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Treating SARS-CoV-2 Virusby RepurposingAnti-Cancer Drugs

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Abstract:
Drug repurposing is a method which involves reutilisation of drugs which were initially developed for a targeted ailment, and are in turn used to treat another. Given the massive cost and slow stride of contemporary drug discovery; the method of repurposing the drugs that already exist, is increasing at an impressive pace and simultaneously gaining a lot of popularity in recent times. Various Deep learning frameworks and a data-driven experimental approach suggests the archetype of drug samples which can be reused. Drug repurposing has immense potential to treat both, common as well as rare diseases and have also proved to be competent to a certain extent. In the current pandemic situation of corona virus disease (COVID-19) caused by the SARS-CoV-2 virus, drug repurposing has served to be a beneficial practice. The current analeptic options are shortly numbered and having said that, its effectiveness is undefined and modest at best. Observations implied that medications for Cancer and COVID-19 share similar goals to overcome like inflammation, inhibition of cell division and moderation of the host microenvironment to control the disease. Multiple researches have been conducted on a global scale and it has been proved that certain anticancer drugs are effective against the SARS-CoV-2 and some have even reached to the stages of being clinically tested. The development of new drugs costs an arm and a leg but moreover it requires a lot of time and if we have learnt something in this pandemic period then it is that, time is a currency in itself. In this review we present how to approach drug repurposing, examine the challenges faced by the researchers and advocate innovative ways to overcome the same while exploring the unrealised potential of drug repurposing.

Keywords- *Anticancer, COVID-19, reutilisation, potential, alternative treatment.*

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I. Introduction

1.1 DRUG REPURPOSING

Drug repurposing (DR) is a method which involves repositioning, re-tasking, reprofiling, rescuing, recycling, redirection and reassigning of drugs to cure an alternative ailment apart from its purpose of production. It can also be defined as a process of identification of a potential to treat newer needs from the existing/failed/already marketed/pro-drugs and the use of newly synthesized drugs to treat diseases outside of the drugs intended analeptic use. It involves establishing new therapeutic uses for drugs already existing drugs which means drugs which are in function or were discontinued or were abandoned or were just a failed experiment. Traditional drug discovery is a time consuming, laborious, highly expensive and high-risk process. The novel approach of drug repositioning has the potential to be employed over traditional discovery program by mitigating the expenses & excessive time consumption for a discovery alongside the risk for a failure. Drug repurposing is a worth-it risk to be taken as it has a reduced risk of failure with a rate of 45% while giving the added benefit of saving up to 5-7 years which would be otherwise consumed if chosen to discover new drugs.
The basic differences in new synthesis of drugs and repurposing the older ones is:

SYNTHESIS OF NEW DRUGS	REPURPOSING OF OLD DRUGS
Synthesis of new drugs is a 5-step process which includes; 1. Discovery and preclinical 2. Safety review, 3. Clinical research 4. FDA review 5. FDA post-market safety monitoring	Repurposing of old drugs is a 4-step process which includes; 1. Compound identification 2. Compound acquisition 3. Development 4. FDA post-market safety monitoring
It is a time-consuming and costly process with high risk of failure.	With the advancement of bioinformatics/cheminformatics tools and availability of huge biological and structural database, drug repositioning has significantly decreased the time and cost of the drug development with reduction in risk of failure.
The traditional approach to drug discovery involves de	In recent years, the use of in silico techniques along with the

novo identification and of new molecular entities (NME).	application of structure-based drug design (SBDD) and artificial intelligence (AI) technology has further accelerated the drug purposing process.

Table 1.1.1

Drug repurposing has gained tons of enthusiasm and considerable momentum over time with about 1/3rd of latest drug approvals being from the currently existing drugs which in-turn generates a revenue of about 25% for the pharmaceutical industries. it had been recently noted that around 30% of the recently approved drugs are repositioned. Global markets proved recently that an estimate of $31.3 billion is that the market price for repurposed drugs.

Drug repurposing had been accidentally discovered within the early 1920s. After a few century of development more approaches were developed for accelerating the method of repositioning. Some most successful and best-known drugs that are emerged out of the DR approach are sildenafil, minoxidil, Depokene , methotrexate etc. for instance , sildenafil originally developed for the treatment of hypertension and angina has currently been wont to treat male erectile dysfunction .

1.2 Mechanism of Infection

The mechanisms of infectivity and pathogenesis of the coronavirus remains not documented however it seems to be quite almost like those of SARS-CoV and MERS-CoV. Transmission microscopy images show that CoVs are spherical-shaped cellular structures with pricky spiked proteins projecting from the virion surface, which make them appear as solar crowns, hence terming them "coronaviruses."

