Trends in the exploitation of novel drug targets

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Abstract | The discovery and exploitation of new drug targets is a key focus for both the pharmaceutical industry and academic biomedical research. To provide an insight into trends in the exploitation of new drug targets, we have analysed the drugs that were approved by the US Food and Drug Administration during the past three decades and examined the interactions of these drugs with therapeutic targets that are encoded by the human genome, using the DrugBank database and extensive manual curation. We have identified 435 effect-mediating drug targets in the human genome, which are modulated by 989 unique drugs, through 2,242 drug–target interactions. We also analyse trends in the introduction of drugs that modulate previously unexploited targets, and discuss the network pharmacology of the drugs in our data set.

Understanding the identity of drug targets that are encoded by the human genome is of great importance for the development of new pharmaceutical products and the allocation of resources within academic and industrial biomedical research. Currently marketed drugs mediate their effects through only a small number of the potential human target proteins. Previously published estimates of the number of current human drug targets range from ~200–400, depending on the method used and how the drug targets were defined and categorized.

In 1996, Drews and Ryser were the first to present an overall estimate of the number of target proteins in humans and pathogens when they put forward an estimate of 483 drug targets, based on an analysis of drugs listed in the ninth edition of The Pharmacological Basis of Therapeutics[1]. They also estimated that the number of potential drug targets in the human genome was ~5,000–10,000, which was influenced by the view at the time that the human genome contained ~300,000 genes[1,2].

After the sequencing of the human genome, Hopkins and Groom[3] estimated that there were 120 drug targets for marketed small-molecule drugs, by analysing the Investigational Drugs database and Pharmaprojects databases. In total, they identified 399 targets for which ligands with drug-like properties (regardless of whether or not they were approved drugs) were known. By expanding from members of the 130 protein families that were found to be drug targets, they also estimated that ~10% of all genes in the genome were pharmacologically tractable. In 2002, the human genome was estimated to contain ~30,000 genes and, of these, ~3,000 genes were suggested to be linked to disease based on the extrapolation of data from the number of antifungal targets in the yeast genome. The overlap between the two sets of genes — estimated to be ~600–1,500 genes in total[3] — was suggested to represent the number of pharmacologically exploitable targets.

In 2006, Imming *et al.*[4] listed 218 drug targets for approved drugs, using — by their own terms — "somewhat arbitrary" definitions for drug targets and drug categories, which led to a lower estimate in comparison. Also in 2006, Overington *et al.*[5] estimated that the human genome contained 266 proteins that could be targeted by pharmacological agents. They were able to assign a total of 324 molecular targets to 1,065 pharmacological agents through a systematic review of the US Food and Drug Administration (FDA) Orange Book and the Center for Biologics Evaluation and Research (CBER) website. This analysis led to the identification of 21,000 active agents, but only 1,357 unique drugs when redundant formulations and non-therapeutic agents were removed[5].

The publicly available DrugBank database, which drew heavily from these earlier data sets, was launched in 2006. The DrugBank database not only has a systematic collection of drug–protein interactions but also contains associations of proteins with consensus genetic annotations, such as Swissprot. The DrugBank database has been expanded by ~60% since its release to include further FDA-approved and experimental drugs, as well as data for almost 1,000 additional drug–target

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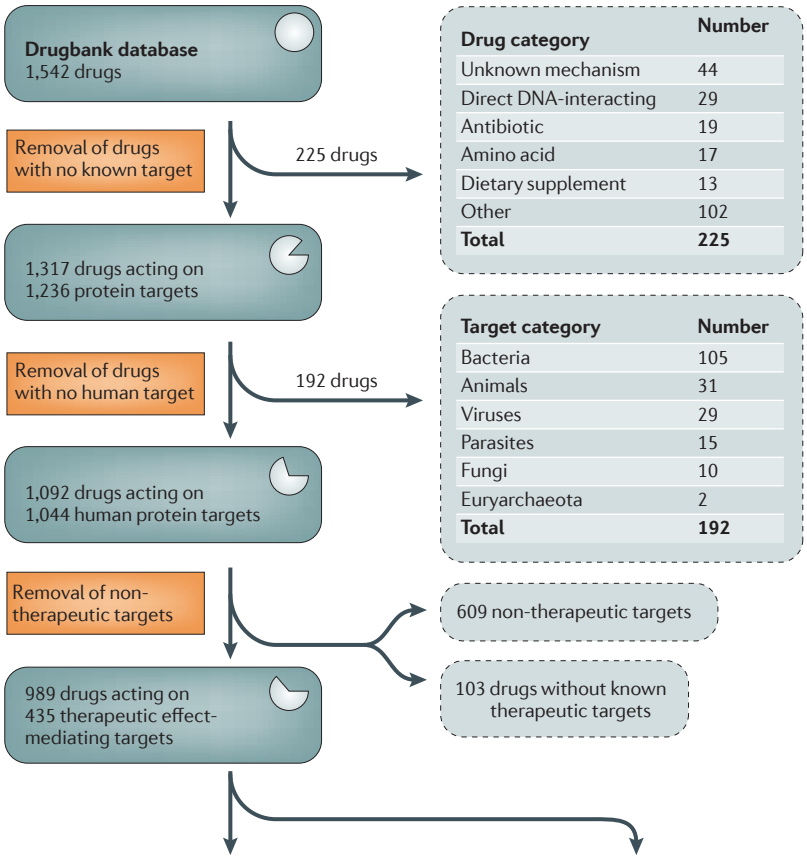
interactions[6–8]. The database currently contains information on ~1,500 experimental, approved and withdrawn drugs, with up to 107 data fields for each drug that contain information including current indications, documented drug–target interactions, target protein accession numbers and pharmacological actions.

In this article, we have analysed the complete data set of pharmacological agents as of May 2009 from the DrugBank database (see FIG. 1 for an overview of the analysis process). Annotations in the DrugBank database that were related to the functional relevance of drug–target interactions were removed because the majority of these interactions were either irrelevant from a disease-treatment perspective or part of the side-effect profile of the pharmacological agent. We therefore performed a manual curation of the database to achieve a reproducible data set of human genes encoding the target proteins that are responsible for the desired pharmacological effects. We also manually curated entries for indications and classified proteins according to molecular function using their Swissprot accession numbers. We retrieved drug approval dates from the FDA and linked these to the drugs in our curated data set to identify trends in drug development. We manually added FDA-approved drugs and drug targets from 2007–2010 into our data set, to account for lag times between the introduction of a new drug and its incorporation into the DrugBank database. In contrast with previous publications in this field, we also provide a specific list of the drugs (see Supplementary information S1 (table)) to aid further analyses.



Drug category	Number
Unknown mechanism	44
Direct DNA-interacting	29
Antibiotic	19
Amino acid	17
Dietary supplement	13
Other	102
Total	**225**

Target category	Number
Bacteria	105
Animals	31
Viruses	29
Parasites	15
Fungi	10
Euryarchaeota	2
Total	**192**

Top 10 drug indications	Number
Antihypertensive agents	108
Antineoplastic agents	91
Anti-inflammatory agents	66
Hypnotics and sedatives	42
Anti-allergic agents	39
Anticonvulsants	37
Anti-arrythmia agents	37
Antipsychotic agents	37
Antidepressants	32
Analgesics	30

Target class	Number
Receptors	193
Enzymes	124
Transporters	67
Other	51

Figure 1 | **Data curation process.** Data were collected from the DrugBank database as of May 2009 and curated manually to identify drugs without known targets and drugs that target gene products of pathogens, such as antiparasitics, antivirals and antibiotics. Specific human gene products that encode therapeutic drug targets were also identified manually among the drug–target interactions. Primary and secondary indications of the drugs were identified by manually curating interaction entries. Drugs and drug targets that were approved by the US Food and Drug Administration between 2007 and 2010, and were not included in the Drugbank database, were added manually.

