The Ruling of Novel Drugs to the Molecular Targets on Variant Pathological

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Abstract. In recent decades, the investigation of novel drugs have not only been fully characterized at the molecular level, but have also been used in significant pharmacogenomic research. Our paper presents the ruling of novel drugs to molecular targets on variant pathological. Furthermore, in this study, we show the map of bioinformatics field work, notably clinicaltrials.gov which is integrated with feeder applications. The study involves literature indexed by Scopus, and PubMed databases, and the search uses a combination of the following keyword variants; "ClinicalTrials.gov AND Genomic", "ClinicalTrials.gov AND repurposing drug". This study used original articles in English which has published during 2022. Thus, the screening results of library sources were narrowed to four original papers that met the inclusion criteria. We map that a total of nine tools have been integrated with each other for the goals of gene analysis and repurposing medication selection, based on a published approach that incorporates bioinformatics tools, which include: Gwas Catalog, National Biobank Consortioum of Taiwan, Cancer Cell Line of Ensiklopedia, HaploReg, STRING, Drugbank, ClinicalTrials.gov, Pubmed.gov, and ConectivityMap. Our review results the present 12 lists of repurposing drugs, two of which (geldanamycin and fulvestrant) have the potential to be developed as breast cancer treatments, two new antidepressant drugs (Sarilumab and Satralizumab), seven new colorectal cancer drugs (sulindac, celecoxib, naproxen rucaparib, ibuprofen, balsalazide, aspirin), and one new drug highly recommended (Belatacept).

Keywords: Bioinformatic tools, Pharmacogenomic, Repurposing drug.

1 Introduction

As a result of recent technological and scientific advances, drug candidates' study and development has undergone noteworthy modifications. Molecular docking is a simulated approach that uses structure and energy matching to find and predict the optimum binding sites between pharmaceutical drugs and target proteins [1]. The combination of molecular and computational methodologies, as well as organic synthesis ap-

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proaches, into drug development has resulted in a tremendous rise in biological, structural, and chemical data availability [2]. The drug research and development process is exceedingly complex, with a high attrition rate and a time span of 10-20 years between the identification of a viable drug candidate and the launch of a new medicine [3].

Therapeutic discovery is currently the most prominent procedure, and it starts with target and lead identification, then moves on to lead optimization and pre-clinical in vitro and in vivo research to find the most powerful compounds that meet the primary requirements for drug development [4]. One of the most demanding and difficult human activities is the development process, which must balance efficacy in health benefits with safety at adequate therapeutic index [5]. Clinicaltrials.gov has been developed by several researchers in developing new drugs [6]–[9].

In recent decades, cancer cell lines have frequently been used as models to investigate cancer biology and cellular response to chemotherapeutic drugs. They have been thoroughly molecularly profiled and employed in large-scale pharmacogenomic research [6]. Last, before making a final determination on their qualities as biomarkers, the great majority of newly discovered chemicals must be critically re-evaluated [10]. More biology-specific cancer biomarkers must be developed urgently so that patients can receive the best possible treatment. Developing more relevant biomarkers for various molecular malignancies of various kinds will be an inescapable biological challenge for cancer treatment. As a result, cancer biomarkers that are biologically-specific must be developed and generated as soon as feasible [11].

Our paper presents the ruling of novel drugs to molecular targets on variant pathological. Furthermore, in this study, we show the map of bioinformatics field work, notably Clinicaltrials.gov which is integrated with the feeder applications.

2 Method

2.1 Literature Search Strategy

The study involves literature indexed by Scopus, and Pubmed databases, and the search uses a combination of the following keyword variants; “ClinicalTrials.gov AND Genomic”, “ClinicalTrials.gov AND repurposing drug”. This study used original articles in English which has published during 2022 (**Error! Reference source not found.**).

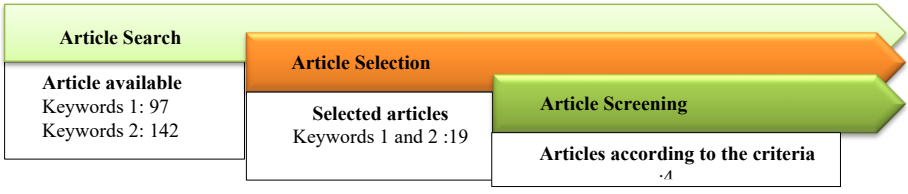

Fig. 1. Literatures study of workflow

2.2 Literature Eligibility and Research Data Extraction

When conducting literature reviews, only library resources that meet the following criteria are used: (a) studies aimed at identifying new treatment candidates (b) an investigation into the efficacy of recently identified treatment candidates for an illness. For every piece of literature, the names of diseases, names of medications, names of molecular targets, names of journals, authors, titles, years, purposes, procedures, findings, and mechanisms are extracted.

