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The Future of Pharmaceuticals: AI Drug Discovery & COVID-19 Treatments

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ABSTRACT

AI Drug Discovery (AIDD) is the implementation of artificial intelligence and computational modeling in the process of finding the ideal medicinal drug for a given ailment; its primary benefit is exponentially speeding up the drug discovery process to about 1 to 2 years, whereas the traditional steps of lead optimization, clinical trials, regulatory approval, and medicinal manufacturing would span approximately 10 years. The COVID-19 pandemic could have been far worse and for a far longer duration if AIDD was not utilized, demonstrating great technological advancement in the field of medicine from the Spanish Flu pandemic in 1918. The benefits of AIDD in areas outside of COVID-19 can be seen in how Wisecube AI developed treatments for Alzheimer's disease, Schrodinger AI was able to suppress tumors through protein analysis, and the drug discovery database of the scientific community is expanded through AIDD algorithms produced by companies like Standigm and Cytoreason. The idea of repurposing, the use of preexisting drugs to be slightly altered to cover completely different ailments, is also enhanced. In terms of COVID-19 treatments, however, AIDD is used to attack the virus through all forms of vaccinology, including protein-based, RNA-based, and mRNA-based vaccines. The Pfizer and Moderna vaccines are recommended the most by the CDC because of their effective innovation with AIDD in mRNA vaccinology. Simply, AIDD accelerates the R&D timeline of finding drug treatments for the prominent diseases that concern global intervention, and the world nears medicinal mastery with the utilization of computers.

Introduction

The typical timeline for a vaccine's development spans approximately ten years and can take up to $1 billion to account for how safe and effective the drug should be. Researchers need this much time to properly formulate the vaccine's composition, including weakened fragments of the virus and the antigen (usually in the form of a protein or sugar) meant to elicit the immune response. (Joi, 2021) Additionally, numerous clinical trials must be conducted to assess the vaccine's long-term safety, efficacy in causing an immune response to the virus, and the appropriate dosage measurements for large-scale use. Only then can the vaccine be submitted for a regulatory approval process, such as that by the Food and Drug Administration (FDA) or Emergency Use Authorization (EAU), and be manufactured at a large enough scale for the public dosage requirement. (Johns Hopkins University of Medicine, 2021) Despite these time-consuming measures needed for the complete development of a vaccine, the Pfizer vaccine for early variants of the SARS-CoV-2 virus that causes COVID-19 became FDA-approved within just one year of the virus's initial sightings in the Wuhan province of China.

The COVID-19 pandemic resulted in an unprecedented crisis for national governments and the world economy, so there existed a global urgency to find a vaccination treatment that could bring the world back to a pre-pandemic lifestyle as swiftly as possible. We should also note that alternate coronaviruses have had illness-inducing effects and have been studied for the last 35 years, although none have been as globally damaging as SARS-CoV-2. (Yang and Leibowitz, 2015) With the newfound implementations of artificial intelligence in drug discovery, the process of finding candidate medicines, vaccines such as those for COVID-19 can be developed by an alternative, quicker

method. This method is AI Drug Discovery, which more and more drug developers are beginning to utilize towards the goal of making the vaccine development process more efficient in times of crisis as the current pandemic.