Drugs and classes of drug targets

The initial curation of the data set involved the identification of drugs without known protein targets, such as drugs that act directly on DNA, dietary supplements and drugs that do not have known protein targets. This resulted in a list of 1,317 drugs that act on 1,236 protein targets. We also identified drugs that were administered as prodrugs and were therefore already present in the data set in their active form, and we identified drugs that act on non-human target genes, such as antibiotics, antiparasitics and antifungals.

This specification resulted in a list of 1,092 pharmacological agents that act on 1,044 human protein targets. We then identified the genes encoding non-therapeutic protein targets (for example, albumin or cytochrome P450 enzymes), as well as agents without therapeutic targets. We used a row-by-row approach in favour of automated methods in which each drug, drug target and interaction was evaluated and validated using current medical literature and publicly available databases. The main effect-mediating targets were identified manually for each drug and therapeutically irrelevant targets or side effect-mediating targets were identified in the data set. This was performed in an effort to create a data set with strictly defined active targets, which could be useful for further bioinformatics analysis of the therapeutic portion of the druggable genome as well as for novel target prediction.

Through this strict manual curation of the DrugBank database (FIG. 1), we identified 435 effect-mediating drug targets in the human genome. These structures are the targets of 989 unique drugs, through 2,242 drug–target interactions (see Supplementary information S1 (table)).

The DrugBank database lists indications for each drug, and these were also validated in the curation process. The most common indication for the drugs in our data set is antihypertensive drugs, followed by antineoplastic and anti-inflammatory agents. Each target-encoding gene was assigned a class according to the molecular function of the gene product using the Swissprot accession numbers. Our curated data set

shows that receptors make up the largest group of drug targets: 193 proteins (44% of the human drug targets) are receptors, and 82 (19%) of these are G protein-coupled receptors (GPCRs). In the overall data set, ~36% of drugs target GPCRs (FIG. 2). GPCRs have been commonly targeted by antihypertensive and anti-allergic drugs. Ligand-gated ion channels, which are the second largest receptor target class, are most commonly targeted by hypnotic drugs and sedatives. The third largest receptor target class, receptor tyrosine kinases — such as the epidermal growth factor receptor — have been targeted frequently by anticancer drugs (intracellular non-receptor kinases, such as ABL, the active site of which is the target of imatinib, are classified as enzymes).

Enzymes are the second largest group of target proteins in the human genome, with 124 target-encoding genes, comprising 29% of all human drug targets (FIG. 2). Hydrolases (EC 3) are the most common class of enzymatic drug targets, comprising 42% of all human enzyme drug targets. They are followed by oxidoreductases (EC 1) and transferases (EC 2), which comprise 27% and 19% of all human enzyme drug targets, respectively. In addition, the majority (78%) of enzyme targets are soluble proteins, not membrane-associated proteins. Anti-inflammatory treatments most frequently act on enzyme targets; for example, the most studied anti-inflammatory target pathway — the eicosanoid metabolic pathway — is modulated via the enzyme targets cyclooxygenase 1 and cyclooxygenase 2, which belong to the oxidoreductase family and are targeted by acetylsalicylic acid. Other common enzyme targets for drugs include DNA polymerases, angiotensin-converting enzyme and the monoamine oxidases.

Target class	Number of proteins	Most common therapeutic actions	Number of drugs
Receptors	**193**	**Antihypertensive, anti-allergic**	**563**
G protein-coupled receptors	82	Antihypertensive, anti-allergic	357
Ligand-gated ion channels	39	Hypnotic and sedative, anticonvulsant	84
Receptor tyrosine kinases	22	Antineoplastic, vasodilator	22
Immunoglobulin-like receptors	21	Immunomodulatory, antineoplastic	28
Other receptors	12	Immunomodulatory, platelet aggregation	11
Nuclear receptors	17	Antineoplastic, hormone replacement	76
Enzymes	**97(27)***	**Anti-inflammatory, antineoplastic**	**234**
EC 1 Oxidoreductases	22(11)	Anti-inflammatory, antineoplastic	85
EC 2 Transferases	21(2)	Antineoplastic, bisphosphonate	33
EC 3 Hydrolases	43(9)	Antihypertensive, vasodilator	96
EC 4 Lyases	3(2)	Antihypertensive, diuretic	11
EC 5 Isomerases	5(0)	Antineoplastic, immunosuppressive	14
EC 6 Ligases	1(1)	Antineoplastic, antifibrinolytic	4
Multiple EC groups	2(2)	Antineoplastic, antiadrenal	3
Transporter proteins	**67**	**Antihypertensive, anti-arrhythmia**	**181**
Voltage-gated ion channels	29	Anaesthetic, anti-arrhythmia	83
Other ion channels	6	Antihypertensive, diuretic	4
Solute carriers	12	Antihypertensive, diuretic	63
Active transporters	7	Antihypertensive, anti-ulcer	19
Other transporters	3	Hypnotic and sedative, anti-anxiety	13
Auxillary transport units	10	Antihypertensive, vasodilator	21
Other	**51**	**Anti-inflammatory, antineoplastic**	**84**
Enzyme-interacting proteins	13	Anti-inflammatory, glucocorticoid	36
Structural and adhesion proteins	11	Antineoplastic	16
Ligands	12	Antirheumatic	15
Other	15	Anti-inflammatory, antineoplastic	24

Figure 2 | **Classification of the currently utilized drug targets that are encoded by the human genome.** The class of drug target was determined by using the Swissprot accession number of the corresponding therapeutic target of each drug. The most common indications for each class are listed, as well as the corresponding number of drugs that target each protein class. *Enzymes are further classified as soluble or membrane-associated; the number in the brackets corresponds to the number of membrane-associated enzymes in each class.

