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Drug repositioning in cancer: The current situation in Japan

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Abstract

Cancer is a leading cause of death worldwide, and the incidence continues to increase. Despite major research aimed at discovering and developing novel and effective anticancer drugs, oncology drug development is a lengthy and costly process, with high attrition rates. Drug repositioning (DR, also referred to as drug repurposing), the process of finding new uses for approved noncancer drugs, has been gaining popularity in the past decade. DR has become a powerful alternative strategy for discovering and developing novel anticancer drug candidates from the existing approved drug space. Indeed, the availability of several large established libraries of clinical drugs and rapid advances in disease biology, genomics/transcriptomics/proteomics and bioinformatics has accelerated the pace of activity-based, literature-based and in silico DR, thereby improving safety and reducing costs. However, DR still faces financial obstacles in clinical trials, which could limit its practical use in the clinic. Here, we provide a brief review of DR in cancer and discuss difficulties in the development of DR for clinical use. Furthermore, we introduce some promising DR candidates for anticancer therapy in Japan.

KEYWORDS

cancer, clinical trial, drug repositioning, intellectual property, Japan

1 | INTRODUCTION

Drug repositioning (DR) is a strategy for drug development that seeks to establish new drugs from existing approved drugs by discovering novel effects or targets of the approved drugs.[1] DR can be likened to finding a baseball player's talent in an active soccer player (Figure 1). DR has generated increasing interest in the past decade owing to its use as an explicit development strategy and substantial benefits over the traditional development of new drugs (de novo drugs) by reducing development risks and facilitating the development process.[1-5] Indeed, the number of publications related to DR in PubMed has increased rapidly since 2004.[6] Moreover, the number of registrations of clinical trials for DR has increased in Japan (Figure 2).

The discovery process for de novo drugs is costly and time-consuming.[7-9] Currently, on average, the cost for conventional de novo discovery and development of a drug is approximately US$2.5bn and requires around 10-15 years for the drug to reach the market.[7,9] In Japan, the average time and costs to launch a drug de novo are 9.2 years and 55 billion yen, respectively.[10] Moreover, only approximately 1 in 10 drugs entering phase I clinical trials is finally approved by the US Food and Drug Administration (FDA), and the proportion is decreased to 1 in 15 for drugs with an oncology indication in the USA.[8]

Repositioned drugs have already been used in humans and tested at various stages of drug development; therefore, such drugs have information available regarding safety, pharmacology and toxicology. In addition, later stages of the process, such as manufacturing and
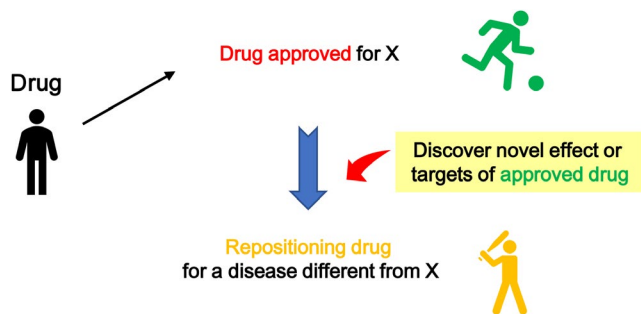
FIGURE 1 Drug repositioning: Discovery strategy of new drugs (baseball player) from existing approved drugs (soccer player)

formulation, can be reused for the new drug product.[5] In oncology, the demand for new therapies continues to increase, and DR could offer a faster and economically more attractive way of fighting malignancies.[11] For example, the drug thalidomide, which was initially used to treat morning sickness but was found to cause malformations in newborns, was successfully repositioned for use in anticancer therapy owing to its anti–angiogenic and anti–inflammatory effects. Thus, thalidomide was approved by the FDA for combination treatment with dexamethasone in patients with multiple myeloma in the USA.[11] This drug was also re–approved for use in patients with multiple myeloma and erythema nodosum leprosum in 2008 in Japan.

