

Table S2. The primary indication, targets and co-occurrence number of multi-target agents.

Agent	Primary indication^[a]	Host target^[b]	MTB target^[c]	Co-occurrence number^[d]
Abacavir	For the treatment of HIV-1 infection, in combination with other antiretroviral agents.	HLA-B; TNF; LST1		21
Adalimumab	For treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and Crohn's disease.	LTA; TNF		275
Alfentanil	For the management of postoperative pain and the maintenance of general anesthesia.	CYP3A4; CYP3A5		0
Alpha-D-Mannose	Unkown	IL6R; MBL2; IL12B; CD209		0
Alprazolam	For the management of anxiety disorder or the short-term relief of symptoms of anxiety and for the treatment of panic disorder, with or without agoraphobia.	CYP3A4; CYP3A5	Rv3455c	3
Amlodipine	For the treatment of hypertension and chronic stable angina.	CYP3A4; CYP3A5		1
Aripiprazole	For the treatment of schizophrenia and related psychotic disorders.	CYP3A4; CYP3A5		0
Astemizole	Astemizole was indicated for use in the relieving allergy symptoms, particularly rhinitis and conjunctivitis. It has been withdrawn from the market however due to concerns of arrhythmias.	CYP3A4; CYP3A5		0
Atorvastatin	May be used as primary prevention in individuals with multiple risk factors for coronary heart disease (CHD) and as secondary prevention in individuals with CHD to reduce the risk of myocardial infarction (MI), stroke, angina, and revascularization procedures. May be used to reduce the risk of cardiovascular events in patients with acute coronary syndrome (ACS). May be used in the treatment of primary hypercholesterolemia and mixed dyslipidemia, homozygous familial hypercholesterolemia, primary dysbetalipoproteinemia, and/or hypertriglyceridemia as an adjunct to dietary therapy to decrease serum total and low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apoB), and triglyceride	CYP3A4; CYP3A5		6

	concentrations, while increasing high-density lipoprotein cholesterol (HDL-C) levels.			
Bisphosphonates	Osteoporosis	VDR; IL1B		57
Bortezomib	For treatment of multiple myeloma in patients who have not been successfully treated with at least two previous therapies.	PSMB8; PSMB9	Rv0350; Rv2109c; Rv2110c	6
Buspirone	For the management of anxiety disorders or the short-term relief of the symptoms of anxiety, and also as an augmentation of SSRI-treatment against depression.	CYP3A4; CYP3A5		0
Caffeine	For management of fatigue, orthostatic hypotension, and for the short term treatment of apnea of prematurity in infants.	CYP3A4; CYP3A5		17
Carbamazepine	For the treatment of epilepsy and pain associated with true trigeminal neuralgia.	HLA-A; HLA-B; CYP3A4; CYP3A5; LTA; TNF; CYP2C19		25
Carfilzomib	Carfilzomib is indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate.	PSMB8; PSMB9		0
Celastrol	Rheumatoid disease	TNF; IL1B		1
Cerivastatin	Used as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Types IIa and IIb) when the response to dietary restriction of saturated fat and cholesterol and other non-pharmacological measures alone has been inadequate.	CYP3A4; CYP3A5		1
Chloroquine	For the suppressive treatment and for acute attacks of malaria due to P. vivax, P.malariae, P. ovale, and susceptible strains of P. falciparum, Second-line agent in treatment of Rheumatoid Arthritis	TLR9; TNF		114
Chlorpheniramine	For the treatment of rhinitis, urticaria, allergy, common cold, asthma and hay fever.	CYP3A4; CYP3A5		2
Cilostazol	For the reduction of symptoms of intermittent claudication (pain in the legs that occurs with walking and disappears with rest).	CYP3A4; CYP3A5		2
Cisapride	For the symptomatic treatment of adult patients	CYP3A4;		0