3 Result and Discussion

3.1 New approaches and future prospects due to bioinformatics

We map that a total of nine tools have been integrated with each other for the goals of gene analysis and repurposing medication selection, based on a published approach that incorporates bioinformatics tools, which include: Gwas Catalog, National Biobank Consortioum of Taiwan, Cancer Cell Line of Encyclopedia, HaploReg, STRING, Drugbank, ClinicalTrials.gov, Pubmed.gov, and ConectivityMap (**Error! Reference source not found.**).

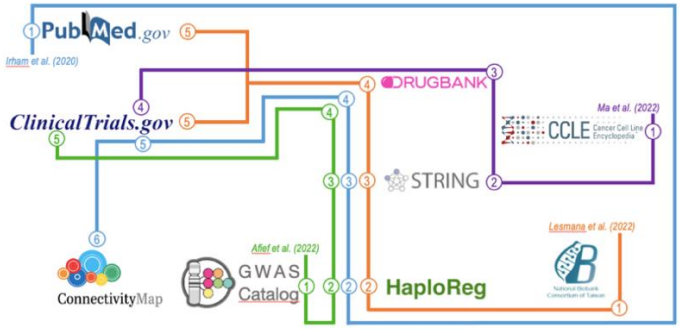

Fig. 2. Map of the Use of Bioinformatics Application Methods

To assess cluster, detection techniques based on protein-protein interactions (PPI) for pharmaceutical target identification and repurposing. The individual PPIs were taken from the STRING and used as raw PPIs in our cell-based PPI network. The target genes for the medications used to treat the cell lines in the CMap database were obtained by using Drugbank. Drugbank is a database that carefully blends knowledge about pharmacological targets with data about drug actions. Drug target research, drug design, and pharmacodynamic prediction have all made frequent use of it. We assessed and validated the percentage of disrupted genes in clusters using data from ClinicalTrials.gov and the literature [6].

In search for novel antidepressants, drug repurposing based on genomic analysis, Extreme Gradient Boost (XGBoost) was used as a machine learning approach. The SNPs came from the Taiwan Biobank dataset. The SNPs were annotated using HaploReg V4.1 in accordance with the five functional annotation sets mentioned above.

The STRING database was utilized prioritize and identify the genes. Following that, overlapping gene targets and medications were discovered using the DrugBank database. Finally, ClinicalTrials.gov and PubMed was used for validation [7].

Colorectal cancer medication repurposing requires a mix genetic variation and a genetic network involved PubMed to the search turned up integrated analyses of genomic drug that are genetically-driven repurposing. Additional CRC-associated genes were discovered using HaploReg v4.1 and added to the list. Additional research, including the usage of the STRING database, was conducted using the biological CRC genetic. Using the DrugBank and Therapeutic Target Database databases, the level of overlap with approved CRC therapeutic target genes was also evaluated (TTD). ClinicalTrials.gov was used to search for medications in clinical trials. Lastly, the CMap database was utilized to evaluate the most effective CRC therapies [8].

Drug repurposing for multiple sclerosis is being driven by the integration of genetic variations and a bioinformatics-based strategy. The criterion required the collection of MS-associated single nucleotide polymorphisms (SNPs) from the GWAS library and their enlargement using HaploReg (v4.1). Advanced study of biological MS risk genes utilizing the STRING database was employed to expand the list of potential genes as drug-target genes. This work used to map an authorized drug using the DrugBank and the Therapeutic Target Database extended list of drug-target genes. ClinicalTrials.gov was used to determine the clinical status of the drug-target genes [9].

To build the cell-based PPI network, data on gene expression from the MCF7 cell line collected from the Broad Novartis Cancer Cell Line Encyclopedia as filtering criteria (CCLE) was used [6]. Prioritized prospective medication repurposing and target genes possibilities for depression by combining SNP data from the Taiwan Biobank database with a machine learning technique and five sets of functional descriptors [7]. As raw PPIs for the cell-based PPI network, human PPIs were acquired from the 10^{th} version of STRING database [6]. The STRING database will be used to expand the list of candidate genes in order to increase the number of potential therapeutic targets [6]–[9].

The single nucleotide polymorphisms (SNPs) related to the spesific disease were collected from the GWAS catalog using the p-value threshold of $5x10^{-8}$ [9], while the HaploReg used for extracting and enlarging SNPs from the GWAS database [9]. On the other research, HaploReg was used to identify neighboring SNPs to spesific disease risk SNPs [8], nevertheless the functional annotation of SNPs (KEGG, PPI, missense, cis-eQTL, and KO mice) was performed [7].

