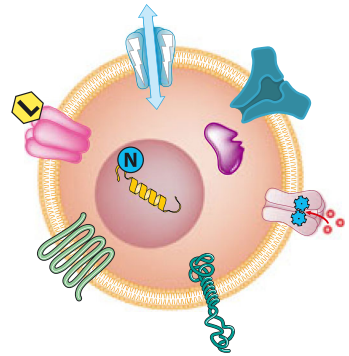
THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: Introduction and Other Protein Targets



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Abstract

The Concise Guide to PHARMACOLOGY 2019/20 is the fourth in this series of biennial publications. The Concise Guide provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology (where available), plus links to the open access knowledgebase source of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. Although the Concise Guide represents approximately 400 pages, the material presented is substantially reduced compared to information and links presented on the website. It provides a permanent, citable, point-in-time record that will survive database updates. The full contents of this section can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.14747. In addition to this overview, in which are identified Other protein targets which fall outside of the subsequent categorisation, there are six areas of focus: G protein-coupled receptors, ion channels, nuclear hormone receptors, catalytic receptors, enzymes and transporters. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. The landscape format of the Concise Guide is designed to facilitate comparison of related targets from material contemporary to mid-2019, and supersedes data presented in the 2017/18, 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

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Introduction

In order to allow clarity and consistency in pharmacology, there is a need for a comprehensive organisation and presentation of the targets of drugs. This is the philosophy of the IUPHAR/BPS Guide to PHARMACOLOGY presented on the online free access database (https://www.guidetopharmacology.org/). This database is supported by the British Pharmacological Society (BPS), the International Union of Basic and Clinical Pharmacology (IUPHAR), the University of Edinburgh and previously the Wellcome Trust. Data included in the Guide to PHARMACOLOGY are derived in large part from interactions with the subcommittees of the Nomenclature Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR). A major influence on the development of the database was Tony Harmar (1951-2014), who worked with a passion to establish the curators as a team of highly informed and informative individuals, with a focus on high-quality data input, ensuring a suitably validated dataset. The Editors of the Concise Guide have compiled the individual records, in concert with the team of Curators, drawing on the expert knowledge of these latter subcommittees. The tables allow an indication of the status of the nomenclature for the group of targets listed, usually previously published in Pharmacological Reviews. In the absence of an established subcommittee, advice from several prominent, independent experts has generally been obtained to produce an authoritative consensus on nomenclature, which attempts to fit in within the general guidelines from NC-IUPHAR. This current edition, the Concise Guide to PHARMACOLOGY 2019/20, is the latest snapshot of the database in print form, following on from the Concise Guide to PHARMACOLOGY 2017/18. It contains data drawn from the online database as a rapid overview of the major pharmacological targets. Thus, there are many fewer targets presented in the Concise Guide compared to the online database. The priority for inclusion in the Concise Guide is the presence of quantitative pharmacological data for human proteins. This means that often orphan family members are not presented in the Concise Guide, although structural information is available on the online database. The organisation of the data is tabular (where appropriate) with a standardised format, where possible on a single page, intended to aid understanding of, and comparison within, a particular target group. The Concise Guide is intended as an initial resource, with links to additional reviews and resources for greater depth and information. Pharmacological and structural data focus primarily on human gene products, wherever possible, with links to HGNC gene nomenclature and UniProt IDs. In a few cases, where data from human proteins are limited, data from other species are indicated. Pharmacological tools listed are prioritised on the basis of selectivity and availability. That is, agents (agonists, antagonists, inhibitors, activators, etc.) are included where they are both available (by donation or from commercial sources, now or in the near future) AND the most selective. The Concise Guide is divided into seven sections, which comprise pharmacological targets of similar structure/function. These are G protein-coupled receptors, ion channels (combining previous records of ligand-gated, voltage-gated and other ion channels), catalytic receptors, nuclear hormone receptors, enzymes, transporters and other protein targets. We hope that the Concise Guide will provide for researchers, teachers and students a state-of-the art source of accurate, curated information on the background to their work that they will use in the Introductions to their Research Papers or Reviews, or in supporting their teaching and studies. We recommend that any citations to information in the Concise Guide are presented in the following format: Alexander SPH et al. (2019). The Concise Guide to PHARMACOLOGY 2019/20: Introduction and Other Protein Targets. Br J Pharmacol 176: S1–S20. In this overview are listed protein targets of pharmacological interest, which are not G protein-coupled receptors, ion channels, nuclear hormone receptors, catalytic receptors, transporters or enzymes.