	with nocturnal heartburn due to gastroesophageal reflux disease.	CYP3A5		
Citalopram	For the treatment of depression. Unlabeled indications include: treatment of mild dementia-associated agitation in nonpsychotic patients, smoking cessation, ethanol abuse, obsessive-compulsive disorder (OCD) in children, and diabetic neuropathy.	CYP3A4; CYP2C19		0
Clarithromycin	An alternative medication for the treatment of acute otitis media caused by <i>H. influenzae</i> , <i>M. catarrhalis</i> , or <i>S. pneumoniae</i> in patients with a history of type I penicillin hypersensitivity. Also for the treatment of pharyngitis and tonsillitis caused by susceptible <i>Streptococcus pyogenes</i> , as well as respiratory tract infections including acute maxillary sinusitis, acute bacterial exacerbations of chronic bronchitis, mild to moderate community-acquired pneumonia, Legionnaires' disease, and pertussis. Other indications include treatment of uncomplicated skin or skin structure infections, helicobacter pylori infection, duodenal ulcer disease, bartonella infections, early Lyme disease, and encephalitis caused by <i>Toxoplasma gondii</i> (in HIV infected patients in conjunction with pyrimethamine). Clarithromycin may also decrease the incidence of cryptosporidiosis, prevent the occurrence of α -hemolytic (viridans group) streptococcal endocarditis, as well as serve as a primary prevention for <i>Mycobacterium avium</i> complex (MAC) bacteremia or disseminated infections (in adults, adolescents, and children with advanced HIV infection).	CYP3A4; CYP3A5	Rv0667; Rv0440	410
Clodronate	For the management of hypercalcemia of malignancy and as an adjunct in the management of osteolysis resulting from bone metastases of malignant tumors.	VDR; IL1B		2
Cocaine	For the introduction of local (topical) anesthesia of accessible mucous membranes of the oral, laryngeal and nasal cavities.	CYP3A4; CYP3A5		84
Codeine	For treatment and management of pain (systemic). It is also used as an antidiarrheal and as a cough suppressant.	CYP3A4; CYP3A5		15

Cpg 52364	Systemic Lupus Erythematosus	TLR9; TLR8		0
Crx-191	Psoriasis and Psoriatic Disorders	IFNG; TNF		0
Cyclophosphamide	Cyclophosphamide is indicated for the treatment of malignant lymphomas, multiple myeloma, leukemias, mycosis fungoides (advanced disease), neuroblastoma (disseminated disease), adenocarcinoma of the ovary, retinoblastoma, and carcinoma of the breast. It is also indicated for the treatment of biopsy-proven minimal change nephrotic syndrome in pediatric patients.	CYP3A4; CYP2C19; IL8	Rv2391; Rv3607c	215
Dapsone	For the treatment and management of leprosy and dermatitis herpetiformis.	CYP3A4; CYP3A5	Rv3608c	138
Dexamethasone	Injection: for the treatment of endocrine disorders, rheumatic D=disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, neoplastic diseases, edematous states, cerebral edema. Ophthalmic ointment and solution: for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe. Ophthalmic solution only: for the treatment of steroid responsive inflammatory conditions of the external auditory meatus Topic cream: for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses Oral aerosol: for the treatment of bronchial asthma and related corticosteroid responsive bronchospastic states intractable to adequate trial of conventional therapy Intranasal aerosol: for the treatment of allergic or inflammatory nasal conditions, and nasal polyps.	VDR; NOS2		228
Dextromethorphan	For treatment and relief of dry cough.	CYP3A4; CYP3A5		3
Diazepam	Used in the treatment of severe anxiety disorders, as a hypnotic in the short-term management of insomnia, as a sedative and premedicant, as an anticonvulsant, and in the	CYP3A4; CYP3A5; CYP2C19		24

	management of alcohol withdrawal syndrome.			
Diltiazem	For the treatment of Hypertension	CYP3A4; CYP3A5		5
Docetaxel	For the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy. Also used as a single agent in the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. It is also used in combination with prednisone, in the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer. Furthermore, docetaxel has uses in the treatment of gastric adenocarcinoma and head and neck cancer.	CYP3A4; CYP3A5		9
Domperidone	For management of dyspepsia, heartburn, epigastric pain, nausea, and vomiting.	CYP3A4; CYP3A5		1
Doxorubicin	Doxorubicin is used to produce regression in disseminated neoplastic conditions like acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, thyroid carcinoma, gastric carcinoma, Hodgkin's disease, malignant lymphoma and bronchogenic carcinoma in which the small cell histologic type is the most responsive compared to other cell types. Doxorubicin is also indicated for use as a component of adjuvant therapy in women with evidence of axillary lymph node involvement following resection of primary breast cancer.	CYP3A4; NOS2; CYP2C19	Rv0005	57
Eplerenone	For improvement of survival of stable patients with left ventricular systolic dysfunction (ejection fraction <40%) and clinical evidence of congestive heart failure after an acute myocardial infarction.	CYP3A4; CYP3A5		0
Erlotinib	For the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. Also for use, in combination with gemcitabine, as the first-line treatment of patients with locally advanced,	CYP3A4; CYP3A5		12