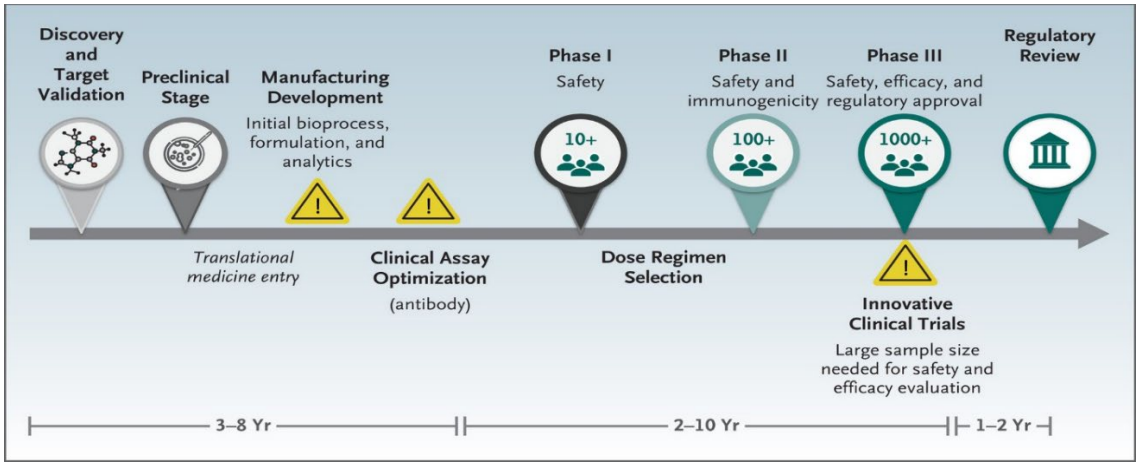

Figure 1. Traditional vaccine R&D timeline without computer-aided drug discovery.

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What is AI Drug Discovery? What can it be used for?

AI Drug Discovery (AIDD) uses artificial intelligence (AI) and computational modeling to shorten the otherwise lengthy process of examining molecules for their application in medicine. In more traditional instances of drug discovery, researchers must use trial-and-error to find the correct molecule or combination of molecules that can induce the desired effect for the whole drug. More specifically, researchers attempt to find a lead, a molecule that can provide a therapeutic benefit to the target disease-causing molecule and subsequently optimize that lead to remove all undesirable properties. (Cuffari, 2021) Lead optimization is similar to a lock-and-key analogy: one must try out every key in a countless selection (the potential lead) to find which one opens the lock (reacts desirably with the target.) Although, that lead can only be considered a medicinal drug after thorough lead optimization. However, this process is very tedious. On average, approximately $2.6 billion is required to develop a single drug, and under 12% of all clinical trials to test the drug result in actual successes. (Sullivan, 2019; Takebe et al., 2018) AIDD can be used to make the drug discovery process more efficient in time and cost, as well as raise the overall success rate of the clinical trials. Instead of finding the perfect key, the computer can work as a GPS to navigate the optimal leads to react with the inputted target.

Using AIDD in Alzheimer's Disease Treatments by Wisecube AI

We can look at the benefits that AI Drug Discovery has provided for the treatment of Alzheimer's Disease. For context, Alzheimer's Disease results from the formation of plaques, made up of amyloid proteins, in select brain regions, which over time result in weakened brain plasticity near synapses. Additionally, modifications to tau proteins caused by Alzheimer's Disease result in dissociation of the neuron's microtubule, which breaks apart and kills the neuron. As neurons die, the amyloid plaques and modified tau proteins spread to other healthy neurons; with enough spread, the gradual degeneration in the brain will lead to symptoms, such as an inability to process, store, or recall information and memories. (NHS, 2021) According to the Alzheimer's Association, in 2021, over 1 in 9 people aged 65 or older suffer from Alzheimer's Dementia. (Alz, 2021) Current drug treatments for Alzheimer's disease can only provide symptomatic relief but do not stop the disease's spread. Examples of these include Donepezil, Rivastigmine,

Galantamine, and Memantine. (Alzheimer's Society, 2017) However, by using AI Drug Discovery, researchers from Wisecube AI are making progress in the clinical treatments, at least in terms of tau proteins. This is done by targeting the CDK5-p25 pathway that allows for phosphorylation, the process that modifies the tau proteins into causing neurodegeneration. Through computational modeling, simulations, and dockings, AI examines CDK5-p25 interfaces and binding pockets to successfully progress in developing anti-tau PPI (protein-protein interaction) inhibitors that could potentially cure Alzheimer's disease beyond just relieving symptoms. (Vettrivel and Yenugonda, 2021; Kanungo et al., 2017).