Acknowledgements

We are extremely grateful to the British Pharmacological Society and the International Union of Basic and Clinical Pharmacology, for financial support of the website and for advice from the NC-IUPHAR subcommittees. We thank the University of Edinburgh, who host the www.guidetopharmacology.org website. Previously, the International Union of Basic and Clinical Pharmacology and the Wellcome Trust (099156/Z/12/Z]) also supported the initiation and expansion of the database. We are also tremendously grateful to the long list of collaborators from NC-IUPHAR subcommittees and beyond, who have assisted in the construction of the Concise Guide to PHARMACOLOGY 2019/20 and the online database www.guidetopharmacology.org.

Conflict of interest

The authors state that there are no conflicts of interest to disclose.

Family structure

Adiponectin receptors

Other protein targets → Adiponectin receptors

Overview: Adiponectin receptors (**provisional nomenclature**, ENSFM00500000270960) respond to the 30 kDa complement-related protein hormone adiponectin (also known as *ADIPOQ*: adipocyte, C1q and collagen domain-containing protein; ACRP30, adipose most abundant gene transcript 1; apM-1; gelatin-binding protein: Q15848) originally cloned from adipocytes [57]. Although sequence data suggest 7TM domains, immunological evidence indicates that, contrary to typical 7TM topology, the carboxyl terminus is extracellular, while the amino terminus is intracellular [111]. Signalling through these receptors appears to avoid G proteins; modelling based on the crystal structures of the adiponectin receptors suggested ceramidase acivity, which would make these the first in a new family of catalytic receptors [98].

Nomenclature	Adipo1 receptor	Adipo2 receptor
HGNC, UniProt	*ADIPOR1*, Q96A54	*ADIPOR2*, Q86V24
Rank order of potency	globular adiponectin (*ADIPOQ*, Q15848) > adiponectin (*ADIPOQ*, Q15848)	globular adiponectin (*ADIPOQ*, Q15848) = adiponectin (*ADIPOQ*, Q15848)

Comments: T-Cadherin (*CDH13*, P55290) has also been suggested to be a receptor for (hexameric) adiponectin [36].

Further reading on Adiponectin receptors

Fisman EZ *et al.* (2014) Adiponectin: a manifold therapeutic target for metabolic syndrome, diabetes, and coronary disease? *Cardiovasc Diabetol* **13**: 103 [PMID:24957699]

Okada-Iwabu M *et al.* (2018) Structure and function analysis of adiponectin receptors toward development of novel antidiabetic agents promoting healthy longevity. *Endocr J* **65**: 971-977 [PMID:30282888]

Ruan H *et al.* (2016) Adiponectin signaling and function in insulin target tissues. *J Mol Cell Biol* **8**: 101-9 [PMID:26993044]

Wang Y *et al.* (2017) Cardiovascular Adiponectin Resistance: The Critical Role of Adiponectin Receptor Modification. *Trends Endocrinol. Metab.* **28**: 519-530 [PMID:28473178]

Zhao L *et al.* (2014) Adiponectin and insulin cross talk: the microvascular connection. *Trends Cardiovasc. Med.* **24**: 319-24 [PMID:25220977]

Blood coagulation components

Other protein targets → Blood coagulation components

Overview: Coagulation as a process is interpreted as a mechanism for reducing excessive blood loss through the generation of a gel-like clot local to the site of injury. The process involves the activation, adhesion (see Integrins), degranulation and aggregation of platelets, as well as proteins circulating in the plasma. The coagulation cascade involves multiple proteins being converted to more active forms from less active precursors, typically through proteolysis (see Proteases). Listed here are the components of the coagulation cascade targetted by agents in current clinical usage.

Nomenclature	coagulation factor V	coagulation factor VIII	serpin family C member 1
HGNC, UniProt	*F5*, P12259	*F8*, P00451	*SERPINC1*, P01008
Selective activators	–	–	heparin (pK_d 7.8) [29], fondaparinux (pK_d 7.5) [72], dalteparin [35], danaparoid [18, 65], enoxaparin [21], tinzaparin [22]
Selective inhibitors	drotrecogin alfa (Antithrombotic effect thought to occur via inhibition of factors Va and VIIIa) [39, 40]	drotrecogin alfa (Antithrombotic effect thought to occur via inhibition of factors Va and VIIIa) [39, 40]	–

