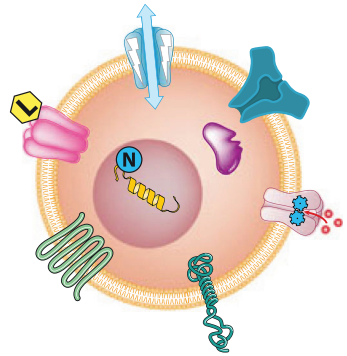
# The Concise Guide to PHARMACOLOGY 2025/26: Introduction and Other Protein Targets

Stephen P. H. Alexander[1], Alasdair J. Gibb[2], Eamonn Kelly[3], Alistair A. Mathie[4], Chloe J. Peach[5], Emma L. Veale[6], John A. Cidlowski[7], Anthony P. Davenport[8], Doriano Fabbro[9], Michael Spedding[10], Jörg Striessnig[11], Jane F. Armstrong[12], O. Peter Buneman[13], Elena Faccenda[12], Simon D. Harding[12], Christopher Southan[12], Jamie A. Davies[12], Katelin E. Ahlers-Dannen[14], Mohammed Alqinyah[15], Thiruma V. Arumugam[16], Christopher Bodle[17], Josephine Buo Dagner[15], Bandana Chakravarti[14], Shreoshi P. Choudhuri[18], Kirk M. Druey[19], Rory A. Fisher[14], Kyle J. Gerber[20], John R. Hepler[21], Shelley B. Hooks[15], Havish S. Kantheti[18], Behirda Karaj[22], Somayeh Layeghi-Ghalehsoukhteh[23], Jae-Kyung Lee[15], Zili Luo[14], Kirill Martemyanov[24], Luke D. Mascarenhas[18], Harrison McNabb[25], Carolina Montañez-Miranda[21], Osita Ogujiofor[18], Hoa Phan[22], David L. Roman[14], Vincent Shaw[26], Benita Sjogren[25], Christopher Sobey[27], Mackenzie M. Spicer[14], Katherine E. Squires[21], Laurie Sutton[28], Menbere Wendimu[15], Thomas Wilkie[18], Keqiang Xie[24], Qian Zhang[25] and Yalda Zolghadri[18]

[1]*Division of Physiology, Pharmacology & Neuroscience, School of Life Sciences, University of Nottingham Medical School, Nottingham, NG7 2UH, UK,* [2]*Research Department of Neuroscience, Physiology and Pharmacology, Division of Biosciences, University College London, Gower Street, London, WC1E 6BT, UK,* [3]*School of Psychology and Neuroscience, University of Bristol, Bristol, BS8 1TD, UK,* [4]*School of Life Sciences, University of Westminster, London, W1W 6UW, UK,* [5]*Division of Physiology, Pharmacology & Neuroscience, School of Life Sciences, Centre of Membrane Proteins and Receptors (COMPARE), University of Nottingham Medical School, Nottingham, NG7 2UH, UK,* [6]*Medway School of Pharmacy, Universities of Kent and Greenwich, Chatham Maritime, Kent, ME4 4TB, UK,* [7]*National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC 27709, USA,* [8]*Clinical Pharmacology Unit, University of Cambridge, Cambridge, CB2 0QQ, UK,* [9]*PIQUR Therapeutics, Basel, 4057, Switzerland,* [10]*Spedding Research Solutions SARL, Le Vésinet 78110, France,* [11]*Pharmacology and Toxicology, Institute of Pharmacy, University of Innsbruck, A-6020, Innsbruck, Austria,* [12]*Institute for Neuroscience and Cardiovascular Research, University of Edinburgh, Edinburgh, EH8 9XD, UK,* [13]*Laboratory for Foundations of Computer Science, School of Informatics, University of Edinburgh, Edinburgh, EH8 9LE, UK,* [14]*University of Iowa, Iowa City, USA,* [15]*University of Georgia, Athens, USA,* [16]*National University of Singapore, Singapore, Singapore,* [17]*University of Pittsburgh, Iowa City, USA,* [18]*University of Texas Southwestern, Dallas, USA,* [19]*National Institute of Health, Bethesda, USA,* [20]*Tetracore Inc., Athens, USA,* [21]*Emory University, Athens, USA,* [22]*University of Michigan, East Lansing, USA,* [23]*Cobel Darou, Shiraz, Iran,* [24]*Scripps Research Institute, Jupiter, USA,* [25]*Purdue University, West Lafayette, USA,* [26]*Michigan State University, East Lansing, USA,* [27]*La Trobe University, Clayton, Australia,* [28]*University of Maryland, Jupiter, USA*




