Combining AI and Quantum Mechanics to Improve Drug and Vaccine Discovery

March 22, 2022   by Andrii Buvailo | Sponsored by **PharmCADD**

The application of Artificial Intelligence (AI) to accelerate and improve drug discovery has been a growing trend for several years in a row, with the increasing number of AI-inspired drug candidates entering clinical trials. While AI proved to be a powerful tool for modeling biological systems and helping generate optimal leads, it is important to remember that deep learning (DL) -- the heart of the modern "AI revolution" -- is only as good as the underlying data used to train models. Since the majority of AI-driven companies are "playing" with classical Newtonian mechanics to describe the motions of atoms and molecules, sometimes they can run into limitations of "classical physics" as a tool to describe biological systems, hence, lower ability to grasp the intricacies of biology.

A small number of companies are combining the latest advances in artificial intelligence research with the application of quantum mechanics (QM) methods to more accurately describe the behavior of the electrons in atoms and molecules, thereby getting better prediction results for, let's say, ligand-target binding scenarios.

One such company, a South Korean biotech PharmCADD, caught my attention recently because of two reasons. One reason was that the company offered a platform-based AI-driven system for drug discovery, involving quantum physics modules -- a promising combination. Another reason -- the company focused on a surprisingly wide diversity of various drug modalities and target types, and it even had a clinical-stage mRNA-vaccine candidate in its pipeline -- in collaboration with an external partner.

Below is my interview with **Dr. Sangwook Wu**, CEO/CTO at PharmCADD, where he explains how their technology operates, what the role of AI and quantum physics in drug discovery is, and how drug makers can partner with such AI-platform companies as PharmCADD to leverage technology and enrich their pipelines with promising assets.

Andrii: Can you briefly introduce yourself and how you became a part of PharmCADD's story? A couple of words about the company's services and your pipeline of products?

Sangwook: In addition to my CEO/CTO position at PharmCADD, I am teaching physics at Pukyong National University in South Korea. Although I earned my bachelor's degree in biochemistry, I realized that my academic interest was in biological physics as well as quantum physics. I followed my interest at the graduate schools and earned my Ph.D. in condensed matter physics at Iowa State University. I learned various computational chemistry principles and machine learning (ML) approaches during my postdoctoral training at the University of North Carolina at Chapel Hill. When I became a faculty member in 2014, the application of computational approaches including the use of AI/ML algorithms in drug discovery was still at the very early stage. Mr. Taehyung Kwon, co-CEO of PharmCADD, quickly realized the huge potential of my research achievements when he visited my research lab, and encouraged me to build a biotech company together. Mr. Kwon and I made a business plan together in late 2018 and registered the company's name in March 2019. That's the history of PharmCADD.

Our business model does not include "fee for service" at the moment, we would rather perform collaborative R&D with partners for an upfront fee (or, technology access fee), milestone-based payment, and royalty payment. We would also want to provide pre-clinically ready small molecule compounds for license-out deals. Currently, we are developing several internal and collaborative pipelines including anticancer drugs (Figure 1). We have also licensed-out thermostable and translationally efficient mRNA sequences of SARS-CoV-2 spike protein to a Korean biotech company, EyeGene. This pipeline is the first mRNA vaccine for COVID-19 in Korea which is in phase 1/2a clinical trial.

