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Review

What patents tell us about drug repurposing for cancer: A landscape analysis

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ABSTRACT

Intellectual property documents (patents and their published applications) are not only collections of legal exclusivity claims but also repositories of scientific and technical information, even though they are not peer reviewed. We have identified and analyzed international disclosures concerning drug repurposing for cancer that were published under the Patent Convention Treaty during the past five years, and show this burgeoning field from an angle that is not routinely captured in review papers of the field. We find that patenting activity for cancer-related new uses for known compounds has been quite constant recently and has targeted mainly small molecule active ingredients that are currently marketed as drugs. Universities contributed most applications, closely followed by corporations. The strong representation of non-academic research institutes from the public and private sector and foundations was surprising and indicates that drug repurposing for cancer has transcended the classical corporate-academia dichotomy. Many of the identified patent documents report findings that are not reflected in the peer review literature (e.g., sumatriptan for mycosis fungoides) or appear there only later (e.g., ibudilast for glioblastoma). Synergistic combinations of several repurposed compounds were also identified, as were two documents related to the repurposing of vaccines. Our findings underscore the necessity for drug repurposers as well as for oncologists to investigate patent documents in addition to the usual peer review literature search to obtain a comprehensive perspective of the state of the art.

1. Introduction

Drug repurposing (also known under the narrower term drug repositioning which implicates new uses of marketed drugs, while drug repurposing also covers discontinued compounds and those that are still in development) has gained an impressive amount of traction recently, not only among non-profit organizations and Open Science advocates but also in the pharmaceutical industry.

Patenting is even more essential in drug repurposing than with new chemical entities because the claims that a redeveloper can patent to protect the invention are limited to (a) the new therapeutic use and (b) new formulations optimally tailored to this new use and the new target population. Existing patents covering the active ingredient itself are either expired (in the case of generics), or the original creator still enjoys patent protection. In either case the compound itself is no longer patentable.

Patent documents are more than legalities protecting intellectual property rights: their second (frequently overlooked) purpose is to disseminate knowledge. Their information content can be considered orthogonal to that of peer review publications. Peer review papers focus on providing cutting-edge scientific insight, while patents tend to reflect what the patent holder (i.e., the assignee) believes could be developed into a marketable product (or could become a trade item in negotiations) on relatively short notice. This technical and commercial angle makes patent documents an extremely valuable additional information source that should never be disregarded in research. Even if so-called “peer review companion papers” are available (which is often, but not nearly always, the case) the patent document tends to lean more towards direct applications.

An analysis of international patent disclosures involving drug repurposing in the life sciences and published under the Patent Convention Treaty in 2011–2014 has shown cancer to be a frequent new target indication, with circulatory system drugs and antiinfectives/antiparasitics contributing the majority of the originally approved indications. However, new therapeutic applications in psychiatry and neurology both surpassed cancer as target indications [1]. That might be explained by the fact that neuropsychiatry has become a relatively neglected field of new drug development, opening more attractive possibilities for drug repurposing than cancer where competition is fierce and requires massive investments.

We have now landscaped the drug repurposing patent scenery in cancer for the past five years using a more descriptive approach.

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2. Methods

Patent codes, which are used to categorize patent subjects, are primarily intended to serve the search needs of patent examiners and other intellectual property specialists. There is no patent code equivalent to the Medical Subject Heading (MeSH) code “Drug repositioning” that would allow quick identification of patents that claim new uses for known agents or drugs. To achieve this, we manually investigated the World Intellectual Property Organization’s PatentScope database for international disclosure documents categorized under code A61 K (supposed to capture all medicinal documents) published between the fourth quarter of 2014 and the present (early third quarter of 2019) for drug repurposing content. Documents that suggested new uses of known compounds based on their titles or abstracts, and documents analyzed for other purposes and found to disclose repurposed uses in their specification or claims parts, were flagged and investigated thoroughly.

3. Results

Our search identified 68 PCT patent applications directly related to the treatment or prevention of cancers or claiming repurposed agents to treat or prevent side effects of cancer therapy. This included a series of 13 documents filed by a corporate applicant from Taiwan with a United States priority and published by the PCT office on the same day in 2016. The members of this series, whose structure is closely related, cover a broad range of known compounds and largely rely on a single experimental methodology, measurement of the cystostatic effect on cancer cell lines. For the descriptive purposes of our analysis, these 13 documents were treated as a single application.

In sharp contrast with peer review publications, where the number of cancer papers related to drug repurposing has shown strong growth during the past five years (data not shown), there was little change over time in our data body: as measured by PCT patent disclosures, potentially patentable innovation concerning drug repurposing for cancer, while considerable and consistent, exhibited little dynamic development recently.

Priority dates (i.e., the dates on which the founding patent document was filed) ranged from 2013 to 2018, peaking in 2015 and 2016 as had to be expected considering the mechanics of patent internationalization. The list of countries where the priority documents were filed is led by the United States (29 documents), the United Kingdom (6), and the continental European Union (9). The strong lead of the United States and the underrepresentation of Asian countries (4 priority documents from South Korea, one each from India and Singapore) can be explained by the fact that many countries decide for a first filing in the United States, especially if the inventors have some relation to the United States. It has also to be noted that, while there can be only one priority document with one priority country per invention, there can be several applicants from several countries.

Corporate applicants, commonly thought to dominate life science patenting, contributed only 29% of the applications while academia had a narrow lead (36%). A group consisting of national health authorities, state-owned research institutes, public-private partnerships and private foundations filed 24% of the documents.

The great majority of inventions (49 documents, 88%) claimed small molecules, almost exclusively for direct anticancer therapeutic purposes (see Table 1). Only 6 documents concerned themselves with measures designed to control side effects of cancer therapy (Table 2). Three documents addressed proteins, antibodies, or vaccines (Table 3).

4. Discussion

As was expected, only a limited number of international patent disclosures concerned with drug repurposing and cancer was published during the past five years, which contrasts sharply with the approximately 370 hits returned by a corresponding PubMed search for the same publication interval. Patents are much more expensive to prepare and file than a peer review manuscript, and – more importantly – they require constant funding to maintain them. A patenting decision is not easily made, and in addition requires involvement of several parties other than the inventors.

While the strong involvement of academia reflects the general surge of university participation in intellectual property protection, its extent was unexpected. Perhaps even more surprising is the strong representation of research institutes and various foundations, which indicates that the concept of drug repurposing has spread far beyond the classic academic-corporate dichotomy.

Only one rare cancer (Hippel Lindau syndrome) was identified as a repurposing target, with subtype-selective beta blockers such as butoxamine and prenalterol disclosed in WO/2019/030151. However, a remarkable aspect of our data is that the claimed new uses very often are in (relative) niche areas of cancer therapy, frequently addressing tumors with specific patterns of antigen overexpression. Examples are cerivastatin and other statins for tumors with fusions or rearrangements of EML4-ALK (WO/2017/123063), or biperiden for MALT + cancers (WO/2016/193339) – two inventions that do not seem to have been reported in the peer review literature. Other such findings reported here, such as the fact that Par-4 secretion induced by the antimalarial drug chloroquine triggers paracrine apoptosis of cancer cells and also inhibits metastatic tumor growth (WO/2016/196614), took longer – in this particular case, until 2017 – to appear in the peer review literature [2]. In yet other cases, e.g., in reporting that the dipeptidylpeptidase-IV inhibitor sitagliptin can enhance cancer immunotherapy by preventing cleavage of the interferon-inducible chemokine CXCL10 (WO/2017/020974) peer review publication was quicker [3].

Because of the many possibilities for tumors to develop resistance against oncology drugs repurposing drug combinations is a particularly attractive option in cancer therapy. Two such patents were identified during our search. WO/2015/170248 combines the antiretroviral drug nelfinavir (a specific inhibitor of HIV protease that also inhibits AKT), the antidiabetic metformin (a stimulator of AMPK), and the dyslipidemia agent rosuvastatin (a HMG-CoA reductase inhibitor) to treat PTEN mutation cancers. Additional presence of p53 mutations is said to further enhance the effect of the triple combination, which has not been reported in the peer review literature. Loss of PTEN is known to activate the PI3K/AKT pathway responsible for radiation resistance in various tumors, which has led to the suggestion that HIV protease inhibitors could act as radiosensitizers [4].

In WO/2018/044369 metformin is combined with simvastatin and the old anti-arrhythmic drug digoxin. This combination is now being tested in a Phase I clinical trial (NCT03889795) in patients with advanced solid tumors that commenced in June 2019. Metformin is to be taken at dinner time, simvastatin at bedtime and digoxin in the morning. The first indications that combining metformin with a statin could reduce hepatocellular carcinoma in diabetics was published in 2015 [5] but adding the cardiac glycoside digoxin which induces cancer cell apoptosis via inhibition of Na + /K + − ATPase pump seems to add synergy that has not been reported in the peer review literature.

Vaccines are generally considered unlikely subjects in drug repurposing: a vaccine is designed to induce immunity against a particular antigen (or set of antigens) and figuring out ways to use it for treating a different condition seems close to impossible. A PubMed search combining the MeSH term “drug repositioning” with the keyword “vaccine” returns 25 hits for the past five years, but only one actually addresses repurposing of existing vaccines [6]. Yet the PCT international patent application record shows two vaccine repurposing documents that were published during our report period; they are based on broadly differing concepts (Table 3).

In WO/2015/059114 the human endogenous retrovirus K (HERV-K) family is supposed to provide an immunological link between the yellow fever virus and breast cancer, which frequently expresses the

Table 1
Patent Convention Treaty Disclosures for Direct Therapeutic Repurposing of Small Molecules for Cancer, Q4/2014-Q3/2019.

Patent discosure	Subject compounds	Original use or mechanism	Cancer type or new mechanism
WO/2014/164730	Acetoheximide Benserazide	Antidiabetic DOPA decarboxylase inhibitor	Enhancing base excision repair in genetic cancer risk
WO/2014/181131	Naltrexone	Pan-opioid receptor antagonist	TLR9 agonism
WO/2015/044762	Cefazolin	Antibacterial	T-cell leukemias
WO/2015/007869	Levobupivacaine	Local anesthesia	Multi-site inhibition oF energy production
WO/2015/079148	Tritoqualine	Anti-allergic (histidine decarboxylase inhibitor)	H4 receptor agonist for acute leukemias
WO/2015/079413	Chlorhexidine Pyrvinium	Antibacterial Antihelminthic	Antimetastatic synaptojanin-2 Inhibitors
WO/2015/101839	Sumatriptan	Oral migraine agent (5-HT1B/1D agonist)	Topical agent for mycosis fungoides
WO/2015/120206	Moclobemide, clorgyline	MAO-A inhibitors	VEGF and bFGF downregulation in gliomas
WO/2015/120254	Disulfiram	Alcohol deterrent (acetaldehyde dehydrogenase inhibitor)	O6-methylguanine-DNA methyltransferase (MGMT) inhibitor
WO/2015/170248	Nelfinavir + metformin + rosuvastatin	Antiretroviral + antidiabetic + dyslipidemia agent	PTEN mutation cancers
WO/2015/187847	Misoprostol Alpostradil	PGE1 agents for obstetrics and erectille dysfunction	Chronic myeloic leukemia
WO/2015/189597	Naltrexone	Pan-opioid receptor antagonist	Priming of cancer cells for PI3K inhibitor treatment
WO/2016/036676	Thioridazine	Antipsychotic	NSCLC with a KRAS mutation and resistance to gefitinib, erlotinib, and mAbs
WO/2016/062265-67 WO/2016/062270-72 WO/2016/062277 WO/2016/062279 WO/2016/062286-87 WO/2016/062289-91	Duloxetine, triamterene, paroxetine, cinacalcet, mycophenolate, prochlorperazine; various antiparasitics, antifungals and antibacterials; immunomodulators; respiratory disease drugs; nebivolol, amlodipine, monobenzone	Various	Cytostatic effect on various solid tumors
WO/2016/077346	Ciclopirox	Antifungal	Notch, Wnt and Hedgehog pathway blocker for bladder cancer
WO/2016/116438	Desloratadine Ebastine	Antiallergics (H1 receptor antagonists)	Not stated
WO/2016/127168	Mebendazole polymorph C	Antiparasitic	Various mechanisms against brain tumors
WO/2016/134486	Canagliflozin	Antidiabetic (SGLT2 inhibitor)	Synergizes with cisplatin and docetaxel; also a radiation sensitizer
WO/2016/141476	Irbesartan	Angiotensin receptor antagonist	P-1 transcriptional complex stimulator
WO/2016/176675	Teratogenic agents	Various	Elimination of cancer stem cells
WO/2016/179481	Deptropine Pizotifen	Antihistamine Headache; antidepressant	Lysosome outward migration inhibitors
WO/2016/193339	Biperiden	Extrapyramidal symptoms in Parkinson's disease	MALT1 expressing cancers
WO/2016/196614	Chloroquine	Antimalarial	Par-4 induction for prostate cancer
WO/2017/011973	Various statins	Dyslipidemia (HMG-CoA reductase inhibitors)	Gastric cancer
WO/2017/020974	Sitagliptin	DPP-IV inhibitor	Prevention of CXCL10 cleavage to enhance immunotherapy
WO/2017/023047	Aripiprazole	Antipsychotic	Multimodal apoptosis enhancer
WO/2017/048197	Niclosamide	Antihelminthic	p53-deficient cells and cancers
WO/2017/123063	Cerivastatin and other statins	Dyslipidemia (HMG-CoA reductase inhibitor)	EML4-ALK-positive NSCLC resistant to ALK inhibitors
WO/2017/127397	Niclosamide	Antihelminthic	Adrenocortical carcinoma

(*continued on next page*)

Table 1 (*continued*)

Patent discosure	Subject compounds	Original use or mechanism	Cancer type or new mechanism
WO/2017/173278	Nitroxoline	Antibacterial	Booster for other oncology drugs
WO/2017/177947	Disulfiram	Alcohol deterrent (acetaldehyde dehydrogenase inhibitor)	Pleuroperitoneal membrane cancers
WO/2017/201501	Riluzole	Neuroprotectant for ALS (Na-channel blocker and NMDA receptor blocker)	Booster for cancer immunotherapeutics
WO/2018/022728	Meglumine	Excipient in imaging agents	Ornithine decarboxylase inhibitor for skin cancers
WO/2018/022823	Nepicastat Etamicastat Amperozide	Dopamine beta-hydroxylase inhibitors Antipsychotic	Liver carcinoma and other cancers
WO/2018/035446	INT-131 (AMG-131)	PPAR-γ agonist for diabetes	Leukemias, myeloma
WO/2018/044369	Metformin + simvastatin + digoxin	Antidiabetic + anti-dyslipidemic + anti-arrythmic	Synergistic inhibition of proliferative pathways
WO/2018/065771	Pimozide	Antipsychotic	Triple negative breast cancer overexpressing Ran
WO/2018/091961	Metformin	Antidiabetic	Booster for epothilone A in ROS-induced apaptosis
WO/2018/118910	Dipyramidole Dilazep	Vasoactive adenosine reuptake inhibitors	SLC29A2; oncogene suppressors
WO/2018/119262	Ibudilast	Antiasthmatic (MIF and PDE inhibitor)	Glioblastoma
WO/2018/128517	Niclosamide	Antihelminthic	Ras overexpressing cancers
WO/2018/132899	Rosiglitazone	PPAR-γ agonist for diabetes	Lung metastasis of osteosarcoma
WO/2018/138510	Mebendazole	Antihelminthic	Triple negative breast cancer overexpressing Ran
WO/2019/030151	ICI 118,551 Butoxamine Prenalterol	β2-selective betablockers	Hippel-Lindau disease
WO/2019/060409	Ondansetron Clozapin Clofazimine	Antiemetic Anticonvulsant Anti-leprosy agent	Connexin-46 inhibitors for glioblastoma
WO/2019/066469	Febuxostat Topiroxostat	Xanthine oxidase inhibitors	Metastasis inhibitors
WO/2019/138203	Hydroxychloroquine	Antimalarial	Triple-negative breast cancer

HERV-K envelope protein. At the time of filing it had been known that its binding by a monoclonal antibody could inhibit growth of breast cancer cells in vitro, and of human breast cancer xenotransplants in mice [7] but the essential role of this envelope protein for tumorigenesis and metastasis of breast cancer had not yet not been established [8,9]. The inventors conducted a retrospective registry-based study, comparing breast cancer epidemiology in a large cohort of women who had been vaccinated against yellow fever with non-vaccinated women from the same Italian region. In vaccinated women aged 40–54 years the risk of breast cancer was reduced by two thirds if vaccination was 2–6 years past. The protective effect (which was not seen in younger and older age groups) vanished after 8–10 years. There seems to have been no peer review report yet.

When the U.S. patents underlying international patent application WO/2017/027757 were filed in 2015, our knowledge of oncolytic poxvirus therapy was not nearly as advanced as it is today [10] but this patent application might have been an important milestone. Autologous carrier cells (preferably adipose tissue-derived stromal vascular fraction stem cells or allogeneic umbilical cord-derived mesenchymal-like cells) were used to shield the ACAM2000 live Vaccinia virus vaccine from the immune system, and to aid in tumor targeting. A clinical trial in 25 patients with advanced metastatic solid tumors or hematologic malignancies revealed the induction of activated and memory T cells within one month of treatment, with tumor size reduction up to complete eradication in some patients and with no relevant safety issues. The peer review companion paper [11] took a year longer to publish than the international patent disclosure.

Summary

It can be easily seen how a thorough study of international patent disclosures can provide valuable information on developments concerning drug repositioning for cancer, provided that they are treated not only as legal documents but also as sources of information. Because

Table 2
Patent Convention Treaty Disclosures for Repurposing to treat or prevent side effects of cancer therapy, Q4/2014-Q3/2019.

Patent discosure	Subject compounds	Original use or mechanism	Cancer type or new mechanism
WO/2014/162123 WO/2014/162124	Zoledronate	Bisphosphonate for bone metabolic diseases	Selective protection of non-malignant tissue against cancer radiotherapy
WO/2014/201283	Bevacizumab	Antiangiogenic cancer therapy	Preservation of ovarian function during cancer therapy
WO/2015/138186	Arepitant	Antiemetic (NK-1 receptor antagonist)	Prevention of doxorubicin cardiotoxicity
WO/2017/046357	Elsiglutide	Diarrhea induced by cancer therapy	protecting bone marrow or immune-response during cancer chemotherapy
WO/2019/053723	Adenosine A3 receptor ligands	Various	Managing cytokine release syndrome in cancer immunotherapy

Table 3
Patent Convention Treaty Disclosures for Repurposing of Large Molecules (Proteins and Antibodies) or Vaccines to Treat or Prevent Cancer, Q4/2014-Q3/2019.

Patent discosure	Subject compounds	Original use or mechanism	Cancer type or new mechanism
WO/2015/059114	Stamaril®	Yellow fever vaccine	Breast cancer risk reduction
WO/2016/154748	Desmopressin	Antidiuretic	Synergy with docetaxel in prostate cancer
WO/2017/027757	ACAM2000	Live smallpox vaccine	Immunotherapy for solid tumors

of their nature that targets applications believed to have relatively immediate commercial potential such documents can alert researchers and developers at an early stage, in ways that are orthogonal to peer review papers. Many of the documents that we have identified report repurposing ideas that have no current equivalent in the peer review literature.

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