Further reading on Blood coagulation components

Astermark J. (2015) FVIII inhibitors: pathogenesis and avoidance. *Blood* **125**: 2045-51 [PMID:25712994]

Girolami A *et al.* (2017) New clotting disorders that cast new light on blood coagulation and may play a role in clinical practice. *J. Thromb. Thrombolysis* **44**: 71-75 [PMID:28251495]

Rana K *et al.* (2016) Blood flow and mass transfer regulation of coagulation. *Blood Rev.* **30**: 357-68 [PMID:27133256]

Non-enzymatic BRD containing proteins

Other protein targets → Bromodomain-containing proteins → Non-enzymatic BRD containing proteins

Overview: Bromodomains bind proteins with acetylated lysine residues, such as histones, to regulate gene transcription. Listed herein are examples of bromodomain-containing proteins for which sufficient pharmacology exists.

Nomenclature	bromodomain adjacent to zinc finger domain 2A	bromodomain adjacent to zinc finger domain 2B	CREB binding protein	polybromo 1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4
HGNC, UniProt	*BAZ2A*, Q9UIF9	*BAZ2B*, Q9UIF8	*CREBBP*, Q92793	*PBRM1*, Q86U86	*SMARCA4*, P51532
Selective inhibitors	GSK2801 (pK_d 6.6) [85]	GSK2801 (Binding) (pK_d 6.9) [85]	I-CBP112 (pK_d 6.8) [84]	PFI-3 (Binding) (pK_d 7.3) [95]	PFI-3 (Binding) (pK_d 7.1) [95]

Further reading on Non-enzymatic BRD containing proteins

Fujisawa T *et al.* (2017) Functions of bromodomain-containing proteins and their roles in homeostasis and cancer. *Nat. Rev. Mol. Cell Biol.* **18**: 246-262 [PMID:28053347]

Myrianthopoulos V & Mikros E. (2019) From bench to bedside, via desktop. Recent advances in the application of cutting-edge in silico tools in the research of drugs targeting bromodomain modules. *Biochem Pharmacol* **159**: 40-51 [PMID:30414936]

Nicholas DA *et al.* (2017) BET bromodomain proteins and epigenetic regulation of inflammation: implications for type 2 diabetes and breast cancer. *Cell. Mol. Life Sci.* **74**: 231-243 [PMID:27491296]

Ramadoss M & Mahadevan V. (2018) Targeting the cancer epigenome: synergistic therapy with bromodomain inhibitors. *Drug Discov Today* **23**: 76-89 [PMID:28943305]

Yang CY *et al.* (2019) Small-molecule PROTAC degraders of the Bromodomain and Extra Terminal (BET) proteins - A review. *Drug Discov Today Technol* **31**: 43-51 [PMID:31200858]

Carrier proteins

Other protein targets → Carrier proteins

Overview: Transthyretin (TTR) is a homo-tetrameric protein which transports thyroxine in the plasma and cerebrospinal fluid and retinol (vitamin A) in the plasma. Many disease causing mutations in the protein have been reported, many of which cause complex dissociation and protein mis-assembly and deposition of toxic aggregates amyloid fibril formation [73]. These amyloidogenic mutants are linked to the development of pathological amyloidoses, including familial amyloid polyneuropathy (FAP) [6, 16], familial amyloid cardiomyopathy (FAC) [37], amyloidotic vitreous opacities, carpal tunnel syndrome [63] and others. In old age, non-mutated TTR can also form pathological amyloid fibrils [108]. Pharmacological intervention to reduce or prevent TTR dissociation is being pursued as a theapeutic strategy. To date one small molecule kinetic stabilising molecule (tafamidis) has been approved for FAP, and is being evaluated in clinical trials for other TTR amyloidoses.

Nomenclature	transthyretin
Common abbreviation	TTR
HGNC, UniProt	*TTR*, P02766

Further reading on Carrier proteins

Adams D *et al.* (2019) Hereditary transthyretin amyloidosis: a model of medical progress for a fatal disease. *Nat Rev Neurol* **15**: 387-404 [PMID:31209302]

Dellière S *et al.* (2017) Is transthyretin a good marker of nutritional status? *Clin Nutr* **36**: 364-370 [PMID:27381508]

Galant NJ *et al.* (2017) Transthyretin amyloidosis: an under-recognized neuropathy and cardiomyopathy. *Clin. Sci.* **131**: 395-409 [PMID:28213611]

Yokoyama T & Mizuguchi M. (2018) Inhibition of the Amyloidogenesis of Transthyretin by Natural Products and Synthetic Compounds. *Biol Pharm Bull* **41**: 979-984 [PMID:29962408]

Ruberg FL *et al.* (2019) Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. *J Am Coll Cardiol* **73**: 2872-2891 [PMID:31171094]

CD molecules

Other protein targets → CD molecules

Overview: Cluster of differentiation refers to an attempt to catalogue systematically a series of over 300 cell-surface proteins associated with immunotyping. Many members of the group have identified functions as enzymes (for example, see CD73 ecto-5′-nucleotidase) or receptors (for example, see CD41 integrin, alpha 2b subunit). Many CDs are targeted for therapeutic gain using antibodies for the treatment of proliferative disorders. A full listing of all the Clusters of Differentiation proteins is not possible in the Guide to PHARMACOLOGY; listed herein are selected members of the family targeted for therapeutic gain.

Nomenclature	CD2	CD3e	CD6	CD20 (membrane-spanning 4-domains, subfamily A, member 1)	CD33
Common abbreviation	–	–	–	–	SIGLEC-3
HGNC, UniProt	*CD2*, P06729	*CD3E*, P07766	*CD6*, P30203	*MS4A1*, P11836	*CD33*, P20138
Selective inhibitors	alefacept [19, 62]	–	–	–	–
Antibodies	–	catumaxomab (Binding) [50], muromonab-CD3 (Binding) [28], otelixizumab (Binding) [11]	–	ofatumumab (Binding) (pK_d 9.9) [52], rituximab (Binding) (pK_d 8.5) [91], ibritumomab tiuxetan (Binding), obinutuzumab (Binding) [4, 76], tositumomab (Binding)	lintuzumab (Binding) (pK_d ~10) [12], gemtuzumab ozogamicin (Binding) [9]

Nomenclature	CD52	CD80	CD86	cytotoxic T-lymphocyte-associated protein 4 (CD152)	programmed cell death 1 (CD279)	CD300a
Common abbreviation	–	–	–	CTLA-4	PD-1	–
HGNC, UniProt	*CD52*, P31358	*CD80*, P33681	*CD86*, P42081	*CTLA4*, P16410	*PDCD1*, Q15116	*CD300A*, Q9UGN4
Endogenous ligands	–	–	–	–	programmed cell death 1 ligand 1 (*CD274*, Q9NZQ7) (Binding)	–
Selective inhibitors	–	abatacept (pK_d ~7.9) [51, 103]	abatacept (pK_d ~7.9) [51, 103], belatacept [44]	–	–	–
Antibodies	alemtuzumab (Binding) [26, 86]	–	–	ipilimumab (Binding) (pK_d >9) [30], tremelimumab (Binding) (pK_d 8.9) [32]	pembrolizumab (Binding) (pK_d ~10) [13], nivolumab (Binding) (pK_d 9.1) [31, 42, 43]	–

Comments: The endogenous ligands for human PD-1 are programmed cell death 1 ligand 1 (PD-L1 *aka* CD274 (*CD274*, Q9NZQ7)) and programmed cell death 1 ligand 2 (PD-L2; *PDCD1LG2*). These ligands are cell surface peptides, normally involved in immune system regulation. Expression of PD-1 by cancer cells induces immune tolerance and evasion of immune system attack. Anti-PD-1 monoclonal antibodies are used to induce immune checkpoint blockade as a therapeutic intervention in cancer, effectively re-establishing immune vigilance. Pembrolizumab was the first anti-PD-1 antibody to be approved by the US FDA.

Further reading on CD molecules

Gabius HJ *et al.* (2015) The glycobiology of the CD system: a dictionary for translating marker designations into glycan/lectin structure and function. *Trends Biochem. Sci.* **40**: 360-76 [PMID:25981696]

Vosoughi T *et al.* (2019) CD markers variations in chronic lymphocytic leukemia: New insights into prognosis. *J Cell Physiol.* **234**: 19420-39 [PMID:31049958]

Methyllysine reader proteins

Other protein targets → Chromatin-interacting transcriptional repressors → Methyllysine reader proteins

Overview: Methyllysine reader proteins bind to methylated proteins, such as histones, allowing regulation of gene expression.