Figure 1. PharmCADD's Pipelines
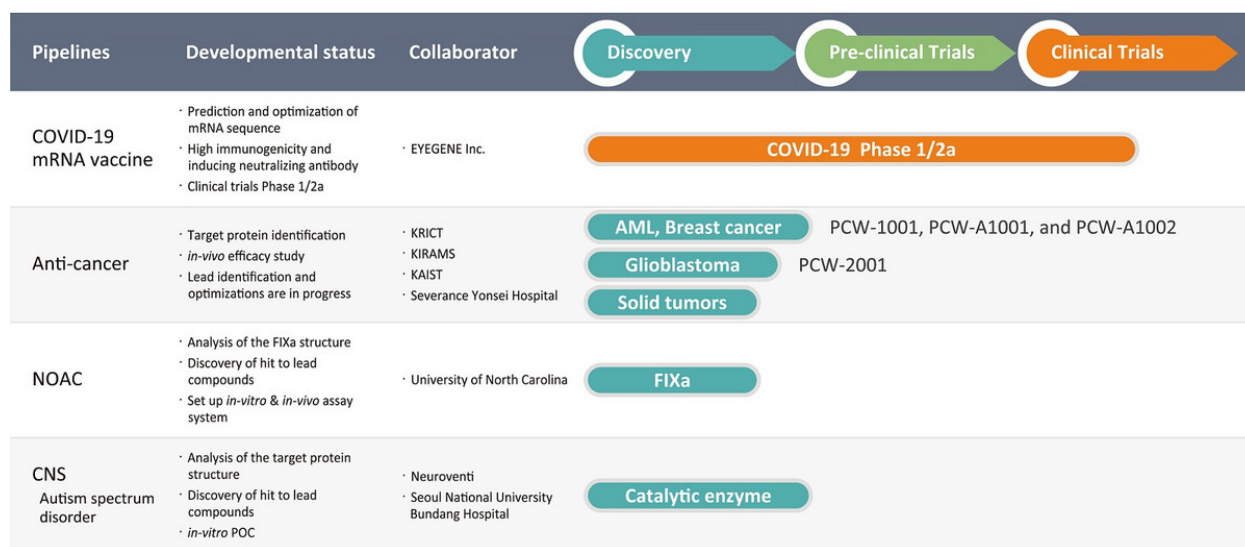
Andrii: So, the company is developing both therapeutics and vaccines -- those are quite different things. How do you manage to run programs in those different areas simultaneously? What resources, including funding and team, do you have for such diverse scope of R&D efforts?

Sangwook: As you mentioned, development strategies for small molecule therapeutics and for vaccines are quite different. I haven't dreamed to develop both modalities when I formed the R&D team. As you might expect, I built R&D team focusing on small molecule therapeutics at first. However, COVID-19 came to us unexpectedly and the need for therapeutics became an imminent and urgent issue. Fortunately, I had research experience in nucleic acid 3D structure, and some of my R&D team members were trained in RNA sequence optimization research at MIT. In collaboration with EyeGene, which has ongoing vaccine programs with a promising liposome delivery technology, I could jump into the mRNA vaccine development program with strong confidence and enthusiasm. We anticipate that this vaccine program would enter into phase 3 in clinical trials in the second half of 2022. The motivation that I would run both small molecule therapeutics and vaccine programs come from the diverse research background and the high quality of my R&D team. PharmCADD has over 50 scientists and engineers in the R&D team, and among them, 35 scientists have Ph.D. degrees in the field of computational chemistry, physics, biology, and Artificial Intelligence. That is why we could carry diverse R&D programs like the kinase inhibitor, PROTAC, GPCR antagonist, drug delivery system (DDS), RNA-based vaccine, and RNA

BiopharmaTrend.com
A fresh viewpoint on drug discovery, pharma, and biotech

info@biopharmatrend.com

Bio
Pharma
Trend

structure-targeting drugs.

As we have been promoting open innovation from our inception, we have multiple R&D collaborations which could fill the scientific gap that we are missing. The collaborators work in the global top institutes including CNRS, IIT, UNC, CMU, KAIST just to name a few. Finally, our R&D effort could not be sustained without funding. As of today, we have secured US $ 25M through series B funding. We are currently preparing for pre-IPO funding rounds and expect to secure substantial R&D money.

Andrii: What does Pharmulator™ do? What are the key components of the platform and what drug and vaccine discovery stages do they serve?

Sangwook: Pharmulator is an AI & Physics-based in-silico drug design platform. It consists of five core modules that employ A.I. algorithms: Protein/RNA 3D Structure Prediction, High throughput virtual Screening, Quantum Calculation, Toxicity Prediction, and Drug Generation (Fig. 2). Those five core modules can provide highly efficient solutions at the discovery stage. Pharmulator could significantly reduce time and cost that are associated with the early drug discovery stage.