Using AIDD to Suppress Tumors by Schrödinger AI

Alzheimer's disease is just one application of CADD's benefits for making progress in previously stagnant treatments of illnesses. Many other digital organizations enhance the benefits of AI Drug Discovery, such as Schrödinger, a physics-based computational platform aimed towards creating innovations for internal drug discovery. Among many contributions to the scientific community, Schrödinger used a computational modeling system known as Maestro to utilize a Protein Preparation Wizard (PPW) and visualize hydration sites of a binding pocket through what is known as a WaterMap. (Leger et al., 2020) Aimed towards the ultimate goal to discover inhibitors that would suppress tumor growth, Schrödinger's Dr. Christopher Higgins applied the PPW, the WaterMap, and Free Energy Perturbation (FEP+), to provide critical information on which molecules would be ideal for binding with the tumor. For example, the WaterMap identified a cluster of hydration sites that could be chemically displaced to increase the potency of the compound. Also, FEP+ was able to automatically explore and synthesize additional parts of the molecule that would have taken far more time and cost. (Higgins, 2020) Schrödinger's drug discovery computations allowed for more chemical space to be understood far faster than using the traditional trial-and-error, lock-and-key methods. The fruits of the study were found in identifying USP7, a protein-coding gene found in tumors, as a target pathway for future cancer treatments, which could further be enhanced with the further continuation of AI Drug Discovery in that field. (Leger et al., 2020).

AIDD Data Database Algorithms by Standigm and Cytoreason

Other examples include the AI Drug Discovery company Standigm's user interface feature called Standigm ASK that indiscriminately finds all potential targets for any given disease. The software is additionally capable of prioritizing certain desired drug-target relationships and can data-mine for literature-based results. (Kim et al., 2020) Cytoreason is a leader in machine-driven learning for drug research and development. Their tuMap algorithm allowed for comparative analysis of data gathered from other single-cell cancer samples. Although single-cell technologies provide deep insight into that specific sample of cancer, there is a limited chance for treatments found in that sample to be generalized across heterogenic cancer patients. When used to meaningfully compare cytometric data for myeloid leukemia samples, the tuMap algorithm was able to identify establishing commonalities between the cellular nature of each sample. The algorithm within itself could also automate the analysis of the comparatively derived data and establish metric standards for future patient evaluation. (Alpert et al., 2021) Cytoreason then held a subsequent longitudinal study of the benefits that the metric standards gathered from the tuMap algorithm for certain cancer patients. The study ascertained that the metrics were effective in establishing a quantitative framework for evaluating the early stages of myeloid leukemia, among other cancers. (Good et al., 2018).

AIDD in Repurposing

The added benefit known as repurposing should also be noted when considering AI Drug Discovery, the use of existing drugs to treat new illnesses. (Zhou et al., 2020) Polypharmacology is a concept that surrounds the idea that interacting

drug molecules can react with multiple targets, which puts the focus of drug discovery on new off-targets from existing drugs. (Reddy and Zhang, 2013) The pharmaceutical technology company Healx is a primary user of artificial intelligence to completely explore all medicinal potentials of a discovered molecule. Healx uses what is known as a Rare Treatment Accelerator and an AI platform called HealNet to promote the "redevelopment" of existing drugs. Essentially, the RTA slightly modifies the existing drugs to redirect, or repurpose, them to target alternatively desired targets. (Jimenez, 2021) Drug repurposing as a whole is becoming less dependent on genomic information and is essentially being made more efficient with computational gatherings of data. In the pressing case of cancer treatments, artificial intelligence-based methods increase the efficacy of target profiling by the computer and, when executed with functional testing of cancer cells, can establish cancer treatments out of other repurposed drugs. (Tanoli et al., 2021) As AI Drug Discovery computationally models the search for the appropriate drugs to treat a crisis-inducing disease like COVID-19, AI can also look back onto existing treatments for other diseases to make further progress.

How were COVID-19 Treatments/Vaccines made with AIDD?

Breaking down the R&D of a COVID-19 Vaccine

There are many reasons why the COVID-19 vaccine's research and development speed was so quick compared to traditional vaccine R&D procedures. Some of which include worldwide collaboration as every developed country toiled to bring about an end to the pandemic, previous knowledge about other coronaviruses, global funding for vaccine research. (MedicalNewsToday, 2021) However, a primary factor is the type of methodology used to develop the vaccine.