Nomenclature	L3MBTL histone methyl-lysine binding protein 3
HGNC, UniProt	*L3MBTL3*, Q96JM7
Selective agonists	UNC1215 [38]

Further reading on Methyllysine reader proteins

Daskalaki MG *et al.* (2018) Histone methylation and acetylation in macrophages as a mechanism for regulation of inflammatory responses. *J Cell Physiol.* **233**: 6495-9507 [PMID:29574768]

Furuya K *et al.* (2019) Epigenetic interplays between DNA demethylation and histone methylation for protecting oncogenesis. *J Biochem.* **165**: 297-299 [PMID:30605533]

Levy D. (2019) Lysine methylation signaling of non-histone proteins in the nucleus. *Cell Mol Life Sci* **76**: 2873-83 [PMID:31123776]

Li J *et al.* (2019) Understanding histone H3 lysine 36 methylation and its deregulation in disease. *Cell Mol Life Sci* in press [PMID:31147750]

Shafabakhsh R *et al.* (2019) Role of histone modification and DNA methylation in signaling pathways involved in diabetic retinopathy. *J Cell Physiol.* **234**: 7839-7846 [PMID:30515789]

Fatty acid-binding proteins

Other protein targets → Fatty acid-binding proteins

Overview: Fatty acid-binding proteins are low molecular weight (100-130 aa) chaperones for long chain fatty acids, fatty acyl CoA esters, eicosanoids, retinols, retinoic acids and related metabolites and are usually regarded as being responsible for allowing the otherwise hydrophobic ligands to be mobile in aqueous media. These binding proteins may perform functions extracellularly (*e.g.* in plasma) or transport these agents; to the nucleus to interact with nuclear receptors (principally PPARs and retinoic acid receptors [82]) or for interaction with metabolic enzymes. Although sequence homology is limited, crystallographic studies suggest conserved 3D structures across the group of binding proteins.

Nomenclature	fatty acid binding protein 1	fatty acid binding protein 2	fatty acid binding protein 3	fatty acid binding protein 4	fatty acid binding protein 5
HGNC, UniProt	*FABP1*, P07148	*FABP2*, P12104	*FABP3*, P05413	*FABP4*, P15090	*FABP5*, Q01469
Rank order of potency	stearic acid, oleic acid > palmitic acid, linoleic acid > arachidonic acid, α-linolenic acid [77]	stearic acid > palmitic acid,oleic acid > linoleic acid > arachidonic acid, α-linolenic acid [77]	stearic acid, oleic acid, palmitic acid > linoleic acid, α-linolenic acid, arachidonic acid [77]	oleic acid, palmitic acid, stearic acid, linoleic acid > α-linolenic acid, arachidonic acid [77]	–
Inhibitors	fenofibrate (pK_i 7.6) [14] – Rat, fenofibric acid (pK_i 6.5) [14] – Rat, HTS01037 (pK_i 5.1) [33] – Mouse	–	–	–	compound 13 (pK_i 8.7) [97]
Selective inhibitors	–	–	–	HM50316 (pK_i >9) [53]	–
Comments	A broader substrate specificity than other FABPs, binding two fatty acids per protein [101].	Crystal structure of the rat FABP2 [79].	Crystal structure of the human FABP3 [112].	–	Crystal structure of the human FABP5 [34].

Nomenclature	fatty acid binding protein 6	fatty acid binding protein 7	peripheral myelin protein 2	fatty acid binding protein 9	fatty acid binding protein 12
HGNC, UniProt	*FABP6*, P51161	*FABP7*, O15540	*PMP2*, P02689	*FABP9*, Q0Z7S8	*FABP12*, A6NFH5
Comments	Able to transport bile acids [113].	Crystal structure of the human FABP7 [7].	*In silico* modelling suggests that PMP2/FABP8 can bind both fatty acids and cholesterol [58].	–	–

Nomenclature	retinol binding protein 1	retinol binding protein 2	retinol binding protein 3	retinol binding protein 4	retinol binding protein 5	retinol binding protein 7
HGNC, UniProt	*RBP1*, P09455	*RBP2*, P50120	*RBP3*, P10745	*RBP4*, P02753	*RBP5*, P82980	*RBP7*, Q96R05
Rank order of potency	–	stearic acid > palmitic acid, oleic acid, linoleic acid, α-linolenic acid, arachidonic acid [78]	–	–	–	–
Inhibitors	–	–	–	A1120 (pIC_{50} 7.8) [106]	–	–

