From the Drugbank Application to the Novel Drugs: A Pharmacogenomic Summary

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Abstract. Computational drug research has grown in popularity in recent decades because to lower risks, time, cost, and resource needs as compared to traditional experimental approaches. The DrugBank application has expanded the number and quality of pharmacological activities and drug metabolic pathways depicted visually. The review elaborated a number of novel drugs and the molecular target mechanisms discovered with DrugBank. The study involves papers indexed by Scopus and Pub Med, the search uses a combination of the following keyword variants; “Drugbank AND Repurposing Drug”, “Drugbank AND Pharmacogenomic”. This study only used original articles in English that were published peer reviewed journals from October 2020 to November 2022. Thus, the screening results of library sources were narrowed to 9 original articles that met the inclusion criteria. Our result highlighted the involvement of 23 drug-targeting molecules in nine specific diseases. The result shows 46 lists of repurposing drugs, four of which have the potential to be developed as prostate cancer treatments, five new drugs for ovarian cancer five new breast cancer drugs, eight new drugs highly recommended for depression, five candidates for atopic dermatitis, two recommended treatment for asthma, a novel drug for multiple sclerosis, and 18 potential medication for chronic hepatitis B.

1 Introduction

The following steps are included in the drug research and development pipeline: a) target identification and validation; b) hit to lead molecule generation; c) led molecule optimization and characterization; d) drug formulation and delivery; e) pharmacokinetics and drug disposition; f) identification of preclinical drug candidates; and g) bioanalytical testing and clinical trials [1]. In recent decades, computational drug discovery has grown in importance because to fewer risks, time, cost, effectiveness, and resources than compared to traditional experimental approaches [2]. Increased computer capacity and in silico technology enabled this. These supplements experimental procedures by narrowing the focus of inquiry and directing in vivo validation [3]. Screening medications or chemicals against various types of cultured cells is one way for increasing the drug-

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target interaction [4]. In silico modeling is another way for scanning the drug-target interactome. For example, molecular docking techniques that make use of the Protein Drug Bank’s massive collection of protein structures have been applied to pharmaceutical repositioning to gather data on off-target therapeutic effects and associated phenotypic outcomes [5].

DrugBank is a free web-based resource that includes thorough drug data with comprehensive drug target and drug action data. It was designed to help in the discovery of in silico drug targets, drug design, Prediction of drug metabolism, prediction of medication interactions, and general pharmacological education [6]. DrugBank offers a number of tools for viewing, organizing, searching, and analyzing text, pictures, URLs, and other data. DrugBank has been utilized in a number of applications since its debut, including the investigation of silicosis [7]. Drugbank is utilized in this study to characterize potential drug candidates for particular illnesses with a target molecular mechanism. In this study, we describe the decision of innovative medications to molecular targets on variant pathogenic variants.

2 Method

The study involves literature indexed by Scopus and Pubmed databases, and the search uses a combination of the following keyword variants, keyword 1: "Drugbank AND Genomic AND Repurposing Drug" and keywords 2 "Drugbank AND Pharmacogenomic". This study only used original articles in English which has no restriction on the year of publication. The library collection took place from October 2022 to November 2022 (Fig. 1).

Published article was identified according to searching strategies in Pub Med (23 papers), Scopus (27 papers).

Remove duplication by reference manager (Zotero) (35 papers)

Articles were identified (47 papers)

Irrelevant to mutation genetic (17 papers), Not Original Article (12 papers), Study outcome did not show to mechanism on molecular target (7 papers)

Articles were screened (12 papers)

Study did not show the specific mechanism of genes (3 papers)

Articles met the inclusion criteria according to the purpose (9 papers)

Fig. 1. Literatures study of workflow
This study only involved outcomes that met all the following criteria; (a) study of identification of new drug candidate discoveries, (b) validation a study of new drug candidate discoveries in a disease. Each literature is extracted by identifying name a journal publication, author's name, year, title, disease, drug, molecular a target, and mechanism.