The spike protein acts together of the most storage unit for the structural proteins of CoVs and also plays a serious role within the interaction between CoVs and its respective host cells.

The host cell entry of SARS-CoV-2 depends on 2 major enzymes angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2).

Human cells which are rich in cell-surface receptor ACE2 which act as an important modulator within the vital sign regulation, are vulnerable to SARS-CoV-2 infection. pertaining to the recently surfaced evidence, the elucidated crystal structure of SARS-CoV-2 showed that its receptor-binding domain (RBD) has an boosted affinity to bind to the human enzyme ACE2.

The receptor-binding motif of the RBD mediates the contact with ACE2. the 2 virus-binding hotspots at the RBD–ACE interface are established by many residue changes of amino-acids in SARS-CoV-2 as compared to the previous SARS-CoV-1. The entry into cells requires the protein S of the viral spike that binds to the receptor ACE2 facilitated by some host cell proteases, like TMPRSS2. This phenomenon which supported protein S priming is exclusive and enables fusion of viral and cellular membranes and escapes from antiviral humoral immune reaction . This interaction seems to be targetable by inhibiting host proteases. this is often the goal that's trying to be achieved by blocking the signals of the host proteases.

II. Anti-Cancer Drugs

2.1 Introduction

Anti-cancer drugs, also known as anti-neoplastic drugs, are substances that effectively aid to treat malignant cancerous cells. Anti-cancer drugs are classified into four general types-alkylating agents, antimetabolites, natural products, and hormones.

Different anti-cancer drugs are used depending on factors like type, severity, location, method of use (surgery/radiation therapy), and the side effects caused by the drug. The selectivity of anti-cancer drugs plays a very important role in aiding to reduce the intensity of side effects pertaining to the drugs' usage. Cancer cells and regular human cells are almost alike, and since anti-cancer agents are usually noxious to regular cells, it may cause various side effects. These side effects include hair loss, sores in the mouth and on other mucous membranes, cardiac abnormalities, extreme nausea and vomiting, and bone marrow toxicity- which can result in anemia and decreased immune resistance. Hence a detailed study should be done specific to the patient's case, and dosages should be administered accordingly so as to minimize the effects caused due to the drug.

Overview of drugs reviewed in this paper: -

COMPOUND NAME	BRAND NAME	CHEMICAL FORMULA	PURPOSE OF PRODUCTION	REPURPOSED TO
Aspirin	Ecosprin, Sprin, Aspro, Eprin and Delisprin	$C_9H_8O_4$	To reduce minor aches &pain, fever, and inflammation.	Anti-inflammatory effect of aspirin aiding to reduce blood clots.
Janus Associated Kinase	Jakafi	$C_{17}H_{18}N_6$	To treat Leukaemia (blood cancer).	To ease out covid19 patients who suffer from hyperinflammation or subsequent to lung pathology.
Carmofur	TCI	$C_{11}H_{16}FN_3O_3$	Acid ceramidase inhibitor to	Inhibitor of main protease (M^{pro}) of

			destroy certain cancerous cells	SARS-CoV-2 which is the key enzyme of the virus.

2.2 Aspirin

Aspirin (figure 5.2.1), also known as acetylsalicylic acid ($C_9H_8O_4$), is a very common drug used to reduce pain, fever, and inflammation. It is prominently used to prevent cardiovascular disease.

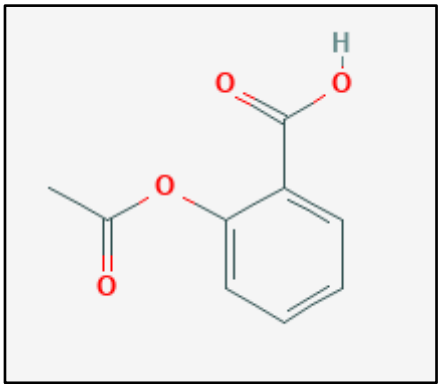

Figure 5.2.1- Structure of Aspirin($C_9H_8O_4$)

Aspirin for treating Cancer:

It is observed that substances which induce thrombocytopenia (abnormally low levels of platelets) reduce metastases (development of secondary malignant growths at a distance from a primary site of cancer), led to the discovery of aspirin as an anti-cancer drug. A rise in the circulation of platelets during the late stages of cancer, is known to promote cancer cell growth at sites of metastases. Inducing low doses of aspirin showed reduction in the pro-carcinogenic action of platelets. A study from 1988 portrayed that regular use of aspirin significantly lowered the risk of developing colorectal cancer. A study led by Dr. Chan of Harvard, concluded that the use of aspirin for 6 years or more could result in 19% decrease in the risk of colorectal cancer and 15% decrease in risk of any type of gastrointestinal cancer.