Nomenclature	retinaldehyde binding protein 1	cellular retinoic acid binding protein 1	cellular retinoic acid binding protein 2
HGNC, UniProt	*RLBP1*, P12271	*CRABP1*, P29762	*CRABP2*, P29373
Rank order of potency	11-*cis*-retinal, 11-*cis*-retinol > 9-*cis*-retinal, 13-*cis*-retinal, 13-*cis*-retinol, all-*trans*-retinal, retinol [17]	tretinoin > alitretinoin stearic acid > palmitic acid, oleic acid, linoleic acid, α-linolenic acid, arachidonic acid [78]	–

Comments: Although not tested at all FABPs, BMS309403 exhibits high affinity for FABP4 (pIC50 8.8) compared to FABP3 or FABP5 (pIC50 <6.6) [23, 97]. HTS01037 is reported to interfere with FABP4 action [33]. Ibuprofen displays some selectivity for FABP4 (pIC_{50} 5.5) relative to FABP3 (pIC_{50} 3.5) and FABP5 (pIC_{50} 3.8) [56]. Fenofibric acid displays some selectivity for FABP5 (pIC_{50} 5.5) relative to FABP3 (pIC_{50} 4.5) and FABP4 (pIC_{50} 4.6) [56]. Multiple pseudogenes for the FABPs have been identified in the human genome.

Further reading on Fatty acid-binding proteins

Gajda AM *et al.* (2015) Enterocyte fatty acid-binding proteins (FABPs): different functions of liver and intestinal FABPs in the intestine. *Prostaglandins Leukot. Essent. Fatty Acids* **93**: 9-16 [PMID:25458898]

Glatz JF. (2015) Lipids and lipid binding proteins: a perfect match. *Prostaglandins Leukot Essent Fatty Acids* **93**: 45-9 [PMID:25154384]

Hotamisligil GS *et al.* (2015) Metabolic functions of FABPs–mechanisms and therapeutic implications. *Nat Rev Endocrinol* **11**: 592-605 [PMID:26260145]

Matsumata M *et al.* (2016) Fatty acid binding proteins and the nervous system: Their impact on mental conditions. *Neurosci. Res.* **102**: 47-55 [PMID:25205626]

Osumi T *et al.* (2016) Heart lipid droplets and lipid droplet-binding proteins: Biochemistry, physiology, and pathology. *Exp. Cell Res.* **340**: 198-204 [PMID:26524506]

Notch receptors

Other protein targets → Notch receptors

Overview: The canonical Notch signalling pathway has four type I transmembrane Notch receptors (Notch1-4) and five ligands (DLL1, 2 and 3, and Jagged 1-2). Each member of this highly conserved receptor family plays a unique role in cell-fate determination during embryogenesis, differentiation, tissue patterning, proliferation and cell death [3]. As the Notch ligands are also membrane bound, cells have to be in close proximity for receptor-ligand interactions to occur. Cleavage of the intracellular domain (ICD) of activated Notch receptors by γ-secretase is required for downstream signalling and Notch-induced transcriptional modulation [20, 66, 83, 109]. This is why γ-secretase inhibitors can be used to downregulate Notch signalling and explains their anti-cancer action. One such small molecule is RO4929097 [54], although development of this compound has been terminated following an unsuccessful Phase II single agent clinical trial in metastatic colorectal cancer [94].

Aberrant Notch signalling is implicated in a number of human cancers [46, 68, 88, 104], with demcizumab and tarextumab identified as antibody inhibitors of ligand:receptor binding [74].

Nomenclature	notch receptor 1	notch receptor 2	notch receptor 3	notch receptor 4
HGNC, UniProt	*NOTCH1*, P46531	*NOTCH2*, Q04721	*NOTCH3*, Q9UM47	*NOTCH4*, Q99466
Comments	Various types of activating and inactivating *NOTCH1* mutations have been reported to be associated with human diseases, for example: aortic valve disease [25, 61], Adams-Oliver syndrome 5 [92], T-cell acute lymphoblastic leukemia (T-ALL) [107], chronic lymphocytic leukemia (CLL) [75] and head and neck squamous cell carcinoma [1, 93].	–	–	Notch receptor 4 is a potential therapeutic molecular target for triple-negative breast cancer [47, 64].