First, we should examine the many types of methodologies to develop any traditional vaccine, particularly the genetic coding step that tells the virus to elicit the desired immune response. DNA vaccines are meant to be recognized as foreign DNA so the immune system can take the proper steps to eliminate the foreign DNA; however, no such vaccines are commercially available. Vector virus vaccines send the vaccine's gene in the form of an unreproductive virus that cannot cause disease. The Johnson & Johnson and AstraZeneca COVID-19 vaccines are vector virus vaccines. (Offit, 2021) Finally, the CDC-preferred Pfizer and Moderna vaccines are made by mRNA (messenger RNA) genetic coding. mRNA is the genetic code used to make a protein. The mRNA of the virus's spike protein, which attaches the virus to the cell, is implanted in the vaccine so that the immune system essentially creates the virus's spike protein, and subsequently creates antibodies for it as the mRNA degrades. So, if the real virus enters your body, the immune system already has the information to make antibodies to fight off the spike protein. (Offit, 2021) mRNA vaccine development has been used before, such as for the Zika virus, rabies, and CMV. However, its combination with AIDD makes the COVID-19 vaccine relatively unique.

Protein-Based AI Drug Discovery to Treat COVID-19

COVID-19 treatment drug discovery has incorporated AI in numerous ways. An example of protein-based AI drug discovery is when BenevolentAI was able to find repurposed treatment for COVID-19 from a drug for rheumatoid arthritis known as Baricitinib by using AI to target the inhibition of the AAK1 protein. (Richardson et al., 2020) Cyclica Inc. investigated for candidate drugs that can be repurposed for COVID-19 treatment, incorporating polypharmacology, through the data-mining of PolypharmDB, a resourceful database of drugs with their protein bindings. Similar to other repurposing drug discovery methodologies, Cyclica Inc. targeted the joint inhibition of TMPRSS2 and cathepsin B and identified 30 candidates to repurpose for COVID-19 treatment drugs. (Redka et al., 2020).

RNA-Based AI Drug Discovery to Treat COVID-19

There are also RNA-based treatments for COVID-19 surrounding AI, which are more applicable to the vaccine's R&D. By forming a reaction with the RNA, itself, there are more limited subsequent effects on the infected cell because the treatment strategy is carried out before long-term viral influence. Earlier, pre-pandemic research of coronaviruses established databases of information on the ribosomal frameshift of a coronavirus, as distinguished from other viruses. (Plant and Dinman, 2008). Computational data mining of similar ribosomal frameshifts, translations of RNA by the influence of mRNA from other molecules, is the connecting step between the database and the computing of which molecules' mRNA will desirably translate the viral RNA. As mentioned before, a vaccine relies on antigens to elicit an immune response. If we take the AI-based analysis of treatment drugs for COVID-19 a step further, AI is used to find repurposed drugs to serve as antigens in the vaccine. A study with a Random Forest algorithm undertakes this strategy as CADD predicts effective antigens in a long list that, when put under specific computational criteria, can narrow down the most accurate antigens. This method can be called reverse vaccinology. (Rahman et al., 2019) Algorithms similar to a modified Random Forest will develop accurately and speedily ranked lists of potential treatments.

AI Drug Discovery to make a COVID-19 Vaccine (Pfizer & Moderna)

As concluded from the results, vaccinologists are leaning towards drug discoveries that exploit the spike proteins because of their uniqueness in SARS-CoV-2. The Pfizer and Moderna vaccines both utilize mRNA copies of the spike protein. AI algorithms expanded and made the mRNA samples far more accurate; in one month, Moderna went from 30 manual mRNA samples to thousands of automated ones. (Johnson, 2021) As per RNA-based vaccine developments, the body receives information to battle the virus's entry into the cell, signifying that the vaccine has carried out its job. (NebraskaMed, 2021) The world continues to get closer to pre-COVID-19 times, and AI Drug Discovery has exponentially sped up the way there.

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