	unresectable or metastatic pancreatic cancer.			
Estradiol	For the treatment of urogenital symptoms associated with post-menopausal atrophy of the vagina (such as dryness, burning, pruritus and dyspareunia) and/or the lower urinary tract (urinary urgency and dysuria).	CYP3A4; CYP3A5	Rv1017c	45
Etanercept	For treatment of severe active rheumatoid arthritis in adults, severe juvenile idiopathic arthritis, ankylosing spondylitis, and severe plaque psoriasis.	LTA; TNF; TNFRSF1B		308
Etidronic Acid	For the treatment of symptomatic Paget's disease of bone and in the prevention and treatment of heterotopic ossification following total hip replacement or due to spinal cord injury.	VDR; IL1B		0
Everolimus	Everolimus is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. Indicated for the treatment of adult patients with progressive neuroendocrine tumors of pancreatic origin (PNET) with unresectable, locally advanced or metastatic disease. Indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. Indicated for the treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. Indicated in pediatric and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.	AKT1; MTOR		5
Felodipine	For the treatment of mild to moderate essential hypertension.	CYP3A4; CYP3A5		0
Fentanyl	For the treatment of cancer patients with severe pain that breaks through their regular narcotic therapy.	CYP3A4; CYP3A5		13
Finasteride	For the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an	CYP3A4; CYP3A5		3

	enlarged prostate to: Improve symptoms, reduce the risk of acute urinary retention, reduce the risk of the need for surgery including transurethral resection of the prostate. Also used for the stimulation of regrowth of hair in men with mild to moderate androgenetic alopecia (male pattern alopecia, hereditary alopecia, common male baldness).			
Fluvoxamine	For management of depression and for Obsessive Compulsive Disorder (OCD). Has also been used in the management of bulimia nervosa.	CYP3A4; CYP2C19		1
Glucosamine	Glucosamine is usually used in the treatment of osteoarthritis, although its efficacy is still in question.	IFNG; TNF; IL1B		57
Haloperidol	For the management of psychotic disorders (eg. schizophrenia) and delirium, as well as to control tics and vocal utterances of Tourette's syndrome (Gilles de la Tourette's syndrome). Also used for the treatment of severe behavioural problems in children with disruptive behaviour disorder or ADHD (attention-deficit hyperactivity disorder). Haloperidol has been used in the prevention and control of severe nausea and vomiting.	CYP3A4; CYP3A5	Rv0350	9
Heme	Unkown	CYP3A4; ALOX5; NOS2	Rv1485	213
Hydrocortisone	For the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Also used to treat endocrine (hormonal) disorders (adrenal insufficiency, Addisons disease). It is also used to treat many immune and allergic disorders, such as arthritis, lupus, severe psoriasis, severe asthma, ulcerative colitis, and Crohn's disease.	CYP3A4; CYP3A5		380
Imatinib	For the treatment of Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML), Ph+ acute lymphoblastic leukaemia, myelodysplastic/myeloproliferative diseases, aggressive systemic mastocytosis, hypereosinophilic syndrome and/or chronic eosinophilic leukemia (CEL), dermatofibrosarcoma protuberans, and malignant gastrointestinal stromal tumors	CYP3A4; CYP3A5		11