Further reading on Notch receptors

Arumugam TV *et al.* (2018) Notch signaling and neuronal death in stroke. *Prog. Neurobiol.* **165-167**: 103-116 [PMID:29574014]

Borggrefe T *et al.* (2016) The Notch intracellular domain integrates signals from Wnt, Hedgehog, TGFβ/BMP and hypoxia pathways. *Biochim. Biophys. Acta* **1863**: 303-13 [PMID:26592459]

Palmer WH *et al.* (2015) Ligand-Independent Mechanisms of Notch Activity. *Trends Cell Biol.* **25**: 697-707 [PMID:26437585]

Previs RA *et al.* (2015) Molecular pathways: translational and therapeutic implications of the Notch signaling pathway in cancer. *Clin. Cancer Res.* **21**: 955-61 [PMID:25388163]

Takebe N *et al.* (2015) Targeting Notch, Hedgehog, and Wnt pathways in cancer stem cells: clinical update. *Nat Rev Clin Oncol* **12**: 445-64 [PMID:25850553]

Regulators of G protein Signaling (RGS) proteins

Other protein targets → Regulators of G protein Signaling (RGS) proteins

Overview: Regulators of G protein signalling (RGS) proteins display a common RGS domain that interacts with the GTP-bound Gα subunits of heterotrimeric G proteins, enhancing GTP hydrolysis by stabilising the transition state [8, 99, 100], leading to a termination of GPCR signalling. Interactions through protein:protein interactions of many RGS proteins have been identified for targets other than heteromeric G proteins. Sequence analysis of the 20 RGS proteins suggests four families of RGS: RZ, R4, R7 and R12 families. Many of these proteins have been identified to have effects other than through targetting G proteins. Included here is RGS4 for which a number of pharmacological inhibitors have been described.

RZ family

Other protein targets → Regulators of G protein Signaling (RGS) proteins → RZ family

Overview: The RZ family of RGS proteins is less well characterized than the other families [69]. It consists of RGS17 (also known as RGSZ2), RGS19 (also known as GAIP) and RGS20 (with several splice variants including RGSZ1 and Ret-RGS). All members contain an N-terminal cysteine string motif [49] which is a site of palmitoylation and could serve functions in membrane targeting, protein stability or aid protein-protein interactions [2, 49]. However, the function in the case of RZ family RGS proteins is not yet fully understood. Members of the RZ family of RGS proteins are the only RGS proteins that have selective GTPase activating-protein (GAP) activity for $G\alpha_z$, a function that resulted in the name of the family [27, 59, 105, 110]. However, the members of the RZ family are able to also GAP $G\alpha_{i/o}$ members with varying selectivity.

Nomenclature	regulator of G-protein signaling 17	regulator of G-protein signaling 19	regulator of G-protein signaling 20
Common abbreviation	RGS17	RGS19	RGS20
HGNC, UniProt	*RGS17*, Q9UGC6	*RGS19*, P49795	*RGS20*, O76081

R4 family

Other protein targets → Regulators of G protein Signaling (RGS) proteins → R4 family

Overview: This is the largest family of RGS proteins.

Nomenclature	regulator of G-protein signaling 1	regulator of G-protein signaling 2	regulator of G-protein signaling 3	regulator of G-protein signaling 4
Common abbreviation	RGS1	RGS2	RGS3	RGS4
HGNC, UniProt	*RGS1*, Q08116	*RGS2*, P41220	*RGS3*, P49796	*RGS4*, P49798
Selective inhibitors	–	–	–	RGS4 inhibitor 11b (pIC_{50} 7.8) [102], CCG-50014 (pIC_{50} 7.5) [10, 102], RGS4 inhibitor 13 (pIC_{50} 7.3) [102]

Nomenclature	regulator of G-protein signaling 5	regulator of G-protein signaling 8	regulator of G-protein signaling 13	regulator of G-protein signaling 16	regulator of G-protein signaling 18	regulator of G-protein signaling 21
Common abbreviation	RGS5	RGS8	RGS13	RGS16	RGS18	RGS21
HGNC, UniProt	*RGS5*, O15539	*RGS8*, P57771	*RGS13*, O14921	*RGS16*, O15492	*RGS18*, Q9NS28	*RGS21*, Q2M5E4

R7 family

Other protein targets → Regulators of G protein Signaling (RGS) proteins → R7 family

Overview: This family of RGS proteins shows some selectivity for Gai/o proteins.

