover, pharmacological interventions, which we predicted would block such transition, effectively locked cells into a viral infection-refractory state. This approach may constitute a new paradigm for efficiently identifying host-directed antivirals."

The group’s success draws on technologies and models focused on cancer drug discovery developed in the Califano Lab at Columbia University. “What is most remarkable is that a methodology developed to study cancer cells and developmental programs would work so effectively in prioritizing drugs for a highly virulent infectious disease,” emphasized Dr. Andrea Califano, Co-Founder of DarwinHealth and Professor/Chair, Department of Systems Biology, Columbia University (https://news.columbia.edu/news/deciphering-cancer-messy-and-complex-were-here-it) "The generalizability of the approach suggests that this could lead to rapid prioritization of treatments against other viral infections and future pandemics.”

“Until now, host cell-directed therapy (HDT) for viral infections has remained elusive. To our knowledge, this is the first time an integrated experimental and computational biological model of viral infection has been used to both dissect and successfully target and reprogram the regulatory logic imposed on a host cell by an infecting pathogen to facilitate viral hijacking,” explained Dr. Gideon Bosker, CEO and Co-Founder of DarwinHealth. “As such, our proprietary R&D pipeline, based on VIPER technology, is ideally positioned to be leveraged by biopharma partners to screen, discover and validate novel and existing pharmacologic agents that, due to mechanisms conferring ‘viral contraception’ at the host cell transcriptional level, can potentially be therapeutically effective against a broad spectrum of viral infections. Moreover, HDT-based approaches, such as the one we report, by directly targeting multiple, validated host interactors, may mitigate vulnerability to viral mutation-mediated alterations that potentiate immune evasion during infection.”

The DarwinHealth model reported in ***Communications Biology*** can be used as an expeditious way to identify and screen established pharmacologic therapies with low toxicity across a broad spectrum of mechanisms and viral pathogens—including coronaviruses and influenza—to identify host cell-directed therapies that may prove effective as either a direct, stand-alone intervention or as a complementary approach to direct antiviral treatments, including protease inhibitors and other agents.

“We believe the model we report—its methods, results, and applications—represents an exciting experimental approach for dissecting virus-host cell interactions that are amenable to pharmacologic targeting,” added Dr. Bosker, “We anticipate broad interest among scientists working on critical topics in host-microbe interactions and drug discovery in the context of viral infections and emerging pandemics, for

which accelerating the pace of discovery and reducing costs associated with traditional drug development processes are of paramount importance."

About DarwinHealth

DarwinHealth: Precision Therapeutics for Cancer Medicine is a "frontiers of cancer," biotechnology-focused company, co-founded by CEO Gideon Bosker, MD, and Professor Andrea Califano, Clyde and Helen Wu Professor of Chemical Systems Biology and Chair, Department of Systems Biology at Columbia University. The company's technology was developed by the Califano lab over the past 15 years and is exclusively licensed from Columbia University.

DarwinHealth utilizes proprietary, systems biology algorithms to match virtually every cancer patient with the drugs and drug combinations that are most likely to produce a successful treatment outcome. "Conversely, these same algorithms also can prioritize investigational drugs and compound combinations of unknown potential against a full spectrum of human malignancies, as well as novel cancer targets," explained Dr. Bosker, "which make them invaluable for pharmaceutical companies seeking to both optimize their compound pipelines and discover mechanistically actionable, novel cancer targets and compound-tumor alignments."

DarwinHealth's mission statement is to deploy novel technologies rooted in systems biology to improve clinical outcomes of cancer treatment. Its core technology, the VIPER algorithm, can identify tightly knit modules of master regulator proteins that represent a new class of actionable therapeutic targets in cancer. The methodology is applied along two complementary axes: First, DarwinHealth's technologies support the systematic identification and validation of druggable targets at a more foundational, deep state of the cancer cell's regulatory logic so we and our scientific partners can exploit next generation actionability based on fundamental and more universal tumor dependencies and mechanisms. Second, from a drug development and discovery perspective, the same technologies are capable of identifying potentially druggable novel targets based on master regulators, and upstream modulators of those targets. This is where the DarwinHealth oncotectural approach, with its emphasis on elucidating and targeting tumor checkpoints, provides its most important solutions and repositioning roadmaps for advancing precision-focused cancer drug discovery and therapeutics.

The proprietary, precision medicine-based methods employed by DarwinHealth are supported by a deep body of scientific literature authored by its scientific leadership, including DarwinHealth CSO, Mariano Alvarez, PhD, who co-developed the company's critical computational infrastructure. These proprietary strategies leverage the ability to reverse-engineer and analyze the genome-wide regulatory and signaling logic of the cancer cell, by integrating data from *in silico, in vitro*, and *in vivo* assays. This provides a fully integrated drug characterization and discovery platform designed to elucidate, accelerate, and validate precise developmental trajectories for pharmaceutical assets, so their full clinical and commercial potential can be realized. For more information, please visit: www.DarwinHealth.com.

END