3 Results and Discussion

3.1 Main result: drug repositioning candidates for the novel treatments

Our result shows 46 lists of repurposing drugs, four of which (dasatinib, sunitinib, flavopiridol, gevatinib) have the potential to be developed as prostate cancer treatments, five new drugs for ovarian cancer (ciplastin, cyclosporin, bisphenol a, progesterone, sunitinib), five new breast cancer drugs (hypericin, ingenol ebutate, d-myoinositol-hexasulphate, hyperforin, carboxyatractyloside), eight new antidepressant drugs that are highly recommended (pioglitazone, rosiglitazone, doxycycline, pramipexole, ketamine, spermidine, sarilumab and sentralizumab), five candidates for atopic dermatitis (baracitinib, tofacitinib, ruxolitinib, upadacatinib, memolotinib), two recommended treatment for asthma (sarilumab and sentralizumab), a novel drug for multiple sclerosis (belatacept), and 18 potential medication for chronic hepatitis b (simvastatin, rifampin, nefirapine, zidovudine, abacafir, atazanafir, etravirine, efavirenz, tolbutamide, prednisone, pioglitazone, propofol, esomeprazole, ribavirin, lamivudine, metformin, hydroxizine, arginine (Table 1).

<table>
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<th>Novel Drug</th>
<th>Ref.</th>
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<td>Ciplastin, cyclosporin, bisphenol A, progesterone, sunitinib</td>
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<td>MCF-7</td>
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### 3.2 Molecular target for novel treatment on prostate cancer

An atypical non-receptor tyrosine kinase ACK1 (activated CDC42 kinase 1) is widely expressed and integrates and transmits signals from a variety of ligand-activated receptor tyrosine kinases, including EGFR, HER2, and PDGFR. When ACK1 interacts with ty267 (Tyr oc2ikinase), it is activated and inhibits cell apoptosis, resulting in a rise in androgen receptor transcription, which is important in the development of prostate cancer. Dasatinib, sunitinib, flavopiridol, and gevatinib are four medicines used to treat prostate cancer [8]. Dasatinib can be used for the treatment of prostate cancer because of its mechanism of inhibiting ACK1 kinase activity and inhibiting Tyr 267-induced AR phosphorylation [17]. Dasatinib treatment is more effective than docetaxel treatment in bone metaltase patients, but it has the same success rate as doxetaxel treatment in glandular metaltase patients [18].

Sunitinib, a receptor tyrosine kinase inhibitor with several targets, is approved to treat advanced kidney cancer, imatinib-resistant gastrointestinal stromal cancer, pancreatic adenocarcinoma, and other solid-organ malignancies [19]. Sunitinib is a small molecule inhibitor of VEGFR (Vascular Endothelial Growth Factor Receptor), PDGFR (Platelet-Derived Growth Factor Receptor) and other receptor tyrosine kinases that is authorized for the treatment of prostate cancer. A dual inhibition of the VEGF and PDGF pathways may be an important therapy strategy in advanced prostate cancer, which might be accomplished using a multitargeted inhibitor such as sunitinib [20].

Flavopiridol is a cyclin-dependent kinase inhibitor with tentative anti-prostate cancer cell line activity. However, using flavoridol as a single treatment in advanced prostate cancer patients does not produce the best results, thus it must be paired with chemotherapy [21]. Gefatinib is a tyrosine kinase inhibitor that specifically suppresses EGFR growth as well as GAK (G-associated kinase) activity [22]. Gefatinib can be used with luteolin since it is less effective in prostate cancer patients. Gefatinib and luteolin function by blocking GAK jinase activity in Thr cells, decreasing EGFR kinase activity, and triggering cell death [23].

### 3.3 Molecular target for novel treatment on ovarian cancer

PSAT1 (Phosphorine Aminotransferase 1) and HMGA 1 (High Mobility Group At Hook 1) have a role in the progression of ovarian cancer by increasing cytosine and adenosine
methylation, which promotes cell death and an increase in the number of cancer cells. In ovarian cancer, HMGA1 and PSAT1 can be employed as biomarkers for treatment. Several medications, including ciplastin, progesterone, bisphenol A, cyclosporin, and sunitinib, can be used to treat ovarian cancer [9]. Cisplatin increases OSR2 mRNA expression when it interacts with HMGA1, but it decreases PSAT1 mRNA expression when it interacts with PSAT1. Cisplatin is the most effective medicine for ovarian cancer therapy [24].