Nomenclature	regulator of G-protein signaling 6	regulator of G-protein signaling 7	regulator of G-protein signaling 9	regulator of G-protein signaling 11
Common abbreviation	RGS6	RGS7	RGS9	RGS11
HGNC, UniProt	*RGS6*, P49758	*RGS7*, P49802	*RGS9*, O75916	*RGS11*, O94810

R12 family

Other protein targets → Regulators of G protein Signaling (RGS) proteins → R12 family

Overview: The R12 family consists of RGS10, 12 and 14. RGS12 and 14 are large proteins with additional domains that can participate in protein-protein interactions and other functions. In contrast, RGS10 is a small protein consisting of the RGS domain and small N- and C-termini, similar to members of the R4 family. However, sequence homology of the RGS10 RGS domain clearly places it in the R12 family [45]. The $G\alpha_{i/o}$-Loco (GoLoco) motif in RGS12 and 14 has GDI activity (for Guanine nucleotide Dissociation Inhibitor) towards $G\alpha_{i1}$, $G\alpha_{i2}$ and $G\alpha_{i3}$ [41, 87]. Through this activity RGS12 and RGS14 can inhibit G protein signaling both by accelerating GTP hydrolysis and by preventing G protein activation. Splice variants of RGS12 and RGS14 also contain membrane targeting and protein-protein interaction domains [80, 89, 90].

Nomenclature	regulator of G-protein signaling 10	regulator of G-protein signaling 12	regulator of G-protein signaling 14
Common abbreviation	RGS10	RGS12	RGS14
HGNC, UniProt	*RGS10*, O43665	*RGS12*, O14924	*RGS14*, O43566

Further reading on Regulators of G protein Signaling (RGS) proteins

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Sigma receptors

Other protein targets → Sigma receptors

Overview: Although termed 'receptors', the evidence for coupling through conventional signalling pathways is lacking. Initially described as a subtype of opioid receptors, there is only a modest pharmacological overlap and no structural convergence with the G protein-coupled receptors; the crystal structure of the sigma1 receptor [81] suggests a trimeric structure of a single short transmembrane domain traversing the endoplasmic reticulum membrane, with the bulk of the protein facing the cytosol. A wide range of compounds, ranging from psychoactive agents to antihistamines, have been observed to bind to these sites.

Nomenclature	sigma non-opioid intracellular receptor 1	σ2
HGNC, UniProt	*SIGMAR1*, Q99720	*TMEM97*, Q5BJF2
Agonists	–	1,3-ditolylguanidine [48] – Guinea pig
Selective agonists	PRE-084 [96], (+)-SKF 10.047	–
Antagonists	–	SM 21 (pIC_{50} 7.2) [55]
Selective antagonists	NE-100 (pIC_{50} 8.4) [70], BD-1047 (pIC_{50} 7.4) [60]	–
Labelled ligands	[^{3}H]pentazocine (Agonist)	[^{3}H]-di-o-tolylguanidine (Agonist)
Comments	–	The sigma2 receptor has been reported to be TMEM97 [5], a 4TM protein partner of NPC1, the Niemann-Pick C1 protein, a 13TM cholesterol-binding protein.

Comments: (-)-pentazocine also shows activity at opioid receptors. The sigma2 receptor has recently been reported to be TMEM97 [5], a 4TM protein partner of NPC1, the Niemann-Pick C1 protein, a 13TM cholesterol-binding protein.

Further reading on Sigma receptors

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Tubulins

Other protein targets → Tubulins

Overview: Tubulins are a family of intracellular proteins most commonly associated with microtubules, part of the cytoskeleton. They are exploited for therapeutic gain in cancer chemotherapy as targets for agents derived from a variety of natural products: taxanes, colchicine and vinca alkaloids. These are thought to act primarily through β-tubulin, thereby interfering with the normal processes of tubulin polymer formation and disassembly.

Nomenclature	tubulin alpha 1a	tubulin alpha 4a	tubulin beta class I	tubulin beta 3 class III	tubulin beta 4B class IVb	tubulin beta 8 class VIII
HGNC, UniProt	*TUBA1A*, Q71U36	*TUBA4A*, P68366	*TUBB*, P07437	*TUBB3*, Q13509	*TUBB4B*, P68371	*TUBB8*, Q3ZCM7
Inhibitors	–	–	vinblastine (pIC_{50} 9), eribulin (pIC_{50} 8.2) [67], paclitaxel (Mitotic cell cycle arrest in A431 cells) (pEC_{50} 8.1) [71], colchicine (pIC_{50} 8) [15], cabazitaxel, docetaxel, ixabepilone, vincristine	combretastatin A4 (pIC_{50} 8.2) [24]	–	–

Further reading on Tubulins

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