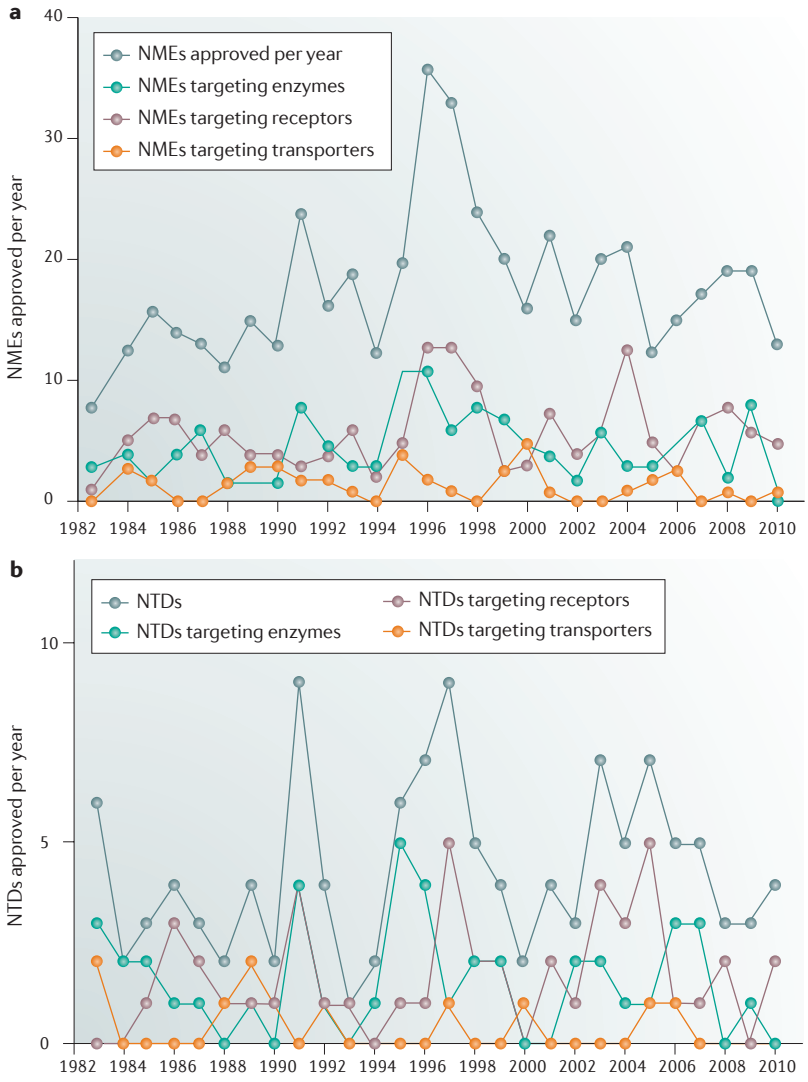


Figure 3 | **Number of new drugs affecting targets that are encoded by the human genome, and drugs affecting previously unexploited targets, that were approved by the FDA from 1983–2010.** Approval dates were retrieved from the catalogue of US Food and Drug Administration (FDA) Approved Drug Products (see the Drugs@FDA website). Drugs were divided into subcategories according to a general classification of their target structure (**a**) and whether the drug acts on a previously exploited or unexploited (novel) target structure in the human genome. The number of drugs with novel targets (NTDs) overall and in the target subcategories is shown in panel **b**. Three innovation peaks are apparent in this panel: 1990–1993, 1994–2000 and 2001–2008. These innovation peaks are discussed in detail in the section '30 years of drug target innovation'. NMEs, new molecular entities.

Transporter proteins are the third most common class of targets, with 67 target-encoding genes that comprise 15% of all human drug targets (FIG. 2). These proteins facilitate the movement of specific substrates such as ions, nutrients and metabolites across lipid membranes. This category encompasses voltage-gated ion channels, active transporters and solute carriers among other transporter proteins, and is commonly targeted by antihypertensive drugs, diuretics, anaesthetics and anti-arrhythmic drugs. Voltage-gated ion channels, which are often targeted by anaesthetics and anti-arrhythmic drugs, are the most common type of transporter drug target (FIG. 2).

30 years of drug target innovation

To determine trends in drug development, we accessed drug approval dates from the FDA, via the Drugs@FDA website and the FDA Orange Book. We were able to determine the FDA approval date for 747 drugs. Drugs that were approved before 1982 were omitted from further analysis owing to a cut-off point in the Orange Book for drugs that were approved before this date, leaving 520 drugs that were approved from 1982 until the end of 2010 (FIG. 3a).

On average, we found that ~18 (17.9) new drugs targeting human proteins have been approved for marketing by the FDA every year, of which ~4 (4.3) act on novel target structures that are encoded by the human genome, which corresponds well to previously reported figures by Yildirim and colleagues[9]. However, our estimates are slightly lower, which is most likely to be due to our focus on human genome targets (for example, novel virus-encoded targets for diseases such as HIV were excluded from our analysis). It is apparent from these data that the majority of new drugs that have been approved since 1982 act on previously exploited human protein targets.

There was no apparent decrease in the rate of approval of new drugs targeting structures encoded by the human genome between 1982 and 2010, according to our data set (linear regression was performed in Prism v5.02 for Windows, GraphPad Software, Inc. San Diego). Interestingly, we also did not observe an overall decrease in the approval rate of novel target drugs (NTDs) — that is, drugs that act on previously unexploited targets encoded by the human genome (TABLE 1). The rate of innovation in terms of the exploitation of drug targets thus appears to be stable over the past 30 years, although it should be noted that the research and development investment made to achieve this has increased dramatically during this period.

The innovation rate for NTDs has a 'pulsing' appearance, with three distinct 'innovation peaks' (FIG. 3b). There are some interesting similarities and differences between the approvals comprising these peaks. For example, the first observed peak between 1990 and 1993 is shorter than the others, but NTD approvals for the most common types of targets — GPCRs, hydrolases, transferases and isomerases — occurred at a proportionally similar rate to other peaks. NTDs that were introduced during this period include ondansetron, an anti-emetic selective 5-hydroxytryptamine receptor 3 antagonist (approved in 1991), and the asthma therapy nedocromil (approved in 1992), which targets the cysteine leukotriene receptor 1. Although the majority of NTDs modulate targets in previously exploited areas of the proteome, there is also a trend towards an increase in the number of protein types that are targeted by NTDs in the later two innovation peaks. For example, during the period of the second innovation peak (1994–2000), the first drug that targeted integrins — the cardiovascular drug abciximab (approved in 1997) — was introduced. During the period of the third innovation peak (2001–2008), the first kinase inhibitor for treating cancer (imatinib; approved in 2001) and the first drug targeting Fc receptors (the asthma drug omalizumab; approved in

Table 1 | **Introduction of drugs with new human genome-encoded targets**

Drug	Target gene*	Therapeutic class	Year of approval	Drug classification
New drugs introduced: 1983–1989				
Bumetanide	*SLC12A2*	Diuretics	1983	Small molecule
Divalproex sodium	*ABAT*	Anticonvulsant agents, antimanic agents	1983	Small molecule
Indapamide	*KCNE1*	Antihypertensive agents, diuretics	1983	Small molecule
Etoposide	*TOP2A*	Antineoplastic agents	1983	Small molecule
Cyclosporine	*PPP3R2*	Immunosuppressive agents	1983	Small molecule; fungal extract
Bentiromide	*PNLIP*	Diagnostic agents	1983	Small molecule
Amrinone	*PDE4B*	Cardiotonic agents, phosphodiesterase inhibitors	1984	Small molecule
Trilostane	*HSD3B1*	Antiadrenal agents	1984	Small molecule (now withdrawn)
Auranofin	*IKBKB*	Antirheumatic agents	1985	Small molecule
Marinol	*CNR1*	Anti-emetic agents	1985	Small molecule
Cilastatin	*DPEP1*	Adjuvants, enzyme inhibitors	1985	Small molecule
Muromonab	*CD3E*	Immunosuppressive agents	1986	Biotechnological; monoclonal antibody
Interferon alfa-2a (recombinant)	*IFNAR1*	Antineoplastic agents, immunomodulatory agents	1986	Biotechnological; recombinant protein
Urofollitropin	*FSHR*	Fertility agents	1986	Biotechnological; recombinant protein
Tranexamic acid	*PLAT*	Antifibrinolytic agents	1986	Small molecule
Terazosin	*ADRA1D*	Antineoplastic agents, antihypertensive agents	1987	Small molecule
Lovastatin	*HMGCR*	Anticholesteraemic agents	1987	Small molecule
Teriparatide‡	*PTHR1*	Diagnostic agents	1987	Biotechnological; synthetic peptide
Octreotide	*SSTR1*	Hormonal antineoplastic agents, hormone replacement agents	1988	Biotechnological; hormone; synthetic peptide
Nicardipine	*CACNA1C*	Anti-arrhythmia agents, antihypertensive agents	1988	Small molecule
Selegiline	*MAOB*	Antiparkinson agents	1989	Small molecule
Epoetin alfa	*EPOR*	Anti-anaemic agents	1989	Biotechnological; recombinant protein
Omeprazole	*ATP4A*	Gastrointestinal anti-ulcer agents	1989	Small molecule
Propafenone	*KCNH2*	Anti-arrhythmia agents	1989	Small molecule
New drugs introduced: 1990–1999				
Bepridil	*CACNA1A*	Anti-arrhythmia agents, antihypertensive agents	1990	Small molecule
Sermorelin	*GHRHR*	Hormone replacement agents	1990	Biotechnological; hormone; synthetic peptide
Ondansetron	*HTR3A*	Anti-emetic agents	1991	Small molecule
Filgrastim	*CSF3R*	Antineutropaenic agents	1991	Biotechnological; recombinant protein
Sargramostim	*CSF2RA*	Immunomodulatory agents	1991	Biotechnological; recombinant protein
Fludarabine	*POLA1*	Antineoplastic agents	1991	Small molecule
Pentostatin	*ADA*	Antineoplastic agents	1991	Small molecule
Pamidronate	*FDPS*	Bisphosphonates	1991	Small molecule
Ticlopidine	*P2RY12*	Platelet aggregation inhibitors	1991	Small molecule
Botulinum toxin type A	*SNAP25*	Neuromuscular blocking agents	1991	Biotechnological; bacterial extract
Finasteride	*SRD5A1*	Anti-baldness agents, antihyperplasia agents	1992	Small molecule
Amlodipine	*CACNA1B*	Antihypertensive agents	1992	Small molecule
Paclitaxel	*TUBB1*	Antineoplastic agents	1992	Small molecule

Table 1 cont. | **Introduction of drugs with new human genome-encoded targets**

Drug	Target gene*	Therapeutic class	Year of approval	Drug classification
Nedocromil	*CYSLTR1*	Anti-allergic agents, anti-asthmatic agents	1992	Small molecule
Cisapride	*HTR4*	Parasympathomimetic agents	1993	Small molecule (now withdrawn)
Abciximab	*ITGB3*	Anticoagulants, antiplatelet agents	1993	Biotechnological; monoclonal antibody
Tacrolimus	*FKBP1A*	Immunosuppressive agents	1994	Small molecule
Candoxatril	*MME*	Antihypertensive agents	1995	Small molecule
Metformin	*PRKAB1*	Hypoglycaemic agents	1995	Small molecule
Losartan	*AGTR1*	Antihypertensive agents	1995	Small molecule
Mycophenolate mofetil	*IMPDH2*	Immunosuppressive agents	1995	Small molecule
Acarbose	*AMY2A*	Hypoglycaemic agents	1995	Small molecule
Amifostine	*ALPPL2*	Radiation-protective agents	1995	Small molecule
Topotecan	*TOP1*	Antineoplastic agents	1996	Small molecule
Latanoprost	*PTGFR*	Glaucoma treatment, intraocular hypertension treatment	1996	Small molecule
Arcitumomab	*CEACAM1*	Diagnostic agents, imaging agents	1996	Biotechnological; monoclonal antibody
Pentosan polysulfate	*FGF1*	Anticoagulants	1996	Small molecule
Capromab	*PSMA*	Diagnostic agents	1996	Biotechnological; monoclonal antibody
Reteplase	*PLG*	Thrombolytic agents	1996	Biotechnological; recombinant protein
Topiramate	*CA2*	Anticonvulsants, antimigraine agents	1996	Small molecule
Troglitazone	*PPARG*	Hypoglycaemic agents	1997	Small molecule
Imiquimod	*TLR7*	Immunomodulatory agents	1997	Small molecule
Ardeparin	*SERPIND1*	Anticoagulant agents	1997	Small molecule
Tiagabine	*SLC6A1*	Anticonvulsant agents	1997	Small molecule
Oprelvekin	*IL11RA*	Thrombotic agents	1997	Biotechnological; recombinant protein
Rituximab	*MS4A1*	Antineoplastic agents	1997	Biotechnological; monoclonal antibody
Fomepizole	*ADH1B*	Antidotes	1997	Small molecule
Becaplermin	*PDGFRB*	Topical anti-ulcer agents	1997	Biotechnological; recombinant protein
Daclizumab	*IL2RA*	Immunosuppressive agents	1997	Biotechnological; monoclonal antibody
Tolcapone	*COMT*	Antiparkinson agents	1998	Small molecule (now withdrawn)
Infliximab	*TNF*	Immunosuppressive agents	1998	Biotechnological; monoclonal antibody
Leflunomide	*DHODH*	Antirheumatic agents	1998	Small molecule
Trastuzumab	*HER2*	Antineoplastic agents	1998	Biotechnological; monoclonal antibody
Thyrotropin alfa	*TSHR*	Diagnostic agents	1998	Biotechnological; recombinant protein
Interferon gamma-1b	*IFNGR1*	Immunomodulatory agents	1999	Biotechnological; recombinant protein
Sirolimus	*FRAP1*	Immunosuppressive agents	1999	Small molecule
Epirubicin	*CHD1*	Antineoplastic agents	1999	Small molecule
Orlistat	*LIPF, PNLIP*	Anti-obesity agents	1999	Small molecule
New drugs introduced: 2000–2010				
Gemtuzumab ozogamicin	*CD33*	Antineoplastic agents	2000	Biotechnological; monoclonal antibody conjugate (now withdrawn)
Botulinum toxin type B	*VAMP1*	Neuromuscular blocking agents	2000	Biotechnological; bacterial extract
Alemtuzumab	*CD52*	Antineoplastic agents	2001	Biotechnological; monoclonal antibody
Imatinib[§]	*BCR–ABL* fusion	Antineoplastic agents	2001	Small molecule
Anakinra	*IL1R1*	Antirheumatic agents	2001	Biotechnological; recombinant protein
Bosentan	*EDNRB*	Antihypertensive agents	2001	Small molecule

Table 1 cont. | **Introduction of drugs with new human genome-encoded targets**

Drug	Target gene*	Therapeutic class	Year of approval	Drug classification
Drotrecogin alfa	*F8*	Antithrombotic agents	2001	Biotechnological; recombinant protein
Nitisinone	*HPD*	Anti-tyrosinaemia agents	2002	Small molecule
Ezetimibe	*NPC1L1*	Anticholesteraemic agents	2002	Small molecule
Alpha-1 proteinase inhibitor	*ELA2*	Enzyme replacement agents	2002	Biotechnological; serum protein
Alefacept	*CD2*	Immunosuppressive agents	2003	Biotechnological; fusion protein
Aprepitant	*TACR1*	Anti-emetic agents	2003	Small molecule
Bortezomib	*PSMB1*	Antineoplastic agents	2003	Small molecule
Efalizumab	*ITGAL*	Immunomodulatory agents; immunosuppressive agents	2003	Biotechnological; monoclonal antibody (now withdrawn)
Gefitinib	*EGFR*	Antineoplastic agents	2003	Small molecule
Omalizumab	*IgE*	Anti-asthmatic agents	2003	Biotechnological; monoclonal antibody
Miglustat	*UGCG*	Glycosphingolipid synthesis inhibitors	2003	Small molecule
Pemetrexed	*GART*	Antineoplastic agents	2004	Small molecule
Bevacizumab	*VEGF*	Antineoplastic agents	2004	Biotechnological; monoclonal antibody
Cinacalcet	*CASR*	Calcimimetic agents	2004	Small molecule
Natalizumab	*ITGA4*	Immunomodulatory agents	2004	Biotechnological; monoclonal antibody
Palifermin	*FGFR2*	Antimucositis agents	2004	Biotechnological; recombinant protein
Dantrolene	*RYR1*	Muscle relaxants	2005	Small molecule
Pramlintide	*RAMP1*	Hypoglycaemic agents	2005	Biotechnological; hormone; synthetic peptide
Exenatide	*GLP1R*	Antidiabetic agents	2005	Biotechnological; hormone; synthetic peptide
Mecasermin	*IGF1R*	Hormone replacement agents	2005	Biotechnological; recombinant protein
Abatacept	*CD80*	Antirheumatic agents	2005	Biotechnological; fusion protein
Sorafenib[§]	*RAF1*	Antineoplastic agents	2005	Small molecule
Sunitinib[§]	*FLT1*	Antineoplastic agents	2006	Small molecule
Lubiprostone	*CLCN2*	Anticonstipation agents	2006	Small molecule
Dasatinib[§]	*SRC*	Antineoplastic agents	2006	Small molecule
Vorinostat	*HDAC1*	Antineoplastic agents	2006	Small molecule
Sitagliptin	*DPP4*	Hypoglycaemic agents	2006	Small molecule
Aliskiren	*REN*	Antihypertensive agents	2007	Small molecule
Eculizumab	*C5*	Immunomodulatory agents	2007	Biotechnological; monoclonal antibody
Maraviroc	*CCR5*	Anti-HIV agents; antiviral agents	2007	Small molecule
Rilonacept	*IL1A*	Anti-inflammatory agents	2008	Biotechnological; fusion protein
Romiplostim	*MPL*	Haematopoiesis-stimulating agents	2008	Biotechnological; fusion protein
Plerixafor	*CXCR4*	Haematopoiesis-mobilizing agents	2008	Small molecule
Canakinumab	*IL1B*	Anti-inflammatory agents	2009	Biotechnological; monoclonal antibody
Ustekinumab	*IL12B*	Antipsoriatic agents	2009	Biotechnological; monoclonal antibody
Ecallantide	*KLK1*	Treatment for hereditary angioedema	2009	Biotechnological peptide
Tocilizumab	*IL6R*	Immunosuppressive agents	2010	Biotechnological; monoclonal antibody
Carglumic acid	*CPS1*	Treatment of hyperammonaemia	2010	Small molecule
Denosumab	*RANKL*	Osteoporosis prophylaxis	2010	Biotechnological; monoclonal antibody
Fingolimod	*S1PR1*	Immunosuppressive agents	2010	Small molecule

*See Supplementary information S2 (box) for a list of all gene names. [‡]A recombinant form of teriparatide was approved as an osteoporosis therapy in 2002. [§]Several inhibitors of protein kinases have more than one target that may underlie their therapeutic activity. One of the target genes that provides the basis for classification of the drug as acting on a previously unexploited target is listed in the table. For a full list of the drug–target interactions in our data set, please see Supplementary information S1 (table).

2003) were approved. As noted above, there was a stable rate of introduction of NTDs that target GPCRs, hydrolases, isomerases and oxidoreductases in all three innovation peaks, and ~50% of all of the drugs that have been approved since 1982 fall into one of these categories.

Closer inspection of the NTDs reveals that small-molecule drugs were the most common class of agents acting on novel targets, comprising 60% of all NTDs, but it also reveals an increase in the development of biotechnology-based NTDs such as monoclonal antibodies and fusion proteins during the past two decades (TABLE 1). The first monoclonal antibody drug that was approved for sale in the United States was muromonab-CD3, which is an immunosuppressant that was approved by the FDA in 1986. Since then, the number of monoclonal antibody drugs has steadily increased, and they now comprise a considerable proportion of all NTDs. In the mid- to late-1990s (1994–2000) monoclonal antibody drugs comprised 24% of all NTDs, and between 2001 and 2010 they comprised 20% of all NTDs. Monoclonal antibodies have also been a major commercial success, with sales rising dramatically in the past decade. For example, the total market for the four most successful monoclonal antibodies — infliximab (Remicade; Centocor Ortho Biotech), rituximab (Rituxan; Genentech/Roche/Biogen Idec), adalimumab (Humira; Abbott) and bevacizumab (Avastin; Genentech/Roche) — increased by a factor of 3.90 from 2004 to 2010, whereas the total global drug market during the same period increased by factor of 1.53, according to data from IMS Health MIDAS (December 2008, 2009 and 2010).

The majority of drugs (14 out of 15) with the highest global sales in 2009 were approved by the FDA during the past 15 years, during the second innovation peak, which is unsurprising as these are the products that still have patent protection and have also had sufficient time to become established in the market. A common feature of all of these drugs is that they target defined protein structures that are encoded by the human genome. This is comparable to 65% of drugs in the DrugBank database that target effect-mediating structures encoded by the human genome. Other target categories include targets that are produced by pathogens, such as viral and bacterial proteins, and non-genomic structures such as extracellular macromolecules and DNA. The DrugBank database also includes various other agents, such as osmotic agents, sclerosing agents, nutrient supplements and inactive diagnostic agents.

The most common indication for NTDs is cancer treatment: ~19% of all NTDs that have been approved since 1983 are anticancer drugs. Advances in the understanding of the molecular basis of cancer during this period have contributed substantially to this trend, and have resulted in a shift from traditional cytotoxic therapies to the development of drugs that specifically target particular proteins that are linked to various cancers, such as small-molecule kinase inhibitors and monoclonal antibodies that bind to proteins on the surface of cancer cells. One notable example is the first marketed small-molecule kinase inhibitor, imatinib (Gleevec; Novartis), which — by inhibiting the mutant BCR–ABL kinase that is present in patients with chronic myeloid leukaemia — dramatically improved disease treatment, and demonstrated the potential of molecular targets in anticancer drug discovery, which are now being widely pursued[10].

GPCRs are clearly the most commonly exploited class of drug targets (FIG. 2) — approximately 36% of all drugs in our data set target GPCRs — and they also represent the largest class of target structures for NTDs that have been approved since 1983; approximately 17% of all targets for which NTDs have been introduced since 1982 have been GPCRs. According to data from IMS Health MIDAS, six out of the 20 drugs (30%) with the highest global sales in 2010 — clopidogrel (Plavix; Sanofi/Bristol-Myers Squibb), quetiapine (Seroquel; AstraZeneca), olanzapine (Zyprexa; Lilly), montelukast (Singulair; Merck), aripiprazole (Abilify; Bristol-Myers Squibb) and valsartan (Diovan; Novartis) — target GPCRs. In addition, 63 out of the 200 drugs (~32%) with the highest sales in the United States in 2009 target GPCRs (see the Drugs.com website). The majority of pharmacologically exploited GPCRs belong to the Rhodopsin family (reviewed in REF. 11).

Other common receptor target structures for NTDs in the period that was studied include cytokine receptors, receptor tyrosine kinases, ligand-gated ion channels and integrins. Enzymes represent the second largest group of novel target structures and most commonly belong to the hydrolase, oxidoreductase or transferase protein families (EC 3, EC 1 and EC 2, respectively). Novel hydrolase targets have been dominated by peptidases and ester hydrolases (EC 3.4 and EC 3.1). Examples of such targets include renin, which is a peptidase that is targeted by the antihypertensive drug aliskiren (Tekturna/Rasilez; Novartis) (approved in 2007) and phosphodiesterase 5, which is an ester hydrolase that is targeted by the erectile dysfunction drug sildenafil (Viagra; Pfizer) (approved in 1998). Novel targets in the transferase family have been dominated by phosphorous-containing group-transferases (EC 2.7) such as 5′-AMP-activated protein kinase, which is indirectly activated by metformin (approved in 1995). However, the exact mechanism of activation of 5′-AMP-activated protein kinase by metformin remains to be established[12]. NTDs that modulate oxidoreductases often target enzymes that act on the CH–OH group of donors, with NAD^+ or $NADP^+$ as the acceptor in redox reactions (EC 1.1.1). Some examples include: 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, which is targeted by the statin class of cardiovascular drugs to reduce high levels of low-density lipoprotein cholesterol; alcohol dehydrogenase, which is targeted by disulfiram for the treatment of alcohol dependency; and inosine 5′-monophosphate dehydrogenases, which are targeted by the immunosuppressive drug mycophenolate mofetil (CellCept; Roche).

Drug–target networks

Protein networks or modules are increasingly being studied in the field of network biology using methods from graph theory, which is a growing field within computer science. Much of network biology has focused on

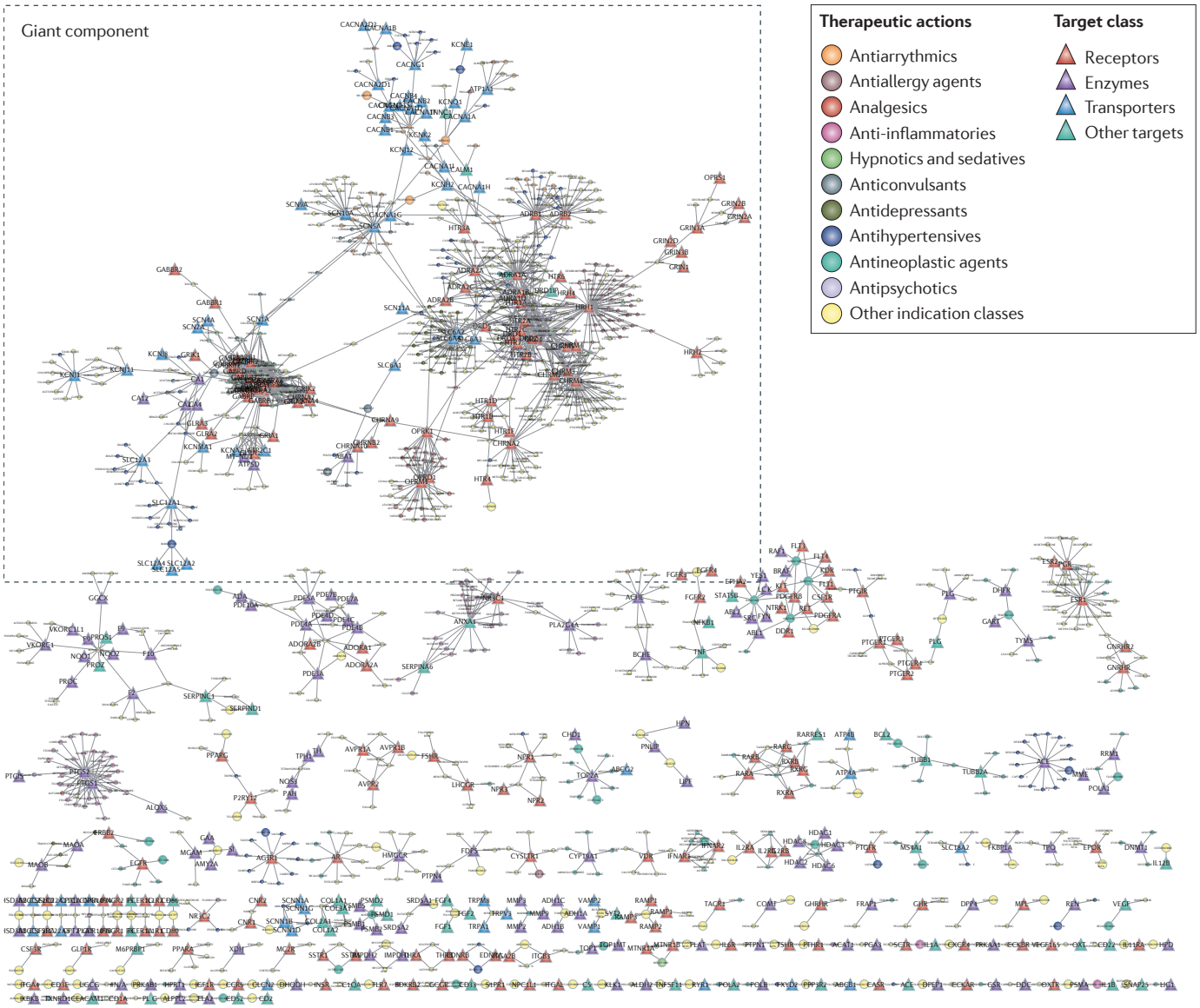


Figure 4 | **Drug–target network: summary.** This figure provides a graphical representation of all of the interactions between drugs and therapeutic drug targets in our curated data set. Nodes represent targets (shown as triangles) and drugs (shown as circles). Novel target drugs (NTDs) are represented with large circles and drugs with established targets are represented with small circles. Interacting drugs and targets are connected with lines. This network was created using Cytoscape. Several isolated components have been identified in our data set, the largest of which we have called the giant component. The giant component includes 49% of all drugs and 30% of all drug targets in our data set. See Supplementary information S3 (figure) to view this drug–target network in greater detail, as well as the labels at full size.

interactions between proteins, which have been called interactome networks. Drug–target interactions have also been studied in this context[9]. The field of interactomics represents a new way to understand the success of drug targets in the context of their functional milieu. Topographical analysis of the complex network of intercellular protein interactions may also lead to new avenues for target prediction[13,14].

We created a drug–target network from our curated data set (which includes 989 drugs and 435 effect-mediating protein targets) by connecting drugs with their known targets (FIGS 4,5,6). The drug–target network was integrated with annotation concerning drug indication, target functional class and novelty (that is, whether the drug targeted a previously unexploited target). The network was viewed in Cytoscape and analysed using local Python scripts.

The drug–target network consists of many subnetworks; that is, clusters of connected drug targets. The largest of these components, which we have called the giant component (FIG. 4), contains 489 drugs (49% of the total) and 131 targets (30% of the total). The giant component includes 50% of all drugs from the top 10 indication classes. The giant component is also biased in terms of the type of targets; 42% of all receptor targets and 66% of all transporter targets are found in the

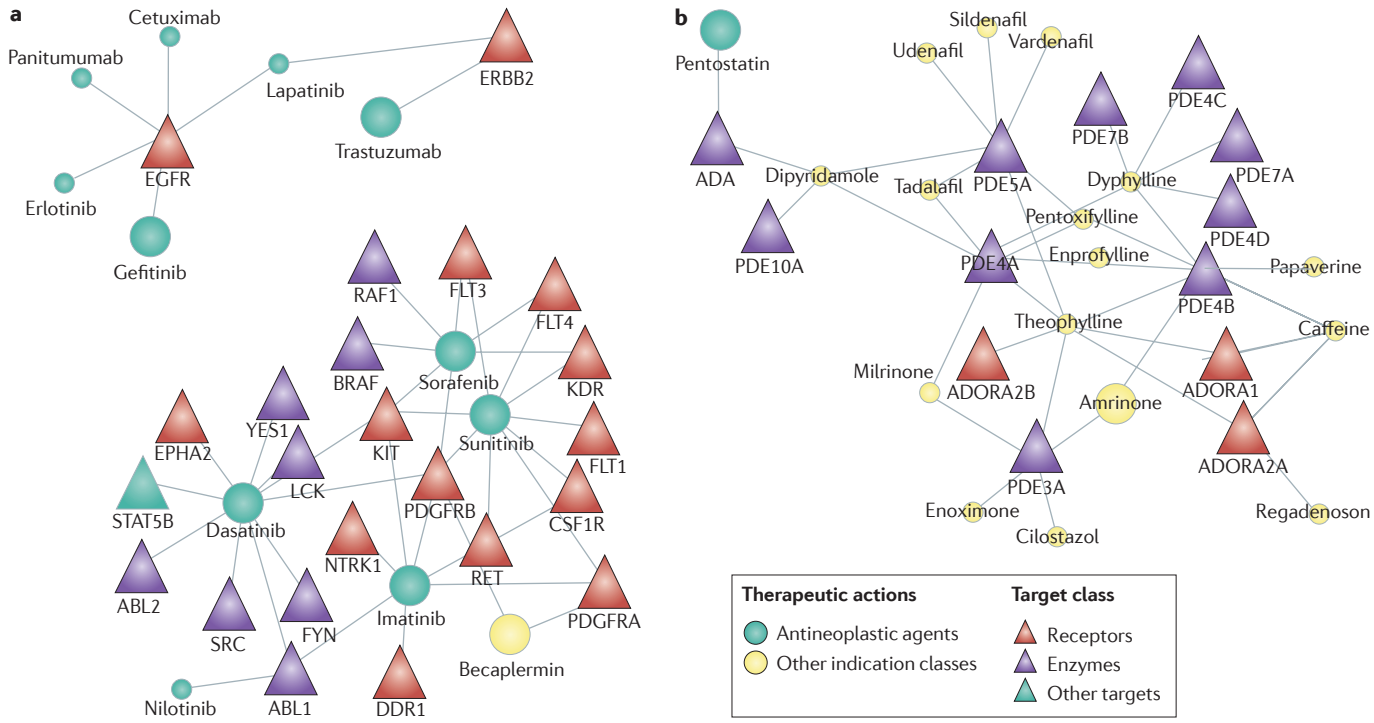


Figure 5 | **Drug–target network: selected networks.** Networks of particular interest from the overall network are shown in this figure. **a** | The interaction networks of receptor tyrosine kinase inhibitors for cancer treatment are depicted. These drugs form two networks that are centred around two receptor tyrosine kinases: the epidermal growth factor receptor (EGFR) and the platelet-derived growth factor receptor subunits A and B (PDGFRA and PDGFRB). Becaplermin, which is approved for the topical treatment of foot ulcers in patients with diabetes, is the only agent in these networks that is not an anticancer drug. However, it has been associated with an increased risk of cancer, and now has a black box warning on its label. **b** | The interaction network of phosphodiesterase (PDE) inhibitors is depicted; the indications of drugs in this network encompass the treatment of asthma and chronic obstructive pulmonary disease (xanthine derivatives theophylline, dyphylline and enprofylline), erectile dysfunction (vardenafil, sildenafil and tadalafil) and congestive heart failure (amrinone, milrinone and enoximone). Platelet aggregation inhibitors (cilostazol, dipyridamole and pentoxifylline), the spasmolytic drug papaverine and the familiar stimulant caffeine are also included in this network. As in Figure 4, nodes represent targets (shown as triangles) and drugs (shown as circles). Drugs with novel targets are represented with large circles and drugs with established targets are represented with small circles. Interacting drugs and targets are connected with lines. The original network was created using Cytoscape. ADA, adenosine deaminase; ADORA1, adenosine receptor A1; CSF1R, macrophage–colony-stimulating factor 1 receptor; DDR1, discoidin domain receptor tyrosine kinase 1; EPHA2, ephrin type A receptor 2; FLT1, fms-like tyrosine kinase 1; KDR, kinase insert domain receptor; LCK, lymphocyte-specific protein tyrosine kinase; NTRK1, neurotrophic tyrosine kinase receptor type 1; STAT5B, signal transducer and activator of transcription 5; YES1, Yamaguchi sarcoma viral oncogene homolog 1.

giant component, whereas only 5% of enzyme targets and 6% of miscellaneous targets are found here. Overall, 58% of the targets in the giant component are receptors and all but one of these are GPCRs or ligand-gated ion channels — two very traditional classes of pharmacological targets. The drugs in the giant component have a significantly higher number of target interactions than drugs in the smaller components ($P < 0.001$; Wilcoxon signed-rank test). Drugs in the giant component have an average of three targets, whereas drugs outside the giant component have an average of 1.5 targets.

Targets within the giant component have a much longer history than the network as a whole, considering the FDA approval dates of drugs within this component. The drugs in the giant component have a median approval year before 1982, which is the cut-off date for drug approvals in our data set. Out of all of the drugs that were approved after 1982 in the giant component, only 12 are NTDs. Hence, it is clear that almost half of all drugs on the market — which represent the indication classes in which a large research effort has been made — share a similar target interaction profile and exploit a limited part of the proteome. In addition, the main innovations within this cluster of successful drugs occurred before the 'one drug, one target' focus of recent times. The success of some of the drugs in the giant component could be due to the fact that they utilize multiple targets. This highlights the importance of polypharmacology and an understanding of the target profile in relation to the interactome for the discovery of new drugs.

Discussion

In this analysis, we observed an approximately steady rate of introduction of new drugs targeting molecules encoded by the human genome, and an approximately steady rate of introduction of NTDs into the US