Figure 2. Platform technology; Pharmulator
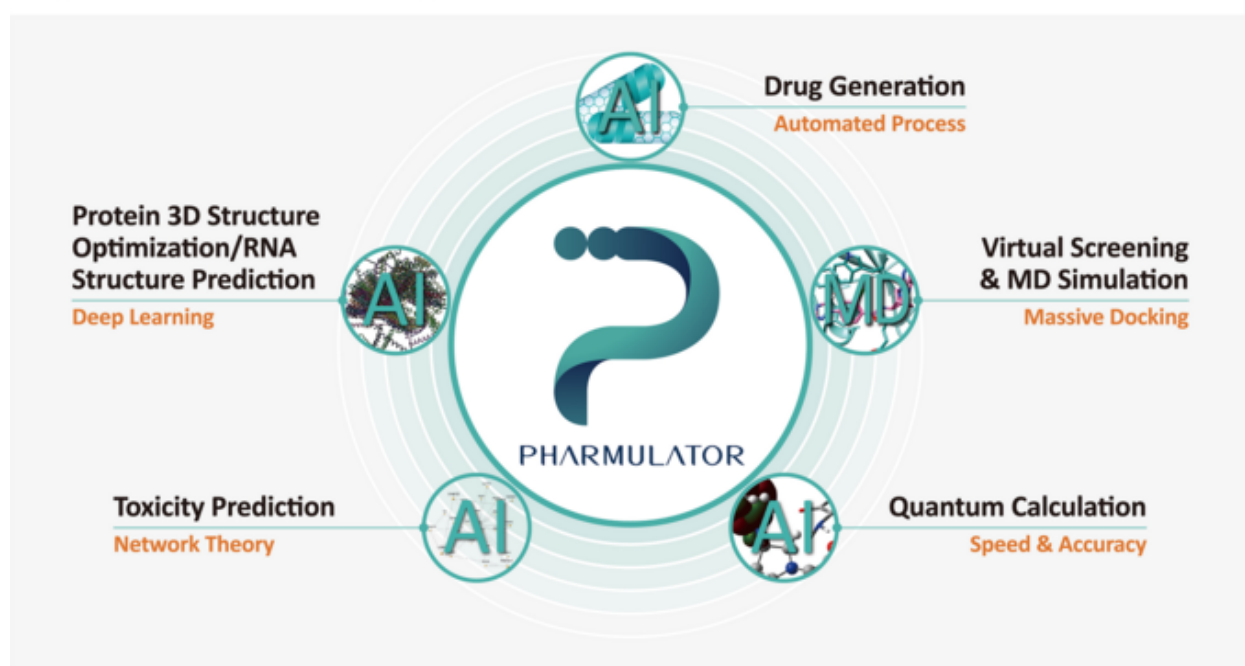
In addition to Pharmulator, we developed a platform technology specific for vaccine discovery: PharmVAC. It is a platform that integrates AI-assisted modeling of 2D/3D RNA Structure and Drug Delivery Systems. It can provide optimal solutions to design, analyze and visualize the optimized RNA sequences for any vaccine candidates. It can simulate how the drug delivery system works in atomistic and coarse-grained scales. PharmVAC also enables us to generate the optimized RNA-targeting small molecules by a combination of five core modules in Pharmulator.

Andrii: What does a typical research program look like at PharmCADD from start to finish? How do you validate your platform's predictions? Do you have your own wet lab facilities or do you prefer outsourcing experimentation to external contractors?

