ImmunityBio Simulates SARS-CoV-2 Spike Protein Binding Using Molecular Dynamics

January 4, 2021

Detailed computer modeling, completed in partnership with Microsoft, explains virulence of COVID-19 and provides key information that may lead to a better understanding of the multiple mutations currently occurring to the "spike" protein as the virus evolves

- Computer-based molecular dynamics simulation allows highly detailed visualization of free (unbound) spike receptor binding domain (S RBD) and dynamic S RBD-ACE2 (angiotensin-converting enzyme 2) interactions that cause infection.
- Free S RBD was modeled for 2.9 milliseconds and dynamic S RBD-ACE2 interactions were modeled for 2 milliseconds, an exceptionally long duration for molecular dynamics simulation that increases the likelihood that the visualized binding interaction accurately portrays what happens in nature.
- Simulation shows that the spike RBD protein is optimized for binding with ACE2, like a key for a lock, which leads to the virus' high infectivity rate.
- The analysis also revealed which areas on spike and ACE2 are important for their interaction— information that can be used to design new drugs to fight COVID-19, including a spike 'decoy' that mimics ACE2 and traps spike/the virus so it cannot bind to the cells of the airway.
- The modeling methodology could be applied to new versions of the virus, such as those that have emerged in the UK, South Africa and, more recently, the US, to determine the potential for greater virulence and/or possible reduction in vaccine efficacy.

CULVER CITY, Calif., January 4, 2021– ImmunityBio, a privately-held immunotherapy company, today announced the results of a highly detailed computer-based molecular dynamics (MD) simulation, conducted in collaboration with Microsoft Corporation, that allowed visualization of the behavior of the SARS-CoV-2 "spike" protein. The simulation provides an explanation for the virulence of the COVID-19 virus and has the potential to give researchers a roadmap for developing tools to disable the virus and future mutated versions.

"These findings demonstrate the extraordinary evolutionary adaption of the spike protein to readily bind and infect host cells," said Patrick Soon-Shiong, MD, Chairman and CEO of ImmunityBio. "We will use this important new data to inform our COVID-19 drug discovery program, advance the ongoing clinical trials of our vaccine candidate, and enhance our ability to understand threats posed by future versions of the SARS-CoV-2 virus, which has become a pressing issue with the spread of novel highly infectious SARS-CoV-2 variants."

The simulations indicate that the spike protein of the virus has evolved to be a nearly ideal fit for the ACE2 receptor—a viral "key" that engages perfectly with the "lock" that, when opened, allows the virus to insert its genetic material into the cell. Even in its free, unbound state, spike RBD assumes a three-dimensional shape that requires almost no adjustment to bind efficiently with host ACE2. This precision fit is what ensures the virus is almost always successful in infecting target cells in the human respiratory tract. Notably, the simulations showed the precise shape of the portion of the protein that binds to ACE2, the receptor binding domain.

The simulations were unique in that interactions between the spike protein and the receptor it targets to gain entry to human cells, known as human angiotensin-converting enzyme 2 (ACE2), were modeled for two milliseconds. This offers scientists a view that is approximately 10,000 times longer than most previous simulations, providing greater confidence in the results.

"Even though we hope that widespread vaccination will greatly reduce COVID-19, we know that not all individuals will get vaccinated and that the first-generation vaccines may not provide complete protection for all," said Dr. Soon-Shiong. "ImmunityBio is developing new therapeutics to treat infected individuals, and many of these therapeutic approaches will benefit from the findings revealed in this simulation."

Researchers are eager to visualize the way the spike protein interacts with ACE2, as well as the molecular profile of the RBD area, as this is what launches an infection. With the information revealed in the ImmunityBio molecular dynamic simulation, researchers have two potential paths forward to create therapies to disarm COVID-19. First, the simulation provides an experimental roadmap for the creation of molecules that would mimic ACE2 in the body—in effect, "dummy" locks to which the virus would bind instead of living cells. The simulation also provides key information that may be used to create therapies that change the shape of the RBD region so the viral "key" no longer fits the cellular "lock."

Microsoft Corporation and NantWorks provided the computing resources for the simulation, which provided detailed views of the most likely natural shape (conformation) of the spike protein. The manuscript and a video detailing the findings of the ImmunityBio molecular dynamic simulation studies is available on preprint server bioRxiv (see link here) and is concurrently undergoing scientific peer-review for publication.

About ImmunityBio

ImmunityBio, Inc. is a late-clinical-stage immunotherapy company developing next-generation therapies that drive immunogenic mechanisms for defeating cancers and infectious diseases. The company's immunotherapy platform activates both the innate (natural killer cell and macrophage) and adaptive (T-cell) immune systems to create long-term "immunological memory." This novel approach is designed to eliminate the need for high-dose chemotherapy, improve upon the outcomes of current CAR T-cell therapies, and extend beyond checkpoint inhibitors.

ImmunityBio's platform is based on the foundation of three separate modalities: antibody cytokine fusion proteins, synthetic immunomodulators, and

second-generation human adenovirus (hAd5) vaccine technologies.

Anktiva™ (ImmunityBio's lead cytokine infusion protein) is a novel interleukin-15 (IL-15) superagonist complex and has received Breakthrough Therapy and Fast Track Designations from the U.S. Food and Drug Administration (FDA) for BCG-unresponsive CIS non-muscle invasive bladder cancer (NMIBC). The company is also in Phase 2 or 3 trials for indications such as first- and second-line lung cancer, triple-negative breast cancer, metastatic pancreatic cancer, recurrent glioblastoma, and soft tissue sarcoma in combination with the company's synthetic immune modulator (Aldoxorubicin).

ImmunityBio is also developing therapies, including vaccines, for the prevention and treatment of HIV, influenza, and the coronavirus SARS-CoV-2 with its second-generation human adenovirus (hAd5) vaccine technologies.

F*orward-Looking Statements*

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include statements concerning or implying that ImmunityBio will be successful in improving the treatment of the novel coronavirus, the timing and results of the clinical development of had5-COVID -19 oral capsule vaccine, or whether ImmunityBio will be successful in gaining regulatory approval of, commercializing or distributing the vaccine. Risks and uncertainties related to these endeavors include, but are not limited to the successful completion of the currently contemplated Phase 1 trials and the currently enrolling Phase 2 trial and subsequent clinical development and FDA approval of the vaccine on the currently anticipated timeline, if at all, as well as manufacturing and distribution challenges., Risks and uncertainties related to this endeavor include, but are not limited to, the company's beliefs regarding the success, cost, and timing of its development activities and clinical trials.

Forward-looking statements are based on management's current expectations and are subject to various risks and uncertainties that could cause actual results to differ materially and adversely from those expressed or implied by such forward-looking statements. Accordingly, these forward-looking statements do not constitute guarantees of future performance, and you are cautioned not to place undue reliance on these forward-looking statements. These forward-looking statements speak only as of the date hereof, and we disclaim any obligation to update these statements except as may be required by law.