	(GIST).			
Indinavir	Indinavir is an antiretroviral drug for the treatment of HIV infection.	CYP3A4; CYP3A5		26
Infliximab	To manage the signs and symptoms, as well as to induce and maintain clinical remission in adults with moderate to severe active Crohn's disease or ulcerative colitis. Also used to manage signs and symptoms of rheumatoid arthritis (in conjunction with methotrexate), ankylosing spondylitis, psoriatic arthritis, and juvenile arthritis.	LTA; TNF		553
Insulin, Porcine	For the treatment of type I and II diabetes mellitus.	HLA-DQB1; HLA-DQA2		0
Interferon Gamma-1B	Interferon gamma-1b is used for the treatment of Chronic granulomatous disease and Osteopetrosis.	IFNGR1; IFNGR2		1
Irinotecan	For the treatment of metastatic colorectal cancer (first-line therapy when administered with 5-fluorouracil and leucovorin). Also used in combination with cisplatin for the treatment of extensive small cell lung cancer. Irinotecan is currently under investigation for the treatment of metastatic or recurrent cervical cancer.	CYP3A4; CYP3A5		5
L-Carnitine	For treatment of primary systemic carnitine deficiency, a genetic impairment of normal biosynthesis or utilization of levocarnitine from dietary sources, or for the treatment of secondary carnitine deficiency resulting from an inborn error of metabolism such as glutaric aciduria II, methyl malonic aciduria, propionic acidemia, and medium chain fatty acylCoA dehydrogenase deficiency. Used therapeutically to stimulate gastric and pancreatic secretions and in the treatment of hyperlipoproteinemias. Parenteral levocarnitine is indicated for the prevention and treatment of carnitine deficiency in patients with end-stage renal disease.	SLC22A4; SLC22A5		9
Lercanidipine	For the treatment of Hypertension, management of angina pectoris and Raynaud's syndrome	CYP3A4; CYP3A5		0
Levomethadyl Acetate	For the treatment and management of opiate dependence. It is sometimes used to treat severe	CYP3A4; CYP3A5		0

	pain in terminal patients.			
Lidocaine	For production of local or regional anesthesia by infiltration techniques such as percutaneous injection and intravenous regional anesthesia by peripheral nerve block techniques such as brachial plexus and intercostal and by central neural techniques such as lumbar and caudal epidural blocks.	CYP3A4; CYP3A5		25
Lovastatin	For management as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels in patients with primary hypercholesterolemia and mixed dyslipidemia. For primary prevention of coronary heart disease and to slow progression of coronary atherosclerosis in patients with coronary heart disease.	CYP3A4; CYP3A5		8
Methadone	For the treatment of dry cough, drug withdrawal syndrome, opioid type drug dependence, and pain.	CYP3A4; CYP3A5		104
Methotrexate	Methotrexate is indicated in the treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole. In acute lymphocytic leukemia, methotrexate is indicated in the prophylaxis of meningeal leukemia and is used in maintenance therapy in combination with other chemotherapeutic agents. Methotrexate is also indicated in the treatment of meningeal leukemia. Methotrexate is used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides (cutaneous T cell lymphoma), and lung cancer, particularly squamous cell and small cell types. Methotrexate is also used in combination with other chemotherapeutic agents in the treatment of advanced stage non-Hodgkin's lymphomas. Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis. Methotrexate is indicated in the management of selected adults with severe, active rheumatoid arthritis (ACR criteria), or children with active polyarticular-course juvenile rheumatoid arthritis.	TLR4; PTPN22	Rv2391	303
Minocycline	For the treatment of infections caused by	ALOX5; IL1B	Rv0667;	65

	susceptible strains of microorganisms, such as Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsial pox and tick fevers caused by Rickettsiae, upper respiratory tract infections caused by Streptococcus pneumoniae and for the treatment of asymptomatic carriers of Neisseria meningitidis.		Rv0440	
Nateglinide	For the treatment of non-insulin dependent-diabetes mellitus in conjunction with diet and exercise.	CYP3A4; CYP3A5		0
Nelfinavir	Used in combination with other antiviral drugs in the treatment of HIV in both adults and children.	AKT1; CYP2C19		15
Nisoldipine	For the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.	CYP3A4; CYP3A5		2
Nitrendipine	For the treatment of mild to moderate hypertension	CYP3A4; CYP3A5		0
Ondansetron	For the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy, postoperation, and radiation. Also used for the treatment of postoperative nausea and vomiting.	CYP3A4; CYP3A5		1
Paclitaxel	Used in the treatment of Kaposi's sarcoma and cancer of the lung, ovarian, and breast. Abraxane® is specifically indicated for the treatment of metastatic breast cancer and locally advanced or metastatic non-small cell lung cancer.	CYP3A4; CYP3A5		17
Paliperidone	For the treatment of schizophrenia.	CYP3A4; CYP3A5		0
Phenytoin	For the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.	HLA-B; CYP2C19		49
Pimozide	Used for the suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment.	CYP3A4; CYP3A5		0
Progesterone	For progesterone supplementation or replacement as part of an Assisted Reproductive Technology (ART) treatment for	CYP3A4; CYP3A5; CYP2C19	Rv1017c	56