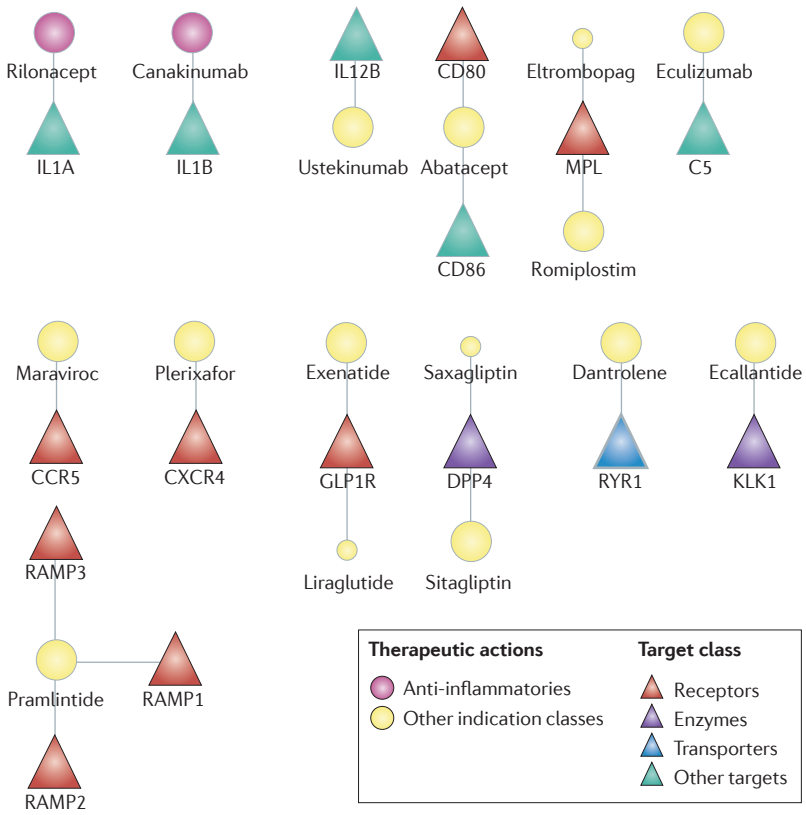


Figure 6 | **Isolated smaller networks of drugs with novel targets that were approved between 2005 and 2010, and their corresponding target-encoding genes.** These smaller networks are of particular interest as they not only represent novel drug targets but also represent novel molecular mechanisms for treatment. Several drugs are included in this panel. These include maraviroc, which inhibits the entry of the human immunodeficiency virus into human cells by blocking CC chemokine receptor type 5 (CCR5) on human lymphocytes. The following antidiabetic drugs are also included: sitagliptin, which was the first dipeptidyl peptidase 4 (DPP4) inhibitor; pramlintide, which is an amylin analogue that interacts with the protein complexes receptor activity-modifying protein 1 (RAMP1), RAMP2 and RAMP3; and exenatide, which is an analogue of a peptide contained in the venom of the Gila monster (*Heloderma suspectum*) and was the first drug to target glucagon-like peptide 1 receptor (GLP1R). The panel also includes the haematopoiesis-stimulating drugs plerixafor, which interacts with CXC chemokine receptor type 4 (CXCR4), and romiplostim, which was the first drug to interact with the thrombopoietin receptor (MPL). Other drugs in this panel include the muscle relaxant dantrolene, which was the first drug to act on ryanodine receptor 1 (RYR1), and ecallantide, which inhibits the protein kallikrein 1 (KLK1) and is indicated for the treatment of hereditary angioedema. This panel also includes the fusion proteins rilonacept, which targets interleukin-1α (IL-1α), and abatacept, which targets T lymphocyte activation antigen CD80 and T lymphocyte activation antigen CD86. The monoclonal antibodies canakinumab (which targets IL-1β), ustekinumab (which targets the p40 subunit of IL-12 and IL-23) and eculizumab (which was the first drug to target complement protein C5) are also included; these monoclonal antibodies are indicated for the treatment of various immunoinflammatory diseases. As in Figure 4, drugs with novel targets (NTDs) are represented with large circles and drugs with established targets are represented with small circles. Interacting drugs and targets are connected with lines. The original network was created using Cytoscape.

market from 1982 to 2010. Three 'innovation peaks' were observed in the rate of introduction of NTDs; the potential factors underlying these peaks are multiple and diverse, ranging from scientific and technological advances to changes in regulatory policy, and are not discussed here. Although the rate of innovation — as assessed by the rate of introduction of new drugs and NTDs — does not appear to have decreased substantially in the period we studied, given the considerable increase in investment in research and development by the pharmaceutical industry during this period[15,16], the lack of an increase in the rate of innovation could be considered as alarming.

Our analysis also highlights that the majority of new drugs that were approved during this period target previously exploited structures that are encoded by the human genome. Our estimate for the number of current drug targets encoded by the human genome is somewhat higher than some previous estimates[3–5], as we have not filtered our data set with regard to gene family redundancies or rule-of-five compliant molecules but instead focused on individual genes (that is, single positions on the genome).

Our analysis of drug–target connections reveals a bias (FIGS 4,5,6). As older drugs have been more thoroughly studied and a higher number of drug–protein interactions have been documented for these drugs, they have higher connectivity in the drug–target network. Newer NTDs, by definition, tend to be disconnected from the giant component of the network, and this is seen with NTDs that were introduced into the market from 2005 to 2010 (FIG. 6). Apart from receptor tyrosine kinase inhibitors and monoclonal antibodies for cancer therapy, which show some degree of interconnectivity by forming a separate subnetwork (FIG. 5), NTDs that were introduced from 2005 to 2010 are all disconnected from the giant component, and instead form small isolated networks consisting of two or three nodes. These smaller networks are, however, of particular interest as they not only represent novel drug targets but also often represent novel molecular mechanisms for treatment. Some examples are given in FIG. 6. Overall, this stresses the complexity of the automatic use of general drug–target connectivity network analysis, and highlights the importance of the specification of the unique non-redundant drug targets, including the distinction between new and old drug targets.

The idea of a unique point of pharmacological intervention for each disease — 'one drug/disease, one target' — has validity in reducing side effects for the treatment of several diseases. However, rigid application of this theory in drug discovery may inadvertently exclude possible leads. In the case of antipsychotic drugs for example, for which the dopamine D2 receptor has been theoretically suggested as the intended target, drug target promiscuity has instead been seen to have more beneficial effects than selective dopamine D2 receptor ligands. In the case of anticancer drugs, however, the focus on selectivity has generated major treatment benefits, as illustrated by the previously mentioned example of imatinib and other kinase inhibitors, although even in these cases it should be noted that these compounds often potently inhibit several kinases. The introduction of monoclonal antibodies as a therapeutic modality has had a major medical impact (particularly in the past decade), as it enables rational target selection and high target specificity. There has been, and continues to be, great interest in

the development of new antibodies within fields such as cancer and inflammation, in which the drug target is often expressed at higher levels in the disease state.

These new opportunities highlight the need to gain a deeper understanding of disease processes at the molecular level for a wider range of targets, as noted in an early paper on drug targets[17]. In recent years, a range of new candidate targets have been identified from genome-wide association studies for several common complex disorders such as obesity, diabetes, cancer and cardiovascular disease. New technologies such as next-generation sequencing will allow these types of studies to be performed on an even larger scale and in closer association with detailed clinical phenotyping, which could help to validate the therapeutic relevance of such targets, which arguably remains one of the crucial challenges in drug discovery research. Simultaneous exploitation of several targets for disease treatment also poses a major challenge owing to the complexity of cellular signalling and drug–protein interactions in the human body. The burgeoning concept of network pharmacology aims to quantify these interactions and could provide a general tool for identifying new targets for rational drug discovery.

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Competing interests statement
The authors declare no competing financial interests.

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Online 'at-a-glance' summary

- Currently marketed drugs mediate their effects via only a limited number of molecular targets. The recent trends in drug development were analysed by extensively matching drugs with drug targets and correlating these with drug approval dates.
- We have identified 435 effect-mediating targets that were encoded by single positions on the human genome.
- We have also observed a steady rate of introduction of new drugs. Furthermore, in our data set there has been no substantial decrease in the number of new drugs approved by the US Food and Drug Administration each year.
- On average, approximately 18 new drugs that act on targets that are encoded by the human genome are approved for the US market every year. The majority of new drugs target previously exploited structures that are encoded by the human genome.
- On average, approximately 4.3 novel target drugs (NTDs) — that is, new drugs that target a previously unexploited molecular target that is encoded by the human genome — are approved for the US market every year.
- Our drug–target network analysis shows a connection between the majority of drugs that form a giant interconnected network that we have termed the 'giant component'. However, NTDs have a greater tendency to be disconnected from the giant component and form small isolated networks. These smaller networks are of particular interest as they not only represent novel drug targets but also often represent new molecular mechanisms for treatment.

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Subject categories Drug Discovery