Bisphenol enhances JADE3 mRNA expression when it interacts with HMGA1, while it decreases PSAT1 mRNA expression when it interacts with PSAT1. Bisphenol can limit cancer cell growth at high concentrations, however, a new study demonstrates that at nanomolar dosages, bisphenol can favorably regulate cell proliferation in ovarian cancer cell lines [25]. Cyclosporine inhibits TSPAN14 mRNA expression when it interacts with HMGA1, but enhances PSAT1 mRNA when it interacts with PSAT1. When progesterone interacts with HMGA1, it increases OSR2 mRNA, but when it interacts with PSAT1, it increases PSAT1 mRNA. Sunitinib increases OSR2 mRNA expression when it interacts with HMGA1, but it decreases PSAT1 mRNA expression when it interacts with PSAT1. Sunitinib inhibits several tyrosine kinases that target VEGFR receptors and receptor protein tyrosine kinases [26]. Sunitinib has been shown to be effective in the treatment of breast and lung cancer [27]. Sunitinib has been shown in preclinical studies to inhibit peritoneal tumor metastasis and tumor angiogenesis [26].

3.4 Molecular target for novel treatment on breast cancer

Six genes that may interact in the development of breast cancer have been discovered, as well as five therapeutic targets (Hyperecin, ingenol ebutate, D-Myo-Inositol, Hiperforin, and Carboxyatractyloside) [10]. Hyperecin has been shown to have cytotoxic and apoptotic effects on breast cancer through MCP 7. (Modified Citrus Pectin 7) [10]. Hyperecin is cytotoxic while also having anticancer characteristics and increasing MCP7 cell apoptosis via ADAMTS1 and ADAMTS3 [28]. Hyperecin activation significantly increases SOD2 (Superoxide dismutase 2) activity in MCP7. [29]. The carrier molecule hyperecin is used to increase the effect of PDT (Photodynamic Therapy) on MCF7 breast cancer cells [30]. The mechanism by which ingenol ebutate interacts with six breast cancer target genes is unclear [10].

Preclinical research indicates that ingenol mebutate is highly efficient against leukemia cells, inducing apoptosis and necrosis [31]. Ingenol mebutate exhibits anticancer efficacy in preclinical investigations by generating primary necrosis [32]. In cancer cells, D-myo-inositol suppresses the EMT (Epithelial-Mesenchymal Transition) molecular pathway [33]. Inositol can block the key molecular pathways in EMT in cancer cells by lowering PI3K (Phosphatidylinositol-3-kinase) synthesis and inhibiting AKT phosphorylation (threonine kinase) [34]. Inositol has little anticancer activity; however, inositol combined with inositol hexaphosphate (IP6) is more effective at inhibiting the development of breast cancer [35]. Hiperforin is anti-inflammatory as well as anti-carcinogenic [10]. Hiperforin inhibits 5-Lipoxygenase, which is also involved in inflammation and carcinogenesis, and thus inhibits the formation of leukotrienes (Microsomal PGE2 Synthase) [36]. Hiperforin has the potential to reduce cancer cell
invasion and metastasis by inhibiting the MEK/ERK signaling pathway, resulting in decreased MMP-2 (Matrix Metalloproteinases 2) and MMP-9 synthesis (Matrix Metalloproteinases 9) [37]. Carboxyatractyloside can block ANT (Adenine nucleotide translocase), which is involved in tumor cell energy metabolism [10]. Carboxyatractyloside activates MPT (Mitochondrial Permeability Transition) to bind to ANT in the c-state [38]. Carboxyatractyloside inhibits ANT by increasing the rate of ATP and ADP exchange in mitochondria [39].

3.5 Molecular target for novel treatment on depression

Pioglitazone and rosiglitazone are selective for PPAR (PPAR) and PPAR gamma subtypes through modifying antioxidant response, neurotransmission, neuroinflammation, and neurologic function [11]. Pioglitazone is a PPAR agonist that can drastically reduce the quantity and morphology of mecroglia in the hippocampus. Pioglitazone is a PPAR agonist that can drastically reduce the quantity and morphology of mecroglia in the hippocampus [40]. In vivo and in vitro, rosiglitazone can protect neurons and astrocytes from depression via targeting PPAR [41]. Doxycycline is one of the medications used to treat depression by inhibiting MMP (Matrix Metalloproteinase) [11]. Doxycycline can alleviate depression by preventing a drop in hypothalamic BDNF (Brain Derived Neurotrophic Factor) levels caused by lipopolysaccharide [42].

Dopaminergic agonists can improve anhedonia while reducing cognitive impairment, a symptom of depression that is less responsive to SSRIs [11]. In resistant depressive individuals, pramipexole has been demonstrated to be effective and well tolerated [43]. Pramipexole is a dopaminergic agonist that selectively stimulates D3 receptors, which are thought to be involved in motor and anhedonic depressive symptoms [44]. Spermide is a short aliphatic amine that plays an important role in homeostatic functions, including the stimulation of nerves via NMDA (N-methyl-D-aspartate) and -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamic receptors [11]. Spermide has a biological role in gene transcription and post-transcriptional modification, synaptic activation regulation, and ion channel modulation in nervous tissue stimulation [45]. Ketamine has the ability to modify AMPA receptors, which are important in antidepressant effects, as well as block NMDA receptors [11]. Ketamine has antidepressant and psychotomimetic effects that occur at the cellular, synaptic, and tissue levels [46].

3.6 Molecular target for novel treatment on depression

IL6R controls systemic inflammation, which is linked to the development of depression. IL6 has two primary signaling pathways that are linked to the development of depression: Anti-inflammatory classical signaling and trans signaling (pro-inflammatory) [12]. Sarilumab and santralizumab are possible antidepressant medications because they target IL6R [12]. Sarilumab is a soluble, membrane-bound IL6Rα-binding monoclonal antibody by inhibiting IL6-mediated signaling pathways [47]. Sarilumab, which targets IL6, lowers CRP levels and relieves severe depression symptoms for Rheumatoid Arthritis patients [48]. Sarilumab binds to the IL6 membrane and inhibits both classical and trans signaling
Satralizumab is a monoclonal antibody (mAb) that inhibits T cell-induced regulation of IL6/IL6R [50].

3.7 Molecular target for novel treatment on atopic dermatitis

JAK-STAT (Janus Kinase-Signal Transducer And Activator Of Transcription) is an intracellular signaling system in Th2 cells that maintains the inflammatory loop by activating and distinguishing the same Th2 and innate immunity cells as well as releasing the proinflammatory cytokines IL-4 and IL-13, which target eosinophils, keratinocytes, B lymphocytes and fibroblasts. JAK inhibitors can be used, including baricitinib, ruxolitinib, upadacitinib, tofacitinib, and molitinib [51]. In the immunopathology of atopic dermatitis, baricitinib is employed as a JAK1 and JAK2 inhibitor through modulating signaling [51]. In phase III studies, the efficacy and safety of baracatinib, upadacitinib, and abrocitinib were examined in conjunction with JAK inhibitors. Baracatinib is a small medication that precisely inhibits JAK1 and JAK2 proteins [52]. Baricitinib is a highly selective oral JAK1 inhibitor [53].

Baricitinib is an orally administered JAK1 and JAK2 inhibitor that inhibits the downstream activity of cytokines implicated in the pathogenesis of atopic dermatitis such as thymic stromal lymphopoietin IL-13, IL-4, IL-22, IL-31, and IL-5 [54]. Upadacitinib inhibits JAK1 by lowering the production of proinflammatory Th2 cytokines such as IL4 [51]. Upadacitinib is an oral JAK inhibitor that inhibits JAK1 more than JAK2, JAK3, or tyrosine kinase2 [55]. Upadacitinib targets JAK1-dependent disease drivers such IL-6 and IFN [56]. Upadacitinib targets JAK1-dependent disease drivers such IL-6 and IFN [56]. Tofacitinib is a JAK1 and JAK2 inhibitor that works by directly suppressing the cytokine IL-4 [51].

Tofacitinib is a JAK1 and JAK3 inhibitor that is ineffective against JAK2 and TYK2 (Tyrosine Kinase 2) [57]. Ruxolitinib, a JAK1 and JAK2 inhibitor, has been shown to reduce proinflammatory cytokine signaling. [51]. Ruxolitinib was the first JAK1 and 2 inhibitor that was both potent and selective in clinical trials [58]. Ruxolitinib is a selective Janus kinase 1 and Janus kinase 2 inhibitor that has the potential to reduce cytokine signaling in the development of Atopic Dermatitis [59]. Memolitinib, a JAK1 and JAK2 inhibitor, can reduce inflammatory cytokine production such as IL4, IL5, IFN-g, and TSLP [51]. Momelotinib (MMB) is a novel JAK1/JAK2 inhibitor that suppresses the signaling of several proinflammatory cytokines; recent research shows that JAK inhibitors may be useful in the treatment of Atopic dermatitis [60].

3.8 Molecular target for novel treatment on multiple sclerosis

CD86 and CD80 can modulate T cell activation and maintain immunological tolerance to antigens. As a result, targeting CD80 and CD86 is the greatest approach for treating multiple sclerosis. Belatacept, which targets CD80 and CD86, can be used to treat multiple sclerosis [15]. Belatacept is a selective inhibitor of the Tfh–B-interacting pathways CD28, CD80, and CD86 [61]. Belatacept acts by preventing coinhibitor signals that control effector T lymphocytes by inhibiting the ligands on CD28 and CTLA-4 (Cytotoxic T Lymphocyte Associated Protein 4). Because it interacts with CD80 and CD86 receptors,
CTLA4 is used as an anti-CD28 signal [62]. Belatacept binds to CD86 and CD80, which are expressed in CD14 monocytes and dendritic cells Lin1/-HLA-DR [63].

3.9 Molecular target for novel treatment on atopic dermatitis

Antibodies against IL-6R To prevent allergen-induced asthma aggravation, ab inhibitors of mIL-6R and sIL-6R incorporate IL-6 signaling trans-stimulators [14]. Sarilumab and satralizumab, which target IL6, might be employed as a novel asthma therapeutic alternatives [14]. Sarilumab has a beneficial therapeutic effect in people who have airway inflammation induced by IL-6 trans signaling activation. Sarilumab is classified as a monoclonal antibody that specifically targets the soluble, membrane-bound IL6R [64]. Satralizumab is a second-generation anti-IL6R monoclonal antibody that has a higher antigen neutralizing activity and a longer plasma half-life than toxilizumab. Treatment with satralizumab reduced the likelihood of recurrence and indicated a favorable therapeutic impact on antibody-mediated illness by inhibiting IL6 [65].

3.10 Molecular target for novel treatment on atopic dermatitis

CD40 signaling must be triggered in order to generate efficient virus-specific CD8+ T-cell responses, which are necessary for viral clearance. HLA-DPB1 has a significant impact on the risk of CHB infection, and HLA-DPB1 expression is linked to CHB infection. HLA-DPB1 expression is necessary for CHB regulation. [16]. CD40 is a protein that is expressed on B cells and antigen-presenting myeloid cells and has a role in antiviral immune response. Research has demonstrated that CD40 is activated during viral infection and that its activation can enhance the host's antiviral capabilities. In transgenic mice, an anti-CD40 agonistic monoclonal Ab (aCD40) injection was adequate to inhibit HBV replication noncytopathically [66]. Statins lower the risk of hepatocellular cancer in persons infected with hepatitis B or C viruses [67]. Ribavirin is used to treat individuals with HCV genotype 1 who have an estimated glomerular filtration rate (EGFR) [68]. Lamivudine may delay clinical progression in people with chronic hepatitis B [69]. Metformin, by the mechanism of hepatocyte distribution and suppression of HbsAg generation, can be used to treat hepatitis B [70].

4 Conclusion

The result shows 46 lists of repurposing drugs, four of which (dasatinib, sunitinib, flavopiridol, gevatinib) have the potential to be developed as prostate cancer treatments, five new drugs for ovarian cancer (ciplastin, cyclosporin, bisphenol a, progesterone, sunitinib), five new breast cancer drugs (hypericin, ingenol ebutate, d-myo-inositol-hexasulphate, hyperforin, carboxyatractyloside), eight new drugs highly recommended for depression (pioglitazone, rosiglitazone, doxycycline, pramipexole, ketamine, spermidine, sarilumab and sentralizumab), five candidates for atopic dermatitis (baracitinib, tofacitinib, ruxolitinib, upadacatinib, memolotinib), two recommended treatment for asthma (sarilumab and sentralizumab), a novel drug for multiple sclerosis (belatacept), and 18 potential medication for chronic hepatitis b
rifampin, nevirapine, zidovudine, abacafir, atazanafir, etravirine, efavirenz, tolbutamide, prednisone, pioglitazone, propofol, esomeprazole, ribavirin, lamivudine, metformin, hydroxizine, arginine).

References


27. T. J. Abrams dkk., “Preclinical evaluation of the tyrosine kinase inhibitor SU11248 as a single agent and in combination with “standard of care” therapeutic agents for the treatment of breast cancer”.