In this current report, we provide a brief review of DR in cancer and discuss difficulties in the development of DR for clinical use. In addition, we introduce some promising examples of DR for anticancer therapy in Japan.

2 | APPROACH FOR DRUG REPOSITIONING

To efficiently reposition drugs that are already approved for human use, careful selection is required, followed by a thorough demonstration of the effectiveness of the drugs in other biological contexts. Here, we provide an overview of three representative methods used

for the selection of effective testing and DR in cancer therapy: activity-based, literature-based and in silico DR.

2.1 | Activity-based drug repositioning

Activity-based DR involves testing of actual drugs using in vitro or in vivo assays.[12] Two public comprehensive drug libraries (ie, Johns Hopkins Clinical Compound Library (JHCCL) and NCGC Pharmaceutical Collection [NPC]) are often used for drug screening in these assays. JHCCL is the largest publicly accessible collection of existing drugs, with approximately 3100 available compounds, many of which are approved by the FDA or its foreign counterparts.[11] NPC was built by the NIH Chemical Genomics Center (NCGC) and possesses 2500 small compounds that have been approved for clinical use by US (FDA), European (European Medicines Agency [EMA]), Japanese (National Health Insurance) and Canadian (Health Canada) authorities.[13] Activity-based DR can employ both protein target-based and cell-based screenings, which shed light on clinical trial outcomes. The antifungal agent itraconazole is a promising anticancer drug that has been explored through this approach using JHCCL.[14]

2.2 | Literature-based drug repositioning

This approach is used to identify licensed noncancer drugs with published evidence of anticancer activity using PubMed, MEDLINE and databases of clinical trials, such as ClinicalTrials.gov or University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), which is used mainly in Japan, chemical databases (DrugQuest) and other large-scale databases.[15] One example of successful use of literature-based DR in cancer is the Repurposing Drugs in Oncology (ReDO) project, which was designed to rapidly identify new and effective cancer treatments characterized by low toxicity and cost-effectiveness.[16] Researchers successfully applied a literature-based approach using all forms of published data to identify compounds to repurpose.[16,17]
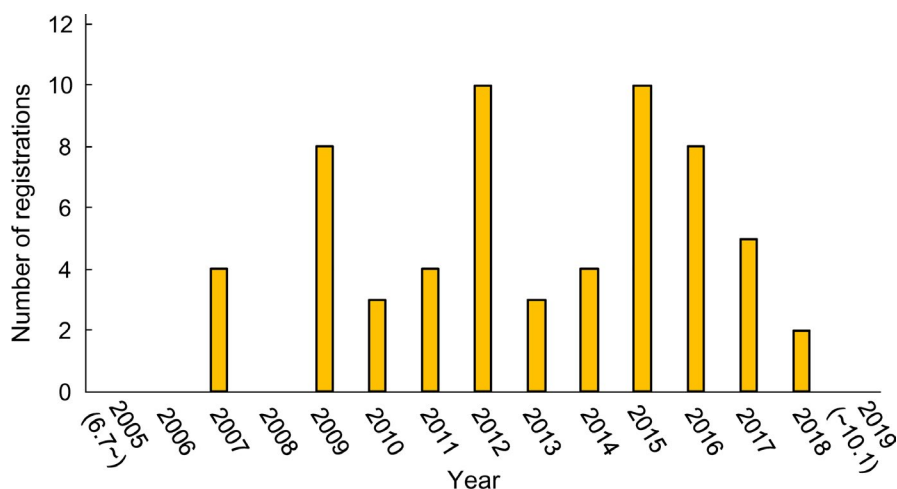
FIGURE 2 The number of registrations of clinical trials for drug repositioning in University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR). UMIN-CTR is one of the major registry systems of clinical trials in Japan

