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TRMP: A Database of Therapeutically Relevant Multiple-Pathways

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Abstract

Disease processes often involve cross-talks between proteins in different pathways. Different proteins have been used as separate therapeutic targets for the same disease. Synergetic targeting of multiple targets has been explored in combination therapy of a number of diseases. Potential harmful interactions of multiple targeting have also been closely studied. To facilitate mechanistic study of drug actions and a more comprehensive understanding the relationship between different targets of the same disease, it is useful to develop a database of known therapeutically relevant multiple pathways. Information about non-target proteins and natural small molecules involved in these pathways also provides useful hint for searching new therapeutic targets and facilitate the understanding of how therapeutic targets interact with other molecules in performing specific tasks. The Therapeutically Relevant Multiple Pathways Database is designed to provide information about such multiple pathways along with related therapeutic targets, corresponding drugs/ligands, targeted disease conditions, constituent individual pathways, structural and functional information about each proteins in the pathways. Cross-links to other databases are also introduced to facilitate the access of information about individual pathways and proteins. This database can be accessed at http://bidd.nus.edu.sg/group/trmp/trmp.asp and it currently contains 11 entries of multiple pathways, 97 entries of individual pathways, 120 targets covering 72 disease conditions together with 120 sets of drugs directed at each of these targets. Each entry can be retrieved through multiple methods including multiple pathway name, individual pathway name and disease name.

Introduction

Proteins and nucleic acids that play key roles in disease processes have been explored as therapeutic targets for drug development(Drews, 2000; Ohlstein *et al.*, 2000). Knowledge of these therapeutically relevant proteins and nucleic acids has facilitated modern drug discovery by providing platforms for drug screening against a pre-selected target (Drews, 2000). It has also contributed to the study of the molecular mechanism of drug actions, discovery of new therapeutic targets, and development of drug design tools (Hopkins and Groom, 2002; Zambrowicz and Sands, 2003). Information about non-target proteins and natural small molecules involved in these pathways is also useful for facilitating the search of new therapeutic targets and for understanding how therapeutic targets interact with other molecules to perform specific tasks.

A number of web-based resources of therapeutically-targeted proteins and nucleic acids are available (Chen *et al.*, 2002; Ji *et al.*, 2003), which provide useful information about the targets of drugs and investigational agents. Cross-talks between proteins of different pathways are common phenomena and these often have therapeutic implications (Abdel-Latif, 1996; Adcock and Caramori, 2001; Alaoui-Jamali and Qiang, 2003; Ignar-Trowbridge *et al.*, 1992; Kumar-Sinha *et al.*, 2002; Minatoguchi *et al.*, 2003; Takayanagi *et al.*, 2000; Zemel, 1998). Cocktail drug combination therapies directed at multiple targets have been explored for a number of diseases including AIDS(Grodesky *et al.*, 2001), cancer(El-Rayes and Philip, 2002; Sagae *et al.*, 2003), Alzheimer disease (Tariot and Federoff, 2003), amyotrophic lateral sclerosis (Kriz *et al.*, 2003), and dyslipidemia(Bays and Stein, 2003). These prompted interest for more extensive exploration of synergistic targeting of multiple targets in drug discovery (Huang, 2002). Potential harmful interactions arising from multiple targeting are also closely watched and studied (Lewis, 2003). Effective drugs with robust phenotypic effects are known to simultaneously affect many proteins in different pathways (Huang, 2002). For instance, in addition to interacting with its main target protein cyclooxygenase, anti-inflammatory drug salicylate is known to affect NF-kB pathway and other connected cellular targets that all normally contribute to perpetuate inflammatory state (Alpert and Vilcek, 2000; Yin *et al.*, 1998). Therefore resources of therapeutically relevant multiple pathways are useful for facilitating the analysis of the potential implications of multiple target-based therapies and for mechanistic study of drug effects.