**Abstract**

The Concise Guide to Pharmacology 2025/26 marks the seventh edition in this series of biennial publications in the British Journal of Pharmacology. Presented in landscape format, the guide provides a comparative overview of the pharmacology of drug target families. The concise nature of the Concise Guide refers to the style of presentation, being clear, accessible, and well-structured, rather than the scope of the content, which spans approximately 500 pages. The Concise Guide summarises the key pharmacological properties of around 1900 human drug targets, and nearly 7000 interactions, involving around 4400 ligands. While the content is a substantially condensed version of the more detailed information and links available at the www.guidetopharmacology.org website, the printed guide serves as a permanent, citable, point-in-time record, that remains stable despite ongoing updates to the online database. The full contents of this publication can be found at https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bph.70229.

The Concise Guides provide expert-curated recommendations of 'Gold Standard' selective pharmacological tools, available either commercially or as donations, which enable the identification of individual drug targets or families of drug targets. While the Concise Guide offers a more streamlined overview, more comprehensive information, including detailed pharmacological profiles and links to multiple online databases, is available through the Guide to Pharmacology website. The 2025/26 edition of the Concise Guide is based on material current as of mid-2025, and supersedes all previous editions, including the 2023/24 Guide, and earlier Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR), and as such provides official IUPHAR classification and nomenclature for human drug targets, where applicable.

In addition to this general overview, which includes a section on 'Other protein targets' that fall outside of the main classifications, the Concise Guide focuses on six key areas: G protein-coupled receptors, ion channels, nuclear hormone receptors, catalytic receptors, enzymes and transporters. Each section includes nomenclature guidance, concise summaries, information of the best available pharmacological tools, key references, and suggestions for further reading.

**Table of contents**

## Introduction to the Concise Guide 2025/26

A goal of the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR) is to provide clarity and consistency in the nomenclature of drug targets. This has been communicated in large part through numerous reviews, many of which are cited in this seventh edition of the Concise Guides of Pharmacology. A more regularly updated resource is the https://www.guidetopharmacology.org website. About 500 researchers worldwide contribute to over 100 NC-IUPHAR subcommittees. The Editors of the Concise Guide have compiled the individual records, in concert with the team of Edinburgh-based database curators, drawing on the expert knowledge of these latter subcommittees, as well as prominent researchers in topic areas lacking subcommittees. In total, over 380 authors from 185 research entities, located in over 150 towns and cities in 27 countries, contributed to one or more of the articles included in the Concise Guide.

The Concise Guide is divided into seven sections, which comprise pharmacological targets of similar structure/function. These are G protein-coupled receptors, ion channels (including ligand-gated, voltage-gated and other ion channels), catalytic receptors, nuclear hormone receptors, enzymes, transporters and other protein targets which don't fall into the other groups. We recommend that any citations to information in the Concise Guide are presented in the following format:

Alexander SPH et al. (2025). The Concise Guide to PHARMACOLOGY 2025/26: Introduction and other targets. *Br J Pharmacol* 182: S1–S23.

The tables included in the Concise Guide provide the current recommended nomenclature for the family of targets listed, often previously published in the journal Pharmacological Reviews. The tables contain 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, which contains over 3 000 human target proteins. A common reason for not including target proteins would be a lack of pharmacological information. 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. Pharmacological profiles described focus on human proteins although data from other species are indicated where the human protein pharmacology is limited. 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 intended as an initial resource, with each family of drug targets having links to additional reviews and resources for greater depth and information. Structural data focus primarily on human gