

Repurposing non-cancer Drugs in Oncology – How many drugs are out there?

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Abstract

Background

Drug repurposing can speed up access to new therapeutic options for cancer patients. With more than 2000 drugs approved worldwide and 6 relevant targets per drug on average, the potential is quantitatively important. In this paper, we have attempted to quantify the number of non-cancer drugs supported by either preclinical or clinical cancer data.

Methods

A PubMed search was performed to identify non-cancer drugs which could be repurposed in one or more cancer types. Drugs needed at least one peer-reviewed article showing an anticancer effect in vitro, in vivo or in humans.

Results

A total of 235 eligible non-cancer drugs were identified (Table 1). Main characteristics of the drugs are summarized in Table 2. 67 (29%) are on the WHO list of essential medicines and 176 (75%) are off-patent. 133 (57%) had human data in cancer patient(s). Four were listed in clinical guidelines, namely thalidomide, all-trans retinoic acid, zoledronic acid and non-steroidal anti-inflammatory drugs (NSAID). Several drugs have shown a survival benefit in randomized trials such as cimetidine (colorectal cancer), progesterone (breast cancer) or itraconazole (lung cancer). Several other drugs induced responses in rare tumours, like clarithromycin, timolol or propranolol.

Conclusion

We have found that the number of off-patent repurposing opportunities is large and increasing. Joint non-commercial clinical development (academics, governments, charities) may bring new therapeutic options to patients at low cost, especially in indications for which the industry has no incentive to invest in.

Introduction

Drug repurposing can speed up access to new therapeutic options for cancer patients. Whereas it is not unusual to attempt to find new cancer uses for existing anticancer drugs, less attention and efforts are made to find anticancer uses of non-cancer drugs¹. However, many non-cancer drugs could be potentially repurposed against cancer though to our knowledge no figures have been put forward so far². One advantage of non-cancer drugs is that they represent a way to adapt to new knowledge about cancer. For instance, Tadalafil (PDE-5 inhibitor, erectile dysfunction), inhibits myeloid-derived suppressor cells (MDSC) in cancer patients³. Or propranolol (beta-blocker, hypertension) reduces proliferation and migration of angiosarcoma models^{4,5}, by blocking beta-adrenergic receptors expressed by angiosarcoma cells⁶.

With more than 2000 drugs approved worldwide and 6 relevant targets per drug on average⁷, the potential is quantitatively important. What's more, with regular new drug approvals, the toolbox that repurposed drugs represent is growing every year. Even antibodies are now being repurposed (e.g. rituximab in pemphigus⁸), sometimes based on the discovery of off-target effects^{9,10}.

When a drug loses its patent protection, the incentives for the market authorization holder are also lost. Sometimes, other private entities attempt to protect the new therapeutic use by various means and undertake a commercial development¹¹. However, this strategy remains financially risky, which makes it less attractive to investors and venture capitalists compared to other biotech investments. We have called these drugs "financial orphan drugs"¹².

In this paper, we have attempted to quantify the number of non-cancer drugs supported by either preclinical or clinical cancer data.

Methods

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A total of 235 eligible non-cancer drugs were identified (Table 1). Main characteristics of the drugs are summarized in Table 2. 67 (29%) are on the WHO list of essential medicines and 176 (75%) are off-patent. 133 (57%) had human data in cancer patient(s). Four were listed in clinical guidelines, namely thalidomide, *all-trans* retinoic acid, zoledronic acid and non-steroidal anti-inflammatory drugs (NSAID). In the first 3 cases, pharmaceutical companies took the lead and re-branded or re-formulated the drugs. This was not the case for NSAIDs, listed in desmoid tumours guidelines and used off-label.

Several drugs have shown a survival benefit in randomized trials such as cimetidine (colorectal cancer)¹³, progesterone (breast cancer)¹⁴ or itraconazole (lung cancer)¹⁵. Of note, several other drugs induced responses in rare tumours, like clarithromycin¹⁶, timolol^{17,18} or propranolol^{19–22}.

Table 1: List of non-cancer drugs with at least one peer-reviewed paper supporting its use against cancer.

Drug	Pharmacological class	Main Indications
Acetazolamide	Carbonic anhydrase inhibitors - ATC Code: S01EC01	Glaucoma, diuretic, epilepsy
Acetaminophen (paracetamol)	NA	Analgesic
Agomelatine	Melatonergic antidepressant	Insomnia
Albendazole	NA	Anthelmintic
Aliskiren	Direct renin inhibitor	Essential hypertension
Allopurinol	Xanthine oxidase inhibitors	Gout
All-trans retinoic acid (tretinoin)	NA	Acne, APL
Alpha-Lipoic Acid	Thioctic acid - A16AX01	Diabetic neuropathy (Germany)
Amantadine	Anticholinergic	Parkinson, Influenza A
Amiloride	Potassium-sparing diuretic	In congestive heart failure or hypertension treated with thiazides, to conserve potassium
Amiodarone	Antiarrhythmic	Ventricular tachycardia/fibrillation
Amitriptyline	Tricyclic Anti-depressant	Depression
Amlodipine	Calcium Channel Blocker	Hypertension
Amodiaquine	Anti-malaria	Malaria
Anakinra	IL-1R antagonist	RA, NOMID, CAPS
Anagrelide	PDE3 inhibitor (Platelet-reducing agent)	Essential thrombocythemia
Aprepitant	Substance P/neurokinin 1 (NK1) receptor antagonist	Nausea, vomiting
Aprotinin	Bovine pancreatic trypsin inhibitor (BPTI)	Perioperative blood loss
Arginine	Essential amino acid	Nutraceutical
Aripiprazole	Atypical antipsychotic	Bipolar disorder, major depressive disorder, autistic disorder
Artesunate	Antiprotozoal, antimalarian	Malaria
Atenolol	Competitive beta(1)-selective adrenergic antagonist	Hypertension, angina pectoris
Atorvastatin	Selective, competitive HMG-CoA reductase inhibitor (anti-cholesterol)	Coronary heart disease, acute coronary syndrome
Atovaquone	Synthetic hydroxynaphthoquinone (antiprotozoal, antimalarian)	Pneumocystis carinii pneumonia, toxoplasmosis
Atrial Natriuretic Peptide	Polypeptide vasodilator	Heart failure
Aspirin	NSAID	Pain, swelling, reduces the risk of a blood clot, prevent further heart attacks or strokes
Auranofin	Gold salt (anti-rheumatic)	RA
Azithromycin	Macrolide antibiotic, semi-synthetic	Bacterial infection, CAP, PID

Bazedoxifene	Selective estrogen receptor modulator	Osteoporosis
Bedaquiline	ATP-synthase inhibitor (antibiotic, diaryl-quinoline)	Tuberculosis
Bemiparin	LMWH (anti-coagulant)	Venous thromboembolism, myocardial infarction
Benserazide	Peripherally-acting aromatic L-amino acid decarboxylase (AADC) or DOPA decarboxylase inhibitor	Parkinson's Disease
Bepridil	Calcium Channel Blocker	Hypertension and chronic stable angina
Bezafibrate	Fibrate	Hyperlipidipemia
Biperiden	Muscarinic antagonist	Parkinson's Disease
Bosentan	Endothelin receptor antagonists	PAH
Bromocriptine	Dopamine agonist	Parkinson's Disease, prevention of lactation
Cabergoline	Dopamine receptor agonist	Hyperprolactinemia
Caffeine	CNS Stimulant	Newborn apnea
Calcitriol	Vitamin D3	Vitamin
Candesartan	Angiotensin Receptor Blocker	Hypertension
Captopril	Angiotensin-converting-enzyme inhibitor	Anti-hypertension
Carbimazole	Imidazole-derivative (antithyroid)	Hyperthyroidism
Carglumic acid	Metabolic alkalosis agent	Hyperammonaemia in N-acetylglutamate synthase deficiency
Carvedilol	Betablocker	Hypertension
Celecoxib	NSAID (COX-2)	OA, RA, JRA, AS, acute pain, primary dysmenorrhea
Cephalexin	Cephalosporin antibiotic	Bacterial infections
Cholecalciferol	Vitamin D3	Vitamin
Chlorpromazine	Phenothiazine (typical antipsychotic)	Psychotic disorders, nausea and vomiting, anxiety, hiccups
Chloroquine	Antimalarial and amebicidal drug	Malaria, Extraintestinal Amebiasis
Cidofovir	Deoxycytidine monophosphate analog	CMV-retinitis in AIDS
Cilnidipine	Calcium Channel Blocker	Hypertension
Cimetidine	Histamine H2-receptor blocker	Duodenal/gastric ulcers, GERD, pathological hypersecretory conditions
Ciprofloxacin	Fluoroquinolone	Antibiotic
Citalopram	Selective Serotonin Reuptake Inhibitors	Depression
Clarithromycin	Macrolide antibiotic	Bacterial infections
Clofocetol	Other antibiotic	Bacterial infections
Clomifene	Synthetic ovulation stimulant	Ovulatory dysfunction
Clomipramine	Tricyclic anti-depressant	Obsessive Compulsive Disorder

Clotrimazole	Imidazole derivative	Fungal infections
Colchicine	Antimitotic alkaloid	Gout
Dalteparin	LMWH (anti-coagulant)	DVT (prophylaxis), unstable angina/non-Q-wave myocardial infarction
Danazol	Antigonadotropins and similar agents	Endometriosis, fibrocystic breast disease, hereditary angioedema
Dapsone	Antibiotic	Dermatitis herpetiformis, leprosy
Deferoxamine	Iron chelating agent	Acute iron intoxication, chronic iron overload
Desmopressin	Vasopressin analogue	Diabetes Insipidus, bedwetting, hemophilia A, von Willebrand's disease
Diclofenac	NSAID	OA, RA, AS
Diflunisal	NSAID	OA, RA, mild to moderate pain
Digitoxin	Cardiac glycoside	Congestive HF, atrial fibrillation, atrial flutter, PAT, cardiogenic shock
Digoxin	Cardiac glycoside	Heart failure, atrial fibrillation
Dimethyl Fumarate	NA	Psoriasis, Multiple Sclerosis
Dipyridamole	Platelet aggregation inhibitor	Thromboembolism Prophylaxis Post-Cardiac Valve Replacement
Disulfiram	Alcohol antagonist	Chronic alcoholism
Donepezil	Acetylcholinesterase inhibitor	Alzheimer's Disease
Doxazosin		Anti-hypertensive
Doxycycline		Antibiotic
Ebastine	Histamine H1-receptor blocker	Allergies
Efavirenz		Anti-retroviral
Eflornithine		
Enalapril	Angiotensin-converting-enzyme inhibitor	Anti-hypertensive
Enoxaparin	LMWH	Anti-coagulant
Epalrestat	Aldose reductase inhibitor	Anti-diabetic
Esomeprazole	Proton Pump Inhibitor	Antacid
Ethacrynic acid	Loop diuretic	Diuretic
Etodolac	NSAID (COX-2)	NSAID
Famotidine	Histamine H2-receptor blocker	Antacid
Fasudil		Vasodilator
Felodipine	Calcium Channel Blocker	Anti-hypertensive
Fenofibrate	Fibrate	Anti-cholesterol
Fingolimob	Sphingosine-1-phosphate receptor modulator	Multiple Sclerosis
Fish oil (EPA/DHA)		Anti-cholesterol
Flubendazole		Anti-parasitic
Fluoxetine		Anti-depressant

Fluspirilene		Anti-psychotic
Fluvastatin		Anti-cholesterol
Fluvoxamine	Serotonin antagonist and reuptake inhibitors	Anti-depressant
Glipizide	Sulfonylureas	Anti-diabetic
Glutamine		Nutraceutical
Griseofulvin		Anti-fungal
Haloperidol		Dopamine antagonist
Hydralazine		Anti-hypertensive
Hydroxychloroquine		
Hymecromone		Antispasmodic
Ibandronate		Bisphosphonate
Ibuprofen		Analgesic
Imipramine	Tricyclic Anti-depressant	Anti-depressant
Imiquimod		
Indomethacin		NSAID
Irbesartan	Angiotensin Receptor Blocker	Anti-hypertensive
Itraconazole		Anti-fungal
Ivermectin		Anti-parasitic
Ketoconazole		Anti-fungal
Ketorolac		NSAID
Lanreotide	Somatostatin analogue	
Lansoprazole	Proton Pump Inhibitor	Antacid
Leflunomide		Arthritis
Levetiracetam		Anti-epileptic
Levofloxacin	Fluoroquinolone	Antibiotic
Licofelone		Osteoarthritis
Lithium		Bipolar disorders
Lidocaine		Anesthetic
Loperamide		Anti-diarrhea
Loratadine	Histamine H1-receptor blocker	Allergies
Losartan	Angiotensin Receptor Blocker	Anti-hypertensive
Lovastatin	Statin	Anti-cholesterol
Loxoprofen	NSAID	Anti-inflammatory
Macitentan	Endothelin receptor antagonists	Pulmonary arterial hypertension
Manidpine	Calcium Channel Blocker	Anti-hypertensive
Maraviroc	CCR5 receptor antagonist	Anti-retroviral
Mebendazole		Anti-parasitic
Meclofenamate		
Megestrol acetate		Hormone
Mefloquine		Anti-malarial
Melatonin		Anti-insomnia

Meloxicam	NSAID	Anti-inflammatory
Memantine	NMDA receptor antagonist	Alzheimer's Disease
Mepacrine (Quinacrine)		Anti-parasitic
Metformin		Anti-diabetic
Methimazole		
Methazolamide		Antiglaucoma, diuretic
Methylnaltrexone	μ -opioid antagonist	Opioid-induced constipation
Metoclopramide		Anti-emesis
Mifepristone		Abortifacient
Minocycline		Antibiotic
Mirtazapine		
Montelukast		
Mycophenolate		Immunosuppressant
Nadroparin		
Naproxen		NSAID
Naltrexone		Opioid receptor antagonist
Nelfinavir		Anti-retroviral
Niclosamide		Anti-parasitic
Nifedipine	Calcium Channel Blocker	Anti-hypertensive
Nifurtimox		
Nimodipine	Calcium Channel Blocker	Anti-hypertensive
Nisoldipine	Calcium Channel Blocker	Anti-hypertensive
Nitazoxanide		Anti-protozoal
Nitisinone		
Nitroxoline		Antibiotic
Nitroglycerine		Nitro-vasodilator
Norethandrolone	Androgen	Aplastic anemia
Noscapine		Anti-tussive
Octreotide		
Olanzapine	Atypical antipsychotic	Anti-psychotic
Olsalazine		Anti-inflammatory
Omeprazole	Proton Pump Inhibitor	Antacid
Orlistat	Lipase Inhibitor	Obesity
Ormeloxifene	Selective estrogen receptor modulator	Contraceptive
Oseltamivir	Neuraminidase inhibitor	Anti-viral
Ouabain		Anti-aryhtmic
Oxcarbazepine	Voltage-gated sodium channel blocker	Epilepsy
Pantoprazole	Proton Pump Inhibitor	Antacid
Penfluridol	Diphenylbutylpiperidine	Anti-psychotic
Pentamidine		Anti-parasitic