Sangwook: PharmCADD's typical drug discovery program starts with a target protein selection. Using Pharmulator, we generate 3D structure of the target protein and perform high throughput virtual drug screening. Once we virtually identify potential hit compounds for the target protein, we could perform a biochemical or cell-based assay to confirm the candidate compounds' activity. We have set up an in-house wet lab facility for this kind of test. The confirmed hit compounds with efficacy would be used as pharmacophores to generate novel lead compounds after going through Pharmulator's AI drug generation and toxicity prediction modules. We always make sure that the lead molecules can be further optimized for the target protein by Molecular Dynamics simulation and subsequent Free Energy calculation in an explicit solvent model. We validate our technology by publishing peer-reviewed papers and collaborative R&D work with outside partners. Our outside R&D partners include investigators of public research institutes like CNRS in France, Korea Institute of Radiological & Medical Sciences (KIRAMS), Korea Research Institute of Chemical Technology (KRICT), and multiple biotech and pharma companies in Korea. As we are in silico focused company, we generally utilize CRO for chemical compound synthesis and in vitro & in vivo drug efficacy tests.

Andrii: You mentioned quantum calculations as a part of your computational strategy -- can you expand on this? What are the specific benefits of using quantum theory in your drug discovery pipeline, why "traditional" computational methods are not sufficient to do the job?

Sangwook: In general, we employ Molecular Dynamics simulation to understand the binding modes of small molecules to the target protein. One of the setbacks of Molecular Dynamics simulation, however, includes inappropriate parameterization of the force fields for certain kinds of small molecules, which leads to inaccurate prediction of binding modes of those small molecules to the target protein. Quantum Mechanics (QM) considers the system at the electronic level. For example, QM/MM calculation works better than conventional molecular mechanics (MM) calculation in the estimation of the binding affinity of a small molecule to target metalloenzyme. In short, using Pharmulator module, we can calculate the quantum chemical properties of the ligand which can be useful in the estimation of the correct binding mode and binding energy of the ligand.

Andrii: What are your thoughts about the "marriage" of artificial intelligence and quantum calculations approaches for drug discovery and vaccine development? What synergies do you see in combining those two areas of technology, even beyond drug discovery?

Sangwook: The combination of artificial intelligence and quantum calculation generates highly efficient synergies. In a conventional way, researchers have to spend a huge amount of time and resources to perform quantum calculations. Typically, an experienced Ph.D. level scientist would need minimum of several hours to complete the quantum calculation of a single compound. And, for some chemical compounds, you may fail to assign accurate partial charges. At PharmCADD, we developed an AI-based quantum chemical calculation module to automate complicated processes. Therefore, we can provide time and quality efficient solutions to perform QM calculations which can be used to predict the best candidates.

Andrii: According to BiopharmaTrend's report "The Landscape of Artificial Intelligence in Pharmaceutical Research", the community of AI-powered drug discovery companies is represented by more than 350 players across the globe, with dozens of companies in the area of target discovery and lead generation. How is Pharmulator™ unique as compared to other solutions?

BiopharmaTrend.com

A fresh viewpoint on drug discovery, pharma, and biotech

Bio
Pharma
Trend

info@biopharmatrend.com

Sangwook: There are many AI-powered drug discovery companies globally. However, there are only a few companies that employ both AI and physics-based approaches for drug discovery. In my mind, Schroedinger and XtalPi would be the most similar companies to PharmCADD in terms of technical approaches. Also, PharmCADD is probably one of a small number of companies with products in the clinical stage. Recently, there was exciting news about Exscientia's AI-based drug programs in clinical trials, and Insilico medicine's development of preclinical ready drugs. As I mentioned earlier, we are co-developing an mRNA vaccine for COVID-19 in phase 1/2a clinical trial in Korea.

Andrii: What do you offer to clients and partners? What does a typical collaboration scenario look like?

Sangwook: PharmCADD has a very flexible business model. Typically, we start drug discovery projects with a selection of disease-relevant target proteins, RNA, or vaccines. Using Pharmulator or PharmVAC, we would generate optimized lead molecules with a strong IP package. The companies that want to enter the biotechnology industry without their own pipeline, or that want to expand discovery/preclinical stage pipeline would be the main business partners. We could also collaborate with clients who prefer to utilize our platform technologies from the inception of a new project. In this case, the client would own the entire IP from the project and PharmCADD would receive a technology access fee and milestone-based and/or royalty payment.

- PharmCADD