2.3 | In silico drug repositioning

In silico DR utilizes public databases and bioinformatics tools to systematically identify interaction networks between drugs and protein targets.[18] This approach has become successful with the large amounts of information on the structure of proteins (structural biology), genomics/transcriptomics/proteomics (omics) and pharmacophores that have accumulated in recent decades, along with the advancements in bioinformatics and computational science. Most pharmaceutical companies have already adopted in silico models for drug discovery from diverse chemical spaces.[11] Using artificial intelligence algorithms and other bioinformatics tools, researchers have attempted to systematically identify interaction networks between drugs and protein targets.[19] Clearly, in silico DR is a powerful technology with significant advantages, including speed and reduced costs.[20,21] Indeed, this approach has three main advantages: (a) robustness of algorithms for gene expression data analysis; (b) cost-effectiveness; and (c) availability of freely accessible resources.[22,23] However, there are some limitations to this approach because it requires high-resolution structural information for the targets. Moreover, information on the disease phenotype or gene expression profiles of drugs is necessary when a screen does not involve protein targets.[11] In silico DR has been recently reviewed elsewhere in detail.[24-27]

The main idea underlying several current methods, including in silico DR, is to identify genes whose expression levels are inversely correlated in the context of disease and drug treatment.[28-32] These three approaches represent alternative and complementary approaches to the discovery of repositioned drugs. Notably, before conceiving any clinical use, in vitro and in vivo studies are essential to confirm predictions and to design clinical trials.

3 | ADVANTAGES OF DRUG REPOSITIONING

Drugs still under patent but shelved after unsuccessful or partially successful clinical trials could have applications in DR. Indeed, for such drugs, many resources have already been spent to develop these drugs, and their use in similar or novel indications could lead to cost savings and avoidance of risks related to drug development. Furthermore, prior extensive investigations of the pharmacokinetic and pharmacodynamic characteristics of drugs can allow researchers to avoid studies assessing drug dosage, safety and toxicity.[19] In a previous report, Pantziarka et al[15] summarized the advantages of DR as follows: availability of pharmacokinetic, pharmacodynamics and posology data; knowledge of safety, toxicity and adverse events; clinical experience derived from the original indications; widespread availability worldwide; understanding of the mechanisms of action and molecular targets of the drug; and low cost. In most cases, DR can allow researchers to avoid carrying out preclinical tests and phase I trials, thereby reducing the cost of the drug development

process (Figure 3). Some estimates have suggested that DR requires an average of 6.5 years and US$300m dollars to approve and launch a drug.[10]

In addition to these advantages of repurposed drugs, repositioned drugs should be considered to treat patients when there are no approved medications or when a patient has exhausted all available treatment options.

4 | LIMITATIONS

Despite the multiple advantages of DR, this approach still has some limitations. First, DR faces financial obstacles in that there are costs associated with licensing a drug for a new indication. The DR process involves intellectual property protection of the repositioned drugs, particularly for drugs that are off patents. Repositioned drugs are currently no longer patentable, resulting in low commercial interest from pharmaceutical companies. DR trials, particularly phase III efficacy trials, are, therefore, at a disadvantage in that they must rely on philanthropic sources for funding.

Next, in general, repurposed drugs are rarely effective in monotherapy, with anticancer activity more frequently observed in association with other repurposed drugs or known cytotoxic drugs.[33] Furthermore, for novel applications, achieving sufficient efficacy by repositioned drugs sometimes requires treatment at higher doses, for an extended treatment period, or with a different formulation compared with the conventional indication. This may result in unexpected side effects, jeopardizing the idea of the "fast-tracking" of the compound due to the necessity for full-scale preclinical and clinical investigations.[34]
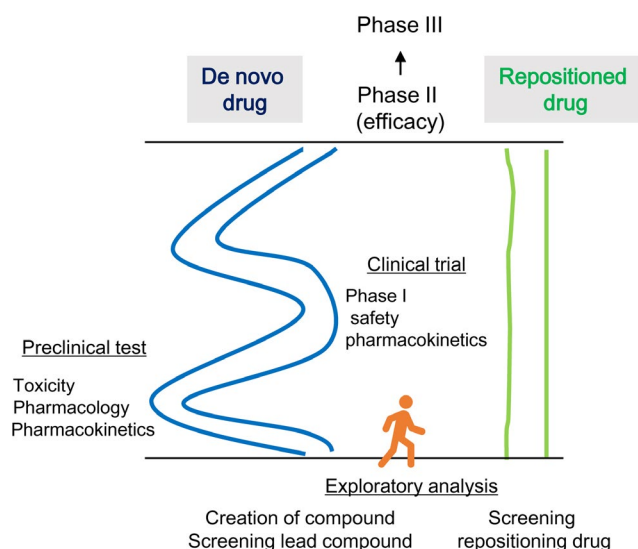
FIGURE 3 Advantage of drug repositioning (DR) over the development of de novo drugs. DR can be used to skip preclinical tests and phase I trials, thereby reducing costs throughout drug development