Pentoxifylline	Xanthine derivative	Peripheral artery disease
Perphenazine	Phenothiazine	Anti-psychotic
Phenylbutyrate		Urea cycle disorders
Phentolamine	Alfa-adrenergic antagonist	Vasodilator
Phenytoin		Anti-epileptic
Pirfenidone		Anti-fibrotic
Pimozide	Diphenylbutylpiperidine	Anti-psychotic
Pioglitazone		Anti-diabetic
Plerixafor		Autologous HSCT
Pravastatin	Statin	Anti-cholesterol
Prazosin		Anti-hypertensive
Pregabalin	Gabapentinoid	Anti-convulsant
Promethazine	Phenothiazine	Anti-psychotic
Propranolol	Betablocker	Anti-hypertensive
Pyrimethamine	Dihydrofolate reductase inhibitor	Anti-parasitic
Pyrvinium pamoate		Anti-parasitic
Quetiapine	Atypical antipsychotic	Anti-psychotic
Rabeprazole	Proton Pump Inhibitor	Antacid
Ranolazine	Voltage-gated sodium channel blocker	Anti-angina
Repaglinide		Anti-diabetic
Ribavirin	nucleoside inhibitor	Anti-viral
Rifabutin		Antibiotic
Riluzole		ALS
Risperidone	Atypical antipsychotic	Anti-psychotic
Ritonavir	Protease inhibitor	Anti-HIV
Roflumilast	PDE-4 inhibitor	COPD
Rosuvastatin	Statin	Anti-cholesterol
Sertraline		Anti-depressant
Sildenafil	PDE-5 inhibitor	Erectile dysfunction
Simvastatin	Statin	Anti-cholesterol
Sirolimus		Inhibit organ transplant rejection
Sodium Bicarbonate		Antacid
Sodium Oxybate		Narcolepsy
Spironolactone		Anti-hypertensive
Sulfasalazine		Anti-rheumatic
Sulindac		NSAID
Tadalafil	PDE-5 inhibitor	Erectile dysfunction
Terbinafine		Anti-fungal
Telmisartan	Angiotensin Receptor Blocker	Anti-hypertensive
Tetrathiomolybdate		Copper toxicosis
Thalidomide	Immunomodulatory imide drug	Leprosy, multiple myeloma

Thiabendazole		Anti-parasitic
Thioridazine	Penothiazine	Anti-psychotic
Ticagrelor		Anti-platelet
Ticlopidine		Anti-platelet
Tigecycline	Glycylcycline	Antibiotic
Timolol	Betablocker	Anti-hypertensive
Tinzaparin	LMWH	Anti-coagulant
Tolfenamic acid	Fenamate NSAIDs	NSAID
Topiramate		Epilepsy
Tranexamic acid		Blood loss
Trazodone	Serotonin antagonist and reuptake inhibitors	Anti-depressant
Triamterene	Potassium-sparing diuretic	Diuretic
Trifluoperazine	Phenothiazine	Anti-psychotic
Ulinastatin	Trypsine inhibitor	Severe sepsis & pancreatitis
Urokinase		
Valproic acid		Anti-convulsant
Valsartan	Angiotensin Receptor Blocker	Anti-hypertensive
Verapamil		Anti-hypertensive
Warfarin	Anti-Vitamin-K	Anti-coagulant
Zoledronate		Bisphosphonate

Table 2: Some features of the 235 drugs listed

	N	%
Human data (<i>at least 1 case report, 1 obs. study or 1 clinical trial</i>)	133	57%
At least 1 clinical trial	124	53%
Drug Off-Patent	176	75%

Discussion

We have found that the number of off-patent repurposing opportunities is large and increasing.

Until now, practice-changing examples have been limited despite the evidence. Joint non-commercial clinical development (academics, governments, charities) may bring new therapeutic options to patients at low cost, especially in indications for which the industry has no incentive to invest in. This may relieve healthcare systems currently under high financial stress.

A change in market authorisation regulation will be required to avoid off-label use.

The Anticancer Fund is actively pursuing this innovative strategy, as exemplified by the granting of an EMA orphan designation for propranolol in angiosarcoma.

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