Drugbank was utilized to identify drug target genes in PPI network based on MCF7 cells [6]. Using the DrugBank database, researchers revealed overlapping gene targets and medicines [7], [8]. An approved increased list of drug-target genes also has been mapped in DrugBank [9].

The proportion and confirming predictions the potential drug were validated using case studies and data from the literature from ClinicalTrials.gov [6], among validation for clinical trials and preclinical studies, even the in vitro and in vivo [7]. ClinicalTrials.gov also was used to find drugs in clinical studies, to determine the clinical status of the therapeutic targets [8], and to establish the clinical status of the drug-target genes [9]. Last, but not the least, the CMap database was used to rank the most promising

medications from the ClinicalTrials.gov to rank medications according to a connection score to prioritize the list of drugs for spesific disease [8].

3.2 Drug repositioning candidates for the novel treatments

Following our review, 12 lists of repurposing drugs were found, including two that may be developed as treatments for breast cancer (geldanamycin and fulvestrant), two new antidepressant medications (sarilumab and satralizumab), seven new medications for colorectal cancer (celecoxib, rucaparib, ibuprofen, naproxen, aspirin, su-lindac), and one highly recommended medication (Belatacept) (**Error! Reference source not found.**).

Table 1. Drug repositioning candidates for the novel treatments

No	Drug	Original Indication	The Novel Indication	Molecular Target	Reference
1.	Geldanamycin	No Available	Breast Cancer	HSP90	[6]
2.	Fulvestrant	Anti-estrogen therapy	Breast Cancer	ER	[6]
3.	Sarilumab	Rheumatoid arthritis	Depression	IL6R	[7]
4.	Satralizumab	Neuromyelitis optica	Depression	IL6R	[7]
5.	Celecoxib	Pain	Colorectal Cancer	PTGS1/PTGS2	[8]
6.	Rucaparib	Advanced Ovarian Cancer	Colorectal Cancer	PARP	[8]
7.	Ibuprofen	Pain	Colorectal Cancer	PTGS1/PTGS2	[8]
8.	Naproxen	Pain	Colorectal Cancer	PTGS1/PTGS2	[8]
9.	Balsalazide	Pain	Colorectal Cancer	PTGS1/PTGS2	[8]
10.	Aspirin	Pain	Colorectal Cancer	PTGS1/PTGS2	[8]
11.	Sulindac	Pain	Colorectal Cancer	PTGS1/PTGS2	[8]
12.	Belatacept	Kidney Transplantation	Multiple sclerosis	CD80 and CD86	[9]

Abbreviation: Cluster of differentiation 80 (CD80), Cluster of differentiation 86 (CD86), Estrogen Receptor (ER), Heat Shock Protein 90 (HSP90), Interleukin 6 receptor (IL6R), Poly (ADP-ribose) polymerase (PARP), Prostaglandin-endoperoxide synthase 1 (PTGS1), Prostaglandin-endoperoxide synthase 2 (PTGS2)

Geldanamycin is a selective HSP90 inhibitor; proteins eluted from immunoprecipitated protein complexes after treatment with geldanamycin were identified as HSP90 client proteins [6]. Geldanamycin (GDM), a Hsp90 inhibitor that failed clinical trials due to hepatotoxicity and instability [12] According to new research, there are four sorts

of hereditary options for breast cancer: radcial, novobiocin, STA-9090, STA-1474 because it has an affinity for interminol ATP on HSP90 [13]. Fulvestrant reduces oestradiol binding to the ER and, once bound, deactivates activating functions 1 and 2 (AF1, AF2), reducing receptor translocation to the nucleus and increasing ER degradation [14]. Fulvestrant is currently the first-line therapy of choice for HR-positive postmenopausal women with MBC [15]. Fulvestrant had the greatest antitumor impact (IC50 0.275 mol, 95% CI 0.035-0.931), while Tamoxifen had the worst (IC50 19.13 mol, 95% CI 9.871-45.323) [16].

Preclinical studies and clinical trials of the drugs sarilumab and satralizumab have potential as a treatment for depression. Sarilumab is a human monoclonal antibody that inhibits the alpha interleukin-6 receptor (IL-6Ra) [17]. Patients suffering from rheumatoid arthritis (RA) are more likely to suffer from executive functions deterioration and mental health problems. Sarilumab is an interleukin-6 receptor antagonist approved for the treatment of individuals with moderate-to-severe RA. Sarilumab therapy significantly lowered the overall RAID score calculated from a baseline. Sarilumab either monotherapy or combo treatment increased RAID scores as well as other PROs and RA disease activity significantly [18]. Sarilumab, an IL-6 inhibitor, improves depression in RA patients. It is also obvious that sarilumab, which inhibits IL-6 and reduces CRP levels, alleviates significant depressive symptoms [19].