	infertile women with progesterone deficiency and for the treatment of secondary amenorrhea. Also used for the reduction of the incidence of endometrial hyperplasia and the attendant risk of endometrial carcinoma in postmenopausal women receiving estrogen replacement therapy, as well as treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology such as fibroids or uterine cancer.			
Propranolol	For the prophylaxis of migraine.	CYP3A4; CYP3A5; CYP2C19	Rv2251	13
Quinine	For the treatment of malaria and leg cramps	CYP3A4; CYP3A5		24
Rilonacept	Rilonacept is currently used in the treatment of cryopyrin-associated periodic syndrome. In May 2012, an advisory panel for the FDA voted 11-0 against the use of Rilonacept for the treatment of gout.	IL1B; IL1A		1
Risperidone	For the treatment of schizophrenia in adults and in adolescents, ages 13 to 17, and for the short-term treatment of manic or mixed episodes of bipolar I disorder in children and adolescents ages 10 to 17. May also be used to manage symptoms of inappropriate behavior due to aggression and/or psychosis in patients with severe dementia.	CYP3A4; AKT1		2
Ritonavir	Indicated in combination with other antiretroviral agents for the treatment of HIV-infection.	CYP3A4; CYP3A5		94
Salmeterol	For the treatment of asthma and chronic obstructive pulmonary disease (COPD).	CYP3A4; CYP3A5		2
Saquinavir	For the treatment of HIV-1 with advanced immunodeficiency together with antiretroviral nucleoside analogues.	CYP3A4; CYP3A5		22
Sildenafil	For the treatment of erectile dysfunction and to relieve symptoms of pulmonary arterial hypertension (PAH).	CYP3A4; CYP3A5		8
Simvastatin	For the treatment of hypercholesterolemia and for the reduction in the risk of cardiac heart disease mortality and cardiovascular events. It can also be used in adolescent patients for the treatment of heterozygous familial	CYP3A4; CYP3A5	Rv2444c	8

	hypercholesterolemia.			
Sirolimus	For the prophylaxis of organ rejection in patients receiving renal transplants.	CYP3A4; CYP3A5; MTOR	Rv2748c	25
Telithromycin	For the treatment of Pneumococcal infection, acute sinusitis, acute bacterial tonsillitis, acute bronchitis and bronchiolitis, lower respiratory tract infection and lobar (pneumococcal) pneumonia.	CYP3A4; CYP3A5		5
Terfenadine	For the treatment of allergic rhinitis, hay fever, and allergic skin disorders.	CYP3A4; CYP3A5		1
Testosterone	To be used as hormone replacement or substitution of diminished or absent endogenous testosterone. Use in males: For management of congenital or acquired hypogonadism, hypogonadism associated with HIV infection, and male climacteric (andopause). Use in females: For palliative treatment of androgen-responsive, advanced, inoperable, metastatic (skeletal) carcinoma of the breast in women who are 1-5 years postmenopausal; testosterone esters may be used in combination with estrogens in the management of moderate to severe vasomotor symptoms associated with menopause in women who do not respond to adequately to estrogen therapy alone.	CYP3A4; CYP3A5		56
Theophylline	For the treatment of the symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases, such as emphysema and chronic bronchitis.	CYP2E1; CYP3A4		63
Trazodone	For the treatment of depression.	CYP3A4; CYP3A5		3
Triazolam	For the short-term treatment of insomnia.	CYP3A4; CYP3A5		1
Verapamil	For the treatment of hypertension, angina, and cluster headache prophylaxis.	CYP3A4; CYP3A5		52
Zaleplon	For the treatment of short-term treatment of insomnia in adults.	CYP3A4; CYP3A5	Rv3610c	0
Zolpidem	For the short-term treatment of insomnia.	CYP3A4; CYP3A5		1

[a] derived from DrugBank (<http://www.drugbank.ca/>).

[b] from the Drug-Gene Interaction database (DGIdb, <http://dgidb.genome.wustl.edu/>).

[c] derived from STITCH (<http://stitch.embl.de/>).

[d] The co-occurrence number is the agent and tuberculosis or Mycobacterium tuberculosis terms in the biomedical literature through the NCBI Medline abstracts by text mining with The Entrez Programming Utilities (E-utilities) (www.ncbi.nlm.nih.gov/books/NBK25501/). When tuberculosis with the agent or Mycobacterium tuberculosis with the agent appeared in the abstract of the same publication, a co-occurrence record was retrieved.