Pathway information can be obtained or extracted from various internet pathway databases and protein databases. These include Expasy Biochemical pathways (http://www.expasy.ch/cgi-bin/search-biochem-index) (Gasteiger *et al.*, 2003), Kyoto Encyclopedia of Genes and Genomes (http://www.genome.ad.jp/kegg)(Kanehisa *et al.*, 2002), Metabolic Pathways of Biochemistry (http://www.gwu.edu/~mpb/)(Miller., 1998), Signaling Pathway database (http://www.grt.kyushu-u.ac.jp/eny-doc/spad.html)(Higashi-ku., 1998), Cell Signaling Networks database (http://geo.nihs.go.jp/csndb)(Takai-Igarashi *et al.*, 1998), Enzymes and Metabolic Pathways (http://emp.mcs.anl.gov)(Selkov *et al.*, 1996), PathDB system for pathways (http://www.ncgr.org/pathdb/)(Schilkey, 2003), Encyclopedia of E. Coli Genes and metabolism (http://www.biocyc.org)(Karp *et al.*, 2002), Biocarta (http://www.biocarta.com)(The BioCarta team, 2003), the University of Minnesota Biocatalysis/Biodegradation database (http://umbbd.ahc.umn.edu)(Ellis *et al.*, 2003), Soybean metabolic pathways (http://cgsc.biology.yale.edu/metab.html)(Shoemaker., 2003), Nicholson minimaps (http://www.tcd.ie/Biochemistry/IUBMB-Nicholson)(Nicholson, 2001), Database of Interacting Proteins (http://dip.doe-mbi.ucla.edu/)(Xenarios *et al.*, 2002), Biomolecular interaction network database (http://www.blueprint.org/bind/bind.php) (Bader *et al.*, 2003), TRANSPATH (http://www.biobase.de/pages/products/databases.html)(Krull *et al.*, 2003), and Signal transduction knowledge environment (http://stke.sciencemag.org/index.dtl) (Gough, 2001).

While information about multiple pathways can be obtained from the existing individual pathway databases, interfaces that integrate multiple pathway maps may provide more convenient platforms for facilitating the analysis of the collective effects of different proteins in separate pathways. Moreover, the existing databases either include significantly more number of pathways than therapeutic ones or they are intended for specific types of pathways that do not cover all of the therapeutic ones, which can sometimes make the search of therapeutically relevant constituents less convenient. It is thus desirable to have a database specifically designed as a convenient source of information about therapeutically relevant multiple pathways to complement existing databases.

In this work, we introduce a Therapeutically Relevant Multiple Pathway (TRMP) database, which gives information about inter-related multiple pathways of a number of diseases and physiological processes. This database provides information about known therapeutic targets within each network of multiple pathways, the corresponding drugs/ligands directed at each of these targets, the constituent individual pathways, and information about the proteins involved in these pathways. Cross-links to other databases are introduced to facilitate the access of information about the constituent individual pathways and the function, sequence, nomenclature, and related literatures of each protein in the pathways.

Database structure and access

TRMP can be accessed at http://bidd.nus.edu.sg/group/trmp/trmp.asp and it can be downloaded upon written request. The use of this database is free for con-commercial purposes. The entries of this database are generated by using the information collected from a comprehensive search of related publications in MEDLINE (Wheeler *et al.*, 2003). Combination of three keywords (disease name, target name, and "pathway") is used in searching the relevant publications. The relevant information is derived primarily from review articles and pharmacology textbooks. Primary articles are also used for clarification purpose. The extracted information is double checked against the referenced articles independently by different persons. All of the references used for generating the pathways are provided in the database. Human data are used for human pathways and proteins. Likewise, the corresponding species data are used for bacterial or viral pathways and proteins. TRMP is updated every 6 months.

Our approach of linking human proteins to the human pathway constituents (with the exception of the viral and bacterial specific ones) is critically based on the assumption that all of the shown pathways happen in human although this may not have been experimentally verified. The pathway models in the review articles and textbooks are often based on the results of a patchwork of experimental systems involving genes and proteins of different species origin. Thus caution is needed in interpreting the molecular interactions and pathway constituents in TRMP. Effort will be paid to promptly update newly reported results to our database.

As TRMP claims to become a medical resource this may lead to dangerous misinterpretations.

Our database currently contains 11 entries of multiple pathways that include 97 distinct individual pathways and 120 therapeutic targets covering 72 different disease conditions. A total of 32 of the 97 distinct individual pathways are included in other pathway databases. The list of multiple pathways and distinct individual pathways are given in the supplementary material which also includes the related diseases, the number and examples of associated known therapeutic targets, and examples of corresponding drugs directed at these targets.

The interactive maps of each pathway entry of TRMP are constructed by using Macromedia FLASH. The corresponding database architect associated with the pathway interactive maps is developed by using Active Server Page with Oracle 9i support. This database has three layers. The top layer is the main graphical user interface with a querying tool for finding specific entries of multiple pathways. The second layer is the graphical interface for the interactive maps of multiple pathways with a browser tool for retrieving additional information. The browser tool can be used both for accessing information about the constituent individual pathways from other databases and for retrieving information about individual targets or non-target proteins directs a retrieving request from TRMP. The third layer is the graphic interface for entries of individual targets or non-target proteins with a browser tool for accessing additional information from other databases.

The TRMP database web interface is shown in Figure 1. This database is searchable by selecting the name of a particular entry of multiple-pathways. It can also be accessed by selection of the name of a disease or the name of an individual pathway from the list provided in the corresponding selection field. Searches involving any combination of these three search or selection fields are also supported.

Figure 2 illustrates the interface for an entry of therapeutically relevant multiple pathways. A therapeutically targeted protein is represented by a red rectangle box and a non-target protein by a yellow or blue rectangle box respectively, with the name of the target or protein included in each respective box. Genes and RNAs are represented by orange boxes so that they can be easily distinguished from proteins. More detailed information about each target can be obtained by clicking the respective red rectangle box which is linked to the corresponding target information page provided in our database. Proteins in the yellow boxes are those with detailed information available. The relevant information can be accessed by clicking a yellow box which is linked to the corresponding protein information page provided in our database. Proteins in the blue boxes are those with only a general name specified in the literature which is not specific enough to determine their identity. As a result, no detailed information about these proteins is available in the current version of our database.

A small molecule ligand is represented by its name and its action of a protein is indicated by a white circular box with one of the following symbols inside. These symbols are +, -, ↑, ↓, P, R, B, D and A which represents activation of the protein, inhibition of the protein, increase of the protein level, decrease of the protein level, protein phosphorylation, release of the protein to extra-cellular environment, binding to the protein with unknown effect, binding to the protein leading to its dimerization, and binding to the protein as an antibody respectively. A pink circular box indicates the site and action of a drug or investigative agent and the type of drug action is represented by the same set of symbols as that for small molecule ligands. More detailed information about the corresponding drugs is represented through a mouse-over-effect upon clicking a relevant pink drug action circular box.

The names of the constituent individual pathways contained in each entry are given. Cross links to other pathway databases are provided for those individual pathways that are described in other pathway databases. The effects of the pathways are given by the green boxes with unregulated dot line which include the description about each effect. There are cases that the actual protein involved in a particular process in a pathway is unidentified. Thus, instead of the actual protein, the related process is described in the same way. In addition, the complex of several proteins is demonstrated by the light-blue boxes with dot line.

Figure 3 gives the interface of a target entry of TRMP, which is similar to that of a non-target protein entry with the exception that the former contain a section for potential therapeutic implications. Information provided include protein name, synonyms, Swissprot AC number, species, gene name and location, protein sequence (AASEQ) and gene sequence (NTSEQ) as well as potential therapeutic implications while applicable. Cross-links to other databases are provided which include Genecard, GDB, Locuslink, NCBI, KEGG, OMIM and SwissProt to facilitate the access of more detailed information about various aspects of the particular target or non-target protein.

Concluding remarks

With rapid advances in proteomics (Dove, 1999), pathways (Huang, 2002) and systems (Schwartz *et al.*, 2000), new information about therapeutically relevant multiple pathways can be incorporated or the corresponding databases can be cross-linked to TRMP to provide more comprehensive information about the therapeutically relevant pathways, related targets and their relationship to other biomolecules and cellular processes.

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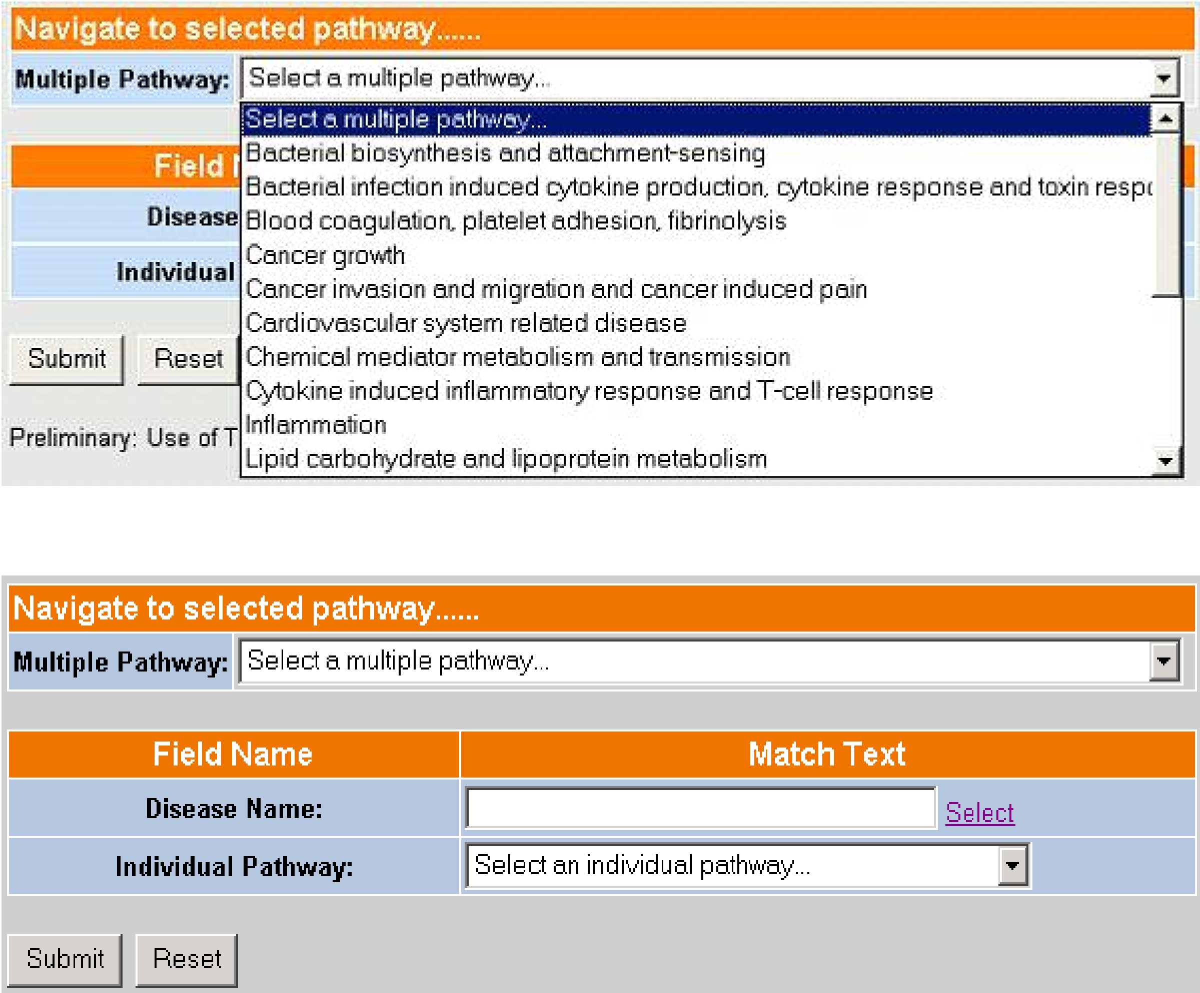
Figure Caption:

Figure 1. The web interface of TRMP. Three types of search mode are supported. This database is searchable by multiple pathway name, individual pathway name, disease name, or any combination of these.

Figure 2. The interface of a multiple pathways entry of TRMP. Each red, yellow, blue, green, and light-blue box represents a therapeutic target, non-targeted protein with detail information, non-targeted protein without detail information, effect or a process a process involving an unidentified protein and protein complex respectively. A white circular box represents the action of small molecule ligands, and a pink circular box represents the site and action of a drug. The symbols +, -, ↑, ↓, P, R, B, D and A in the circular boxes represent activation, inhibition, increased level, decreased level, phosphorylation, release, binding, dimerization and antibody respectively.

Figure 3. The interface of a target entry of TRMP.

Fig 1.



Navigate to selected pathway......
Multiple Pathway:
Select a multiple pathway...
Select a multiple pathway...
Bacterial biosynthesis and attachment-sensing
Bacterial infection induced cytokine production, cytokine response and toxin resp
Blood coagulation, platelet adhesion, fibrinolysis
Cancer growth
Cancer invasion and migration and cancer induced pain
Cardiovascular system related disease
Chemical mediator metabolism and transmission
Cytokine induced inflammatory response and T-cell response
Inflammation
Lipid carbohydrate and lipoprotein metabolism
Submit
Reset
Navigate to selected pathway......
Multiple Pathway:
Select a multiple pathway...
Field Name
Match Text
Disease Name:
Select
Individual Pathway:
Select an individual pathway...
Submit
Reset

Fig 2.

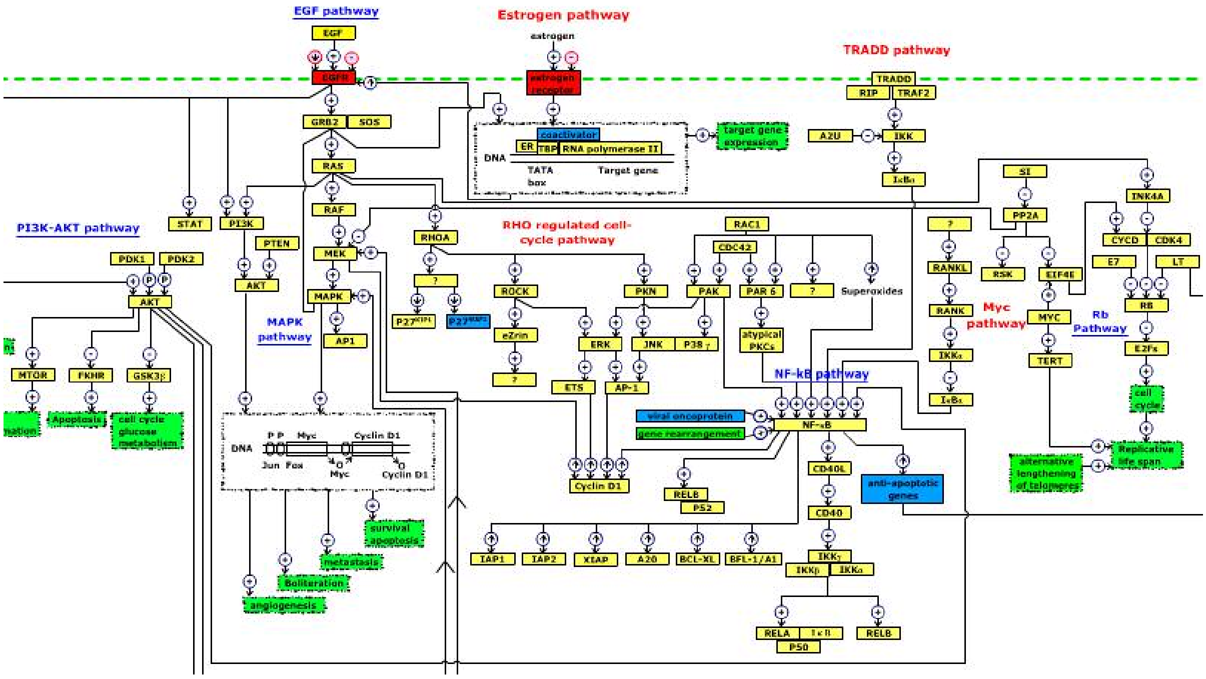

EGF pathway
Estrogen pathway
TRADD pathway
PI3K-AKT pathway
RHO regulated cell-cycle pathway
MAPK pathway
NF-kB pathway
Myc pathway
Rb Pathway

Fig 3

TRMP Detailed Information

Entry Information	
Entry	Estrogen receptor

Subclass Information	
Entry	ESR1
Potential therapeutic implications	TTT0000357
Protein name	Estrogen receptor
Synonyms	ER
	ER-alpha
	ESR1
	Estradiol receptor
AC number	SwissProt: P03372
Species	Homo sapiens (Human)
Function	Nuclear hormone receptor. The steroid hormones and their receptors are involved in the regulation of eukaryotic gene expression and affect cellular proliferation and differentiation in target tissues.
Similarity	Belongs to the nuclear hormone receptor family. NR3 subfamily.
Cross-link	GDB: 119120
	LocusLink: 2099
	NCBI: 4503603
	KEGG: hsa:2099
	OMIM: 133430
Gene name	ESR1 or NR3A1 or ESR
Gene location	6q25.1
GeneCard	GeneCard: GC06P152023

Supplementary Material

Table1 : List of therapeutically relevant multiple pathways, covered diseases, therapeutic targets and examples of drugs in TRMP. The numbers in the brackets are the total number of multiple pathways entries, therapeutic targets and covered diseases in the database.

Multiple pathways (11)	**Number of known therapeutic targets (120)**	**Related diseases (72)**	**Therapeutic targets**	**Examples of drugs**
Bacterial biosynthesis and attachment-sensing	16	Bacterial infection	FabH	FabH inhibitor: thiolactomycin
			FabA/FabZ	FabA/FabZ inhibitor: Decynoyl-NAC
			FabI	FabI inhibitor: Triclosan, Diazoborine, Isoniazid, Ethionamide
			PlsB	PlsB inhibitor: PEA
			FabB/FabH	FabB/FabH inhibitor: Cerulenin
			MurA	MurA inhibitor: foffomycin
			MurB	MurB inhibitor: thiazolidinone, imidazolone
			MurC	MurC inhibitor: phosphinate, L-ala analogs
			MurD	MurD inhibitor: phosphinate
			MurE	MurE inhibitor: phosphinate
			mraY	mraY inhibitor: tunicamycin, liposidomycin, pacidomycin, 5B-D liposidomycin analogs
			MurG	MurG inhibitor: ramoplanin
			ddlA/B	ddlA/B inhibitor: D-cycloserine
			Air	air inhibitor: F-D-ala, D-cycloserine
			Transglucosylase	transglucosylase inhibitor: vancomycin, lipophilic vacomycin, moenomycin, 5E moenomycin analogs
			Transpeptidase	transpeptidase inhibitor: penicillins, cephalosporins, carbapenem, monobactams
Bacterial infection induced cytokine production, cytokine response	5	Sepsis, septic shock, Bacterial infection	LPS	anti-lilip A IgM: HA-1A (Centoxin), E5
				LPS-neutralizing agent: recombinant 23-kDa N-terminal part of BPI, recomninant HDL
			CD14	anti-CD14 monoclonal antibody: 1116¨C1a6-murine immunoglobulin G2a

and toxin response			TNF-alpha	ant-TNF antibody: remicade (infliximab)
			TNF-alpha receptor	TNF-alpha antagonist: enbrel (etanercept)
			nterleukine-6 receptor	nterleukine-6 receptor antagonist
Blood coagulation, platelet adhesion, fibrinolysis	15	Disseminated intravascular coagulation, Von Willebrand's disease, Thrombosis and embolism, Purpura, Hemorrhage	VK reductase	vitamin K antagonist: warfarin
			Factor Xa	cofactor for antithrombin III: Heparin, LMWHs
			Factor IXa	cofactor for antithrombin III: Heparin
			Factor XIa	cofactor for antithrombin III: Heparin
			Factor XIIa	cofactor for antithrombin III: Heparin
			Thrombin	thromin inhibitor: Exanta (ximelagatran)
			Plasminogen	Plasminogen activators: streptokinase, anistreplase, alteplase, duteplase, reteplase, urokinase
				plasminogen inhibitor: tranexamic acid
			TXA	TXA2 synthase inhibitors: dazoxiben
			COX	COXs inhibitor: NSAIDs, aspirin
			TXA2 receptor	TXA2 receptor antagonists: GR321919
			GP IIb/IIIa receptor	GP IIb/IIIa receptor inhibitor: epoprostenol, ticlopidine
				GP IIb/IIIa antagonists: abcixmab and tirofiban
Cancer growth	2	Breast cancer, Colon cancer, Melanoma, Prostate cancer, Hypoxia, Multiple myeloma, Pancreatic cancer, Lung cancer	EFGR	EFGR antisense oligonusleotides: AS-21
				EGFR inhibitors: monoclonal
				antibodies: IMC- C225, ABX-EGF, EMD-72000, TheraCIM-h-R3,mAb-806
				Bispecific antibodies: MDX-447
				EGFR tyrosine kinase inhibitor: ZD1839, OSI-774, CI-1033, EKB-569, PD-0183865, PD-158780, PD-180970, PKI-166, GW-572016
			ER	estrogen receptor antagonist: tamoxifen
Cancer invasion and migration and cancer induced pain	12	Cancer pain, Metastasis	MET	MET antagonist
			PAK	hybrid DNA/RNA antisense oligonucleotide of PAK: AS-PKA-I
			SRC	SRC inhibitor: PD166285
			RAS	RAS inhitor: MKT-077
			CBL	CBL activaor

			RHO	RHO inhibitor
			RAF	RAF inhibitor: BAY-43-9006
			VR1	VR1 antagonist: Dexanabinol
			ETA receptor	ETA receptor antagonist: YM598
			TrKA	monoclonal Anti TrKA Antibody: MNAC13
			P2X3 receptor	P2X3 receptor antagonist: R-enantiomer (A-317344), A-317491
			Intergrin alpha&belta	alpha-v-betal-3 Antibody: Vitaxin
				Alphavbeta3 integrin antagonist: S247, TNP-470
Cardiovascular system related disease	13	hypertension, cardiac failure, progressive renal insufficiency, diabetic nephropathy, erectile dysfunction, Refractory angina, Nasal decongestion , Begin prostatic hypertrophy, Phaeochromocytoma, Coronary artery spasm, Bradycardia, cardiac dysrhythmias, angina, myocardial infarction, cardiogenic shock, heart failure, Cardiac arrhythmias,	ACE	ACE inhibitor: Captopril, Enalapril, Lisinopril, Trandolapril, Ramipril
			Renin	Renin inhibitor: enalkiren
			PDE V	Inhibitor of PDE V: sildenafil
			K+ channel	Activator of K+ channel: Minoxidil
				Activator of K+ channel: Nicorandil
			Angiotensin II subtype I	Angiotensin II subtype I antagonist: Losartan
			Adrenoceptor Á1	Adrenoceptor Á1 agonist: phenylephrine, methoxamine
				Adrenoceptor Á1 antagonist: Prazosin, doxazosin, terazosin
				Adrenoceptor Á1 antagonist: tamsulosin
				Adrenoceptor Á1 antagonist: phenoxybenzamine
			Calmodulin	Calcium antagonist: dehydropyridines (eg. nifedipine)
			myosin-light-chain kinase	Inhibitor of Rho-associated protein kinase: Y27632
			M2 receptor	Antagonist of muscarinic acetylcholine receptor: Atropine, Hyoscine
			β-adrenoceptor	antagonist of β1-adrenoceptor: practolol, atenolol
				agonist of β1-adrenoceptor: dobutamine
			PDE III	Inhibitor of PDE III: milrinone, cilostazol
			voltage-dependant Ca2+ channel	Blocker of voltage-dependant Ca2+ channel: verapamil
			voltage-sensitive	voltage-sensitive sodium channel blockers

			sodium channel	Ia: quinidine, procainamide, disopyramide Ib: lidocaine, phenytoin Ic: flecainide, encainide (Vaughan William's classification)
Chemical mediator metabolism and transmission	13	myasthenia gravis, hypertension, depression, psychosis, asthma, angina, cardiac dysrhythmias, anxiety tremor, glaucoma, hypertension in pregnancy, heart failure, prostatic hyperplasia, nasal decongestion, migraine, gastrointestinal disorder, vomiting; nausea, migraine prophylaxis, Hypotension, Mood disorders, Alzheimer's disease, Parkinson's disease, Schizophrenia, Neuromuscular disorders	Presynaptic nicotinic ACh receptor	Presynaptic nicotinic ACh receptor antagonists: tubocurarine
				nicotinic receptor agonist: suxamethonium
			ACh carrier	ACh carrier inhibitor: vesamicol
			Choline carrier	choline transport inhibitor: hemicholinium, triethylcholine
			Anticholinesterase	Anticholinesterase: neostigmine
			adrenoceptor α2	adrenoceptor α2 agonists: Yohimibine
				adrenoceptor α2 antagonist: clonidine
			MAO	MAO inhibitors: phenelzine, tranylcypromine, isocarboxazid, moclobemide
			Vesicular transporter	Vesicular transporter inhibitor: Reserpine
				Vesicular transporter inhibitor: Tetrabenazine
			NA uptake 1	NA uptake 1 inhibitors: Imipramine
				NA uptake 1 inhibitors: cocaine
			NA uptake 2	NA uptake 2 inhibitors: Phenoxybenzamine
			adrenoceptor β	adrenoceptor β agonist: salmeterol, terbutaline, clenbuterol, isoprenaline
				adrenoceptor β antagonists: propranolol, alprenolol, practolol, metoprolol
			adrenocepotr	non-selective adrenocepotr antagonist: labetalol
				non-selective adrenocepotr antagonist: carvedilol
			adrenoceptor α	adrenoceptor α antagonists: prazosin
				adrenoceptor α antagonists: tamsulosin
				adrenoceptor α agonist: henylephrine, methoxamine
			Serotonin reuptake	Serotonin reuptake inhibitors: fluoxetine, fluvoxamine, paroxetine, citalopram, sertraline
			5-HT receptor	5-HT receptor agonists: sumatriptan
				5-HT receptor agonists: metoclopramide, tegaserod
				5-HT receptor antagonists: ondansetron, granisetron, tropisetron

				5-HT receptor antagonists: dihydoergotamine, methysergide
Cytokine induced inflammatory response and T-cell response	3	rheumatoid arthritis, fever, Inflammation	TNF alpha	anti-TNF alpha antibody: adalimumab, Etanercept
			TNF	anti-TNF agents: adalimumab, Etanercept
			cytochrome P450	cytochrome P450 inducer: Midazolam
Inflammation	15	postmenopausal breast cancer, Cushing's syndrome, HIV, inflammation, asthma, acute attack, heart failure	3-β dehydrogenase	Glucocoticoid synthesis inhibitor: Trilostane
			11-β hydroxylase	beta-hydroxylation inhibitor: metyrapone
			NF-kB	NF-kB inhibitor: geldanamycin
				NF-kB inhibitor: paclitaxel
			PAF receptor	PAF antagonists: lexipafant, apafant
			Phospholipase A2	Inducer of Phospholipase A2's inhibitor lipocortin: Glucocorticoids
			Bradykinin receptor	Bradykinin receptor inhibitors: icatibant
				TXA2 synthase inhibitors: ozagrel, isbogrel
			5-lipoxygenase	5-lipoxygenase inhibitors: Zileuton
			Leukotriene receptor	Leukotriene antagonist: Zafirlukast
				Leukotriene antagonist: montelukast
			PDE	Selective PDE type III inhibitor: milrinone, cilostazol
			Histamine receptor	H1-receptor antagonist: diphenhydramine, promethazine, chlorpheniramine, mequitazine
			COX	inhibitor of COX: NSAIDs
				inhibitor for COX inducting: Glucocorticoids
Viral infection induced effect on cytokine, RNA, viral protein and genome synthesis	8	septic shock, cancer, sepsis, endotoxin shock, viral infection	CD14	Anti-CD14 monoclonal antibody
			TLR9	Toll-like receptor 9 antagonist (CpG DNAs): CpG ODN 7909
			TLR 4	Toll-like receptor 4 antagonist: E5531, E5564
			Protease	Protease inhibitors: saquinavir, nelfinavir, indinavir, ritonavir, amprenavir
			RT	reverse transcriptase inhibitors nucleoside: zidovudine, didanosine, zalcitabine, lamivudine, stavudine, abacavir non-nucleoside: nevirapine, efavirenz
			DNA polymerase	DNA polymerase inhibitors: aciclovir, gancicolvir, tribavirin, foscarnet

			IFN GR1	Interferon
			IFN AR1	Interferon
Lipid carbohydrate and lipoprotein metabolism	18	insulin resistance, obesity, type 2 diabetes, Hyperlipidemia, Diabetes mellitus, Ketoacidosis, Lactic acidosis, Hypercholesterolemia, Diabetes mellitus	Pancreatic lipase	Orlistat
			ACAT2	ACAT inhibitors
			VLDL	inhibitor for VLDL production: fibrates
			LPL	Lipoprotein lipase activators: NO-1886
			ACAT	ACAT inhibitors: Avasimibe, 258441 (Sanwa), FR-182980 (Fujisawa)
			PPAR gamma	PPAR gamma agonists: thiasolidinediones (troglitazone, rosiglitazone, pioglitazone)
			Leptin receptor	OB receptor agonists
			insulin	Blocker of K-ATP channel on B cells: sulfomylureas(tolbutanide, glibenclamide, gilpizide), repaglinide, neteglinide
			Insulin receptor	activator for insulin-stimulated insulin receptor autophosphorylation: TLK19780
			PKA	PKA stimulators
			NPY receptor	NPY receptor antagonists: NYY1 specific: BIBP 3226, BIBO 3304, LY-357897, CP-671906, J-104870, J-115814 NYY5 specific: CGP 71683A, L-152,804
			MC4 receptor	MC4 receptor agonists: MTII, JRH 420-12
			CRH receptor/	CRH receptor/CRH binding proteins antagonists
			PPAR gamma	PPAR gamma agonists: thiasolidinediones (troglitazone, rosiglitazone, pioglitazone)
			LPL	Lipoprotein lipase activators: NO-1886
			ACAT	ACAT inhibitors: Avasimibe, 258441 (Sanwa), FR-182980 (Fujisawa)
			VLDL	inhibitor for VLDL production: fibrates
			HMG-CoA reductase	HMG-CoA reductase inhibitors: Fluvastatin, Lovastatin, Pravastatin, Simvastatin

Supplementary Material

Table 2 List of distinct individual pathways covered in the entries of TRMP database

Name of Individual Pathway		
Acetylcholine pathway	Hypersensitive pathway	Pathway of growth factor induced microfilament bundling
Acetylcholine synthesis pathway	IFN pathway	Pathway of pseudomonas exotoxin induced cell death
Adrenaline pathway	IGF pathway	Pathway of toxins induced block of actin polymerization
Apoptosis pathway	Insulin pathway	Peptidoglycan synthetic pathway
ATII pathway	Integrin-dependent intracellular signaling pathway	PI3K-AKT pathway
Beta-oxidation pathway	Interleukin-1 pathway	Platelet activation pathway
Bile acid recovery pathway	Interleukin-18 pathway	PLC-IP3 pathway
Bradykinin pathway	Interleukin-6 pathway	Plexin-B-mediated pathway
Bradykinin synthesis pathway	IRF-3 activation pathway	Protein absorption pathway
cAMP/PKA/CREB pathway	Leptin pathway	Protein digestion pathway
cAMP-PKA pathway	Leukotriene synthesis pathway	Protein synthesis pathway
Carbohydrate absorption pathway	Lipid absorption pathway	RAC pathway
Carbohydrate digestion pathway	Lipid digestion pathway	RAS pathway
CD14 pathway	Lipid fatty acid synthesis pathway	RAS-signaling pathway
Chemokine signaling pathway	Lipid synthesis pathway	Rb Pathway
Cholesterol synthesis pathway	LPL pathway	RHO regulated cell-cycle pathway
CNP/NPR-B/cGMP pathway	MAO pathway	Rho-Rho-kinase pathway
COX pathway	MAPK pathway	RNA replication pathway
Cpx system pathway	Melanocortin pathway	RNA synthesis pathway
CRH pathway	MET down regulation pathway	Serotonin pathway
Death receptor pathway	MET-dependent invasive growth signaling pathway	Serotonin synthesis pathway
DNA synthesis pathway	Myc pathway	STAT pathway
EGF pathway	MyD88-dependent pathway	TCA pathway
Endothelin pathway	MyD88-independent pathway	TGF pathway
Estrogen pathway	NF-kB activation pathway	TLR signaling pathway
Fatty acid synthesis pathway	NF-kB pathway	TNF signaling pathway
Fibrin formation pathway	Nociceptor signaling pathway	TRADD pathway
Glucocorticoid pathway	Noradrenaline Pathway	TRAIL induced apoptosis pathway
Glucocorticoid synthesis pathway	Noradrenaline synthesis pathway	Wnt signalling pathway
Glucose transport pathway	NOS pathway	
Glycogen synthesis	NPY pathway	
Glycolysis pathway	p53 Pathway	
GnRH pathway	Pathway of arachidonate release	
Hexose monophosphate pathway		
Histamine pathway		