Aspirin as a re-purposed drug for COVID-19:

Many researchers have studied and analyzed the benefits of aspirin while treating the patients of coronavirus, and have observed that a daily dose of aspirin can avoid some issues caused due to the virus.

In a study conducted on 412 people diagnosed with coronavirus, 23% of the patients who were given a light dose of aspirin within a day or 7 days before their admission; reported that 44% of the patients had a low probability of being put on a ventilator and 43% had a low probability of being admitted in the intensive care unit (ICU). 47% of the people were also observed to have a low probability of dying from the virus compared to those who did not ingest aspirin daily.

Covid-19 is known to induce a hypercoagulable state (increased possibility of blood clotting). Studies indicate that around 50% of the patients in the ICU develop blood clots in the lungs or legs. This is caused due to the inflammatory response and involves lining of blood vessels which causes blood to flow sluggishly, resulting in clot formation. This can create a lot of risks because if the clots become larger and break off, it can cause strokes and heart attacks. This is where aspirin could be utilitarian as it is an effective anti-inflammatory drug that could reduce the body's inflammatory response to coronavirus.

While aspirin has several benefits in aiding to curb the effects caused due to COVID-19, it does not prevent us from getting infected by the virus, so ingesting aspirin while being completely healthy could cause several complications including gastrointestinal bleeding. All in all, a common drug like aspirin serves with a lot of advantages and its medicinal benefits can be exploited and repurposed in various conditions.

2.3 Janus-Associated Kinase (JAK) inhibitors

Associated Kinase inhibitors are approved for primary myelofibrosis and polycythaemia vera and these AK inhibitors have started to show promise in the treatment of COVID-19. Promoting immune cell activation and survival genetic programs with implications in the hyperactivity of immune response to infection are relayed in cytokine signalling, by JAK. The phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation can be prevented if kinase inhibitors are proposed as treatments for COVID-19. Transcription (STAT) proteins that are involved in the vital cellular functions, including growth, survival and signalling are interfered by Janus Kinase (JAK) inhibitors during phosphorylation of signal transducer and activator. Janus Kinase inhibitors such as baricitinib have potential

direct antiviral activity through interference with viral endocytosis, theoretically preventing entry into and infection of susceptible cells. Ruxolitinib which is a JAK2 inhibitor is under a series of phase trials for patients suffering from CRS, hyperinflammation, or severe lung pathology subsequent to COVID-19. Incyte- a leading pharmaceutical company has made Ruxolitinib available for COVID-19 patients through an extended access program.The JAK1/2 kinase inhibitor baricitinib is also being extensively trialled for COVID-19 infections and may be working through inhibition of endocytosis. Results are still forthcoming of the completed 2/3 trial of baricitinib with the antivirals lopinavir-ritonavir; but preliminary showed promise with a s week mortality rate of 0% in the treatment arm compared to the 6.4% in the control arm of the study. Also, the JAK 1/3 inhibitor, thought to be ambitious to IL-6 signalling,to facitinib is being trialled for interstitial pneumonia related to SARS-CoV-2 infection. Like the anti-interleukin therapies, Janus-Associated inhibitors should not be used in patients with infections like tuberculosis because it can increase the risk upper respiratory functions and can cause further complications in the patients. More critically Janus-Associated Kinase inhibitors, such as tofacitinib and baricitinib, have black box warnings for associations with increased risk of blood clots, pulmonary emboli, and death. As it is observed that thrombotic issues in COVID-19 is increasing, particular caution should be taken for these particular therapies.

2.4 **CARMOFUR**

Carmofur ($C_{11}H_{16}FN_3O_3$) [figure 5.4.1] or 1-hexylcarbamoyl-5-fluorouracil, abbreviated as HCFU, is a derivative of fluorouracil and is an antineoplastic agent. It has been used to treat carcinomas of breast and gastrointestinal tract.