5 | CLINICAL TRIALS OF DRUG REPOSITIONING IN JAPAN

For searching clinical trials of DR in Japan, we used the following search terms on 1 October 2019: "malignancy" AND "Japan" AND "interventional" using the website of UMIN-CTR (https://www.umin.ac.jp/ctr/index-j.htm), which is a major registry system in Japan that has been recognized by the ICMJE as an "acceptable registry." We then extracted clinical trials related to DR. Among all 7999 trials from June 7, 2005, to October 1, 2019, 63 trials were associated with DR. As shown in Figure 2, the number of registered clinical trials for DR has increased in Japan. We found 29 candidates of repositioned drugs in these 63 trials. These drugs are listed in Table 1. We checked the number of registrations of candidate repositioned drugs around the world using ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home), which is a database of publicly and privately supported clinical studies of human participants conducted worldwide (Table 1). This database is provided by the US National Library of Medicine. To our knowledge, none of the 29 candidates have been clinically approved as repositioned drugs in the world (as of 1 October 2019). Among them, aspirin, zoledronic acid, metformin, atrial natriuretic polypeptide (ANP) and propagermanium (PG) are often subject to clinical trials as repositioned drugs in Japan. We briefly review these five drugs below.

5.1 | Aspirin

Aspirin is the most widely used nonsteroidal anti–inflammatory drug worldwide and functions as a cyclooxygenase (COX)-1 and COX-2 inhibitor to suppress the conversion of arachidonic acid to prostaglandins and thromboxanes.[35] COX-2 promotes inflammation, pain and fever, and the development of colorectal cancer is often promoted by chronic inflammation caused by COX-2 overexpression.[36] Aspirin induces apoptosis via both COX-dependent and COX-independent mechanisms to combat malignancies.[37] The details of clinical trials for aspirin are reviewed elsewhere.[38]

5.2 | Zoledronic acid

Zoledronic acid, a bisphosphonate, is clinically used to treat osteoporosis and cancer-related hypercalcemia and prevents skeletal complications due to bone metastases.[39] Moreover, zoledronic acid inhibits osteoclastic bone resorption through negative regulation of the action of the farnesyl pyrophosphate synthase enzyme in the mevalonate pathway.[12] Zoledronic acid has anticancer effects[40,41] by inhibiting cell proliferation, adhesion, invasion, angiogenesis and bone metastases, and shows immunomodulatory effects, possibly through inhibition of both the Ras/mitogen-activated protein kinase and Akt/mammalian target of rapamycin (mTOR) pathways.[42]

5.3 | Metformin

Metformin, an antidiabetic drug that is used for type 2 diabetes, lowers plasma glucose by suppressing hepatic gluconeogenesis, improving insulin sensitivity, and enhancing peripheral glucose uptake and utilization through activation of AMP-activated protein kinase (AMPK). In the past decade, metformin has also been reported to exhibit anticancer activities. These anticancer effects are mainly mediated by activation of AMPK, which inhibits mTOR, a key mediator of the phosphatidylinositol 3-kinase/Akt signaling pathway in tumor cells that activates the tumor suppressor p53, leading to cancer cell apoptosis.[43,44] Details of clinical trials of metformin are reviewed elsewhere.[38,45]