Satralizumab is a monoclonal antibody that targets the interleukin-6 (IL-6) receptor in people with neuromyelitis optica spectrum disorder (NMOSD) [20]. In addition to these traditional oral preventative care medications, some very effective parenteral monoclonal antibodies, including as rituximab, eculizumab, satralizumab, and inebilizumab, have recently emerged as possible therapy choices. Because the disorder's neurological handicap is known to start suddenly with stepwise development of persistent neurological symptoms, relapse prevention with these preventative drugs is crucial in NMOSD [21]. Satralizumab is an IL-6R-targeting humanized IgG2 recycling monoclonal antibody. It is the first of its kind. It has been explored for the treatment of NMOSD in two phase 3 studies. Both outcomes of the monotherapy trial and there are no other chronic baseline immunosuppression allowed. Additional studies revealed a 79% reduction in relapse probability with satralizumab vs placebo in AQP4-IgG-positive patients [22]. IL-6 signaling is increased in depression and depression-related health behaviors (37).

NSAIDs and specific PTGS2 inhibitors have been shown both in observational and clinical research to have a significant colorectal adenoma or cancer incidence or recurrence chemo preventive potential. Inhibiting PTGS1 and PTGS2 appears to have an active role in CRC prevention through different routes [23]. The PTGS signaling cascade has a colorectal cancer pro-inflammatory molecular signature cancer patients' non-tumor colonic mucosa [24]. Similarly, increased PTGS2 expression leads to increased PGE2 production, which increases cancer cell proliferation via EP2 receptor-mediated signaling. Inhibiting PTGS2 with nonsteroidal anti-inflammatory drugs like aspirin, for example, has been shown to reduce CRC incidence and improve clinical outcomes after CRC surgery [25]. Aspirin therapy improved overall survival in CRC patients, importantly those with positive PTGS2 expression and mutant PIK3CA tumors [26].

Prostaglandins have been connected to the start of tumor growth and carcinogenesis. A small subset of afflicted individuals had a high frequency of the trivial C allele of the single nucleotide polymorphism rs5275, according to PTGS2 sequencing [27]. A key molecular target in the prevention and treatment of CRC is PTGS2 [28]. Early colorectal carcinogenesis is significantly influenced by PTGS2, and stromal cell production of PTGS2 is directly linked to angiogenesis by priming the surrounding normal tissue for the local growth and advancement of the malignant tumor [29].

Because of this, PTGS2 inhibitors are very useful for CRC prevention and therapy both in vivo and in vitro [30]. Clinical investigations including NSAIDs have suggested that upregulation of PTGS2 in colorectal neoplasms may lead to treatment resistance in vivo and carcinogenesis [31]. If a person's CYP1A1 gene is exposed to various environmental pollutants, like PAHs and other xenobiotics, it can change and make them more susceptible to colorectal cancer (CRC) (38).

In silico medication repurposing found Belatacept as a possible MS therapy option. Belatacept binds to CD80 and CD86 on the exterior of cells that presents antigen, inhibiting CD28-mediated T cell co-stimulation [32]. Mutations in genes that encode molecules in the CD28/CTLA-4-CD80/CD86 route may impact not just the chance of getting MS, but also the age at which MS manifests itself [33]. Belatacept binds to CD80 and CD86 on APCs and inhibits both CTLA-4-mediated signals and CD28. As a result, both co-stimulatory and inhibitory signals are reduced in responding T cells [34]. Genetic variations amongst genes encoding molecules in the CD28/CTLA-4-CD80/CD86 route may impact not just the risk of MS, but also the age at which MS manifests. It is critical to look into the mechanisms through which these polymorphisms might also be connected to MS vulnerability and lifespan [35].

4 Conclusion

We map that a total of nine tools have been integrated with each other for the goals of gene analysis and a repurposing medication selection, based on a published approach that incorporates bioinformatics tools, which include: Gwas Catalog, National Biobank Consortioum of Taiwan, Cancer Cell Line of Encyclopedia, HaploReg, STRING, Drugbank, ClinicalTrials.gov, Pubmed.gov, and ConectivityMap. Our review results the present 12 lists of repurposing drugs, two of which (geldanamycin and fulvestrant) have the potential to be developed as breast cancer treatments, two new antidepressant drugs (Sarilumab and Satralizumab), seven new colorectal cancer drugs (sulindac, rucaparib, celecoxib, balsalazide, ibuprofen, naproxen, aspirin), and one new drug highly recommended (Belatacept).

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