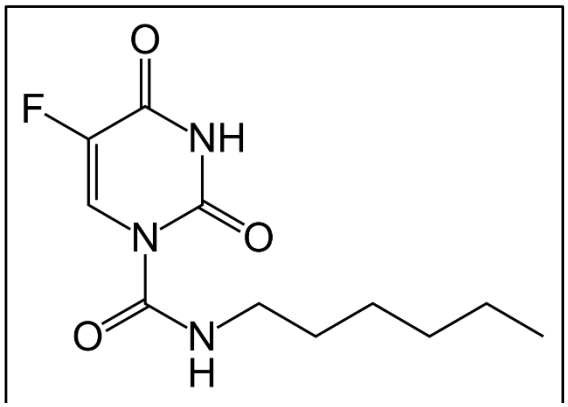

Figure 5.4.1- Structure of HCFU ($C_{11}H_{16}FN_3O_3$)

Carmofur for treatment of Cancer:

Carmofur has properties of being an acid ceramidase inhibitor. Ceramide promotes cancer cells survival, growth and death. Therefore, on the consumption of carmofur, the inhibition of acid ceramidase makes the tumour cells susceptible to the effects of antineoplastic agents and radiation. Carmofur has been used as adjuvant chemotherapy for the treatment of colorectal cancer in countries like China, Japan and Finland for several years now. Many experimental trials and meta-analysis confirm the effectiveness of this drug on patients with breast or gastrointestinal cancer, assisting their survival.

Carmofur has also been known to induce leukoencephalopathy, a condition in which the white matter in the brain is damaged progressively and causes stroke-like symptoms. An experimental trial of this drug being used to treat hepatocellular carcinoma was stopped prematurely because it resulted in 56% candidates being affected with severe side effects, and it was observed that stage 1 and 2 cancer patients did not benefit from this treatment.

Carmofur for treatment of COVID-19:

According to recent studies, the main protease (M^{pro}) of SARS-CoV-2 is a key enzyme and plays an important role in viral replication and transcription, and is therefore the main target for drugs to focus on. Carmofur, an antineoplastic has been observed to act as an inhibitor of this SARS-CoV-2 main protease.

The detailed inhibitory mechanism is yet to be understood; however, the crystal structure demonstrates that carmofur contains an electrophilic carbonyl reactive group which binds covalently to C145, which is a part of the catalytic dyad [refer figure 5.4.2.]As a result, its carboxylic acid tail occupies the hydrophobic S2 subsite of M^{pro} whilst its 5-fluorouracil head is cleaved as product of the new covalent bond that has formed. Carmofur is active during a cell based antiviral assay with an EC_{50} of 24.87 μM. Therefore, it is a very favourable lead compound for the development of new antivirals to target SARS-CoV-2.

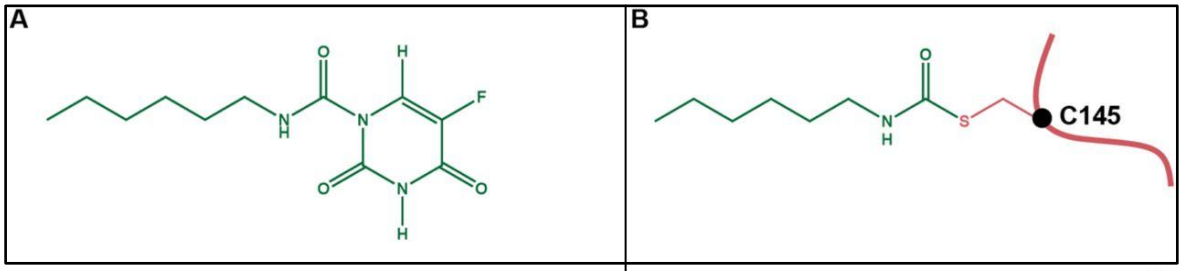

Figure 5.4.2- A: The chemical structure of carmofur. B: The bonded form of carmofur to SARS-CoV-2 M^{pro}. The red curve represents the SARS-CoV-2 M^{pro} polypeptide with Cys145 protruding as a side chain.

III. CONCLUSION AND PERSPECTIVE

Drug repurposing has been proved to be a successful alternate strategy in the drug development domain, having a history of successful repurposing of existing drugs, in which a lot of research was based in non-oncological context. Having said that, there is no guarantee where it can necessarily avoid phase 1 trials of the repurposed drugs. However even if there is a case where phase 1 trials are required, there will always be a substantial amount of existing human data which will inform the structure and dosing schedules of the trial. In this paper, it was researched and reviewed that anti-cancer drugs that could be used to treat the SARS-CoV-2 virus. Before reviewing the repurposed drugs, the team researched on the structure and the genome of the covid19 virus and how does to infect the other living organisms. Having studied the genome everyone is exposed to the revolutionary research conducted by the oncology experts about the anti-cancer drugs that are being repurposed to treat Covid-19.

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