5.4 | Atrial natriuretic polypeptide

Atrial natriuretic polypeptide is a heart peptide hormone that belongs to a family of cardiac-derived and vascular-derived hormones with crucial roles in cardiovascular homeostasis (ie, regulation of blood volume and pressure).[46,47] In addition to its role in cardiovascular homeostasis, ANP has recently been shown to inhibit tumor growth in vitro and in vivo.[48-54] Furthermore, Nojiri et al reported that mice pretreated with ANP exhibit dramatic reductions in lipopolysaccharide-induced pulmonary metastasis in inoculated cancer cells, suggesting that ANP prevents cancer metastasis by suppressing the inflammatory reaction of endothelial cells, thereby inhibiting cancer cell adhesion to vascular endothelial cells.[55] Thus, ANP may be a promising candidate for innovative anticancer therapy.[56,57] The anti–proliferative efficacy of ANP has been demonstrated in: pancreatic adenocarcinoma; breast, prostate, colon, renal, ovarian, small cell and squamous cell lung cancers; and other tumors.[48-54] The JANP phase III clinical study is ongoing in Japan.[58]

5.5 | Propagermanium

Propagermanium is an organic germanium compound that has been used clinically in Japan since 1994. PG is a safe therapeutic agent against hepatitis B virus e antigen (HBe)-positive chronic hepatitis type B. Administration of PG decreases or eliminates HBe antigen and increases anti–HBe antibodies, resulting in seroconversion. Moreover, decreases in HBV-DNA polymerase activity and HBV-DNA content in blood have been reported.[59] PG targets glycosylphosphatidylinositol-anchored proteins that are closely associated with C-C motif chemokine receptors (CCR) and selectively inhibit C-C motif chemokine ligand (CCL) 2/CCR2 signaling.[60] We recently showed that the CCL2/CCR2 signaling pathway in bone marrow-derived stromal host cells promotes cancer metastasis via the formation of premetastatic niches.[61] Furthermore, we showed that the administration of a CCL2 inhibitor, PG, blocked the enhancement of metastasis by inhibiting the formation of premetastatic niches in a mouse model.[61] Based on these findings, we conducted a

TABLE 1 Candidate repositioned drugs with anticancer effect in Japan in UMIN-CTR

Candidate drug	Effect as approved drug	Disease targeted by DR	Number of registrations	UMIN ID	Number of registrations (overseas)[a]
Aspirin	NSAID	CRC, FAP	5	000031532, 000018736, 000018734, 000000698, 000000697	84
Zoledronic acid	Osteoclastic inhibitor	BC, MPM, ATL, PrC, AML	8	000008701, 000008093, 000007569, 000006736, 000003493, 000003261, 000002577, 000000796	62
Nitroglycerin	Angina	NSCLC	2	000001820, 000000813	7
Menatetrenone	Hemostatic agent	HCC	1	000001815	0
Pipsissewa extract	Prostatic hyperplasia	Patients without PrC with high PSA	1	000002126	0
Candesartan cilexetil	Hypertension	HCC, PaC	2	000002435, 000002152	0
Metformin	Diabetes mellitus	Solid cancer, UC, PaC, LC	7	000028405, 000020856, 000020681, 000020306, 000017694, 000004852, 000002210	163
Branched-chain amino acid	Hepatic encephalopathy	HCC	1	000002330	0
Celecoxib	NSAID (COX-2 inhibitor)	HCC	1	000002435	175
Sodium valproate	Seizures	ESCC, PaC, BtC	2	000010817, 000004525	63
Atrial natriuretic polypeptide	Natriuretic peptide hormone	CRC,NSCLC, LC	6	000025877, 000024302, 000019627, 000018851, 000018480, 000004880	0
Irsogladine Maleate	Gastric mucosal protectant	NSCLC	1	000005901	0
Pioglitazone	Diabetes mellitus	HCC	1	000007344	24
Rifampicin	Antibiotic	HCC	2	000007668, 000007667	29
Mefenamic acid	NSAID	Head and neck cancer	1	000007871	0
Cilostazol	Antithrombotic agent	Head and neck cancer	1	000007871	0
Tranilast	Anti–allergy drug	Lymphatic tumor	1	000008210	0
Disulfiram	Alcoholism	HCC	1	000008529	18
Deferoxamine mesilate	Iron chelator	PaC	1	000009054	0
Sulfasalazine	Rheumatoid arthritis	NSCLC (non–SCC), GC	2	000017854, 000010254	5
Ribavirin	Antiviral agent	PrC	1	000012521	21
Azilsartan	Hypertension	PrC	1	000012656	0
Retinoic acid	Vitamin A	Neuroblastoma	1	000013672	72
Itraconazole	Antifungal medication	PaC, solid cancer	3	000025398, 000018388, 000013951	49
Propagermanium	Chronic hepatitis type B	PaC, BC, CRC, GC	6	000027441, 000022494, 000022440, 000022129, 000017123, 000014689	0
Mesalazine	Inflammatory bowel disease	FAP	1	000018736	3
Naftopidil	Prostatic hyperplasia	PrC	1	000022862	0
Cefadroxil	Bactericidal antibiotic	CML	1	000027904	0
Bezafibrate	Hyperlipidemia	NSCLC	1	000029854	0

Abbreviations: AML, acute myeloid leukemia; ATL, adult T-cell leukemia; BC, breast cancer; BtC, biliary tract cancer; CML, chronic myeloid leukemia; CRC, colorectal cancer; ESCC, esophageal squamous cell cancer; FAP, familial adenomatous polyposis; GC, gastric cancer; GyC, gynecologic cancer; HCC, hepatocellular cancer; LC, lung cancer; MPM, malignant pleural mesothelioma; NSAID, nonsteroidal anti–inflammatory drug; NSCLC, non–small cell lung cancer; PaC, pancreatic cancer; PrC, prostate cancer; UC, urological cancer.

[a]The numbers are obtained using ClinicalTrials.gov.

phase I dose-escalation study of PG administration as an antimetastatic drug for perioperative patients with primary breast cancer and showed that PG could be given safely (UMIN000022494).[62] In addition, Kikuchi et al demonstrated that PG has antitumor activity due to its effects on promoting natural killer cell maturation for patients with metastatic gastric or oral cancer.[63] Details of PG are reviewed elsewhere.[64]

6 | CONCLUSIONS

Drug repositioning is a growing endeavor supported by both the pharmaceutical industry and academia due to its advantages of cost savings and time savings relative to the traditional de novo drug development process. The EMA in Europe and the NIH and the FDA in the USA have already launched DR programs to identify new uses for existing pipeline medications developed by the pharmaceutical industry.[17,65] Furthermore, the ReDO project is an ongoing collaborative project that has focused exclusively on the potential use of approved non-cancer medications as sources of new anticancer therapeutics.[15,66] An open-access version is available online via www.redo-project.org/db. This website will be periodically updated to make information available to oncologists as new drugs are added to the database or as new data become available for drugs listed in the database.

Few bioventures support DR in Japan, although there are some DR candidates currently being evaluated in clinical trials in Japan, as described here. However, to promote DR in Japan, three Japanese pharmaceutical companies have started joint implementation of a drug discovery program, Joint Open INnovation of drUg repositioning (JOINUS), using a drug repositioning compound library constructed by these companies in 2017 (https://open-innovation-joinus.jp/joinus/). Nishimura et al described in detail the ongoing efforts to stimulate DR in Japan.[10] Furthermore, the re–establishment of intellectual property for repositioned drugs may solve major problems of DR for practical use in patients.

Drug repositioning provides a rational, evidence-based and cost-effective approach for cancer treatment, although there are some practical limitations in clinical use. In Japan, the *Clinical Trials Act* was enacted in 2017 to establish procedures for the conduct of clinical trials, which may affect the number of new clinical trial registrations for DR candidates. We believe that DR is valuable and may result in the addition of new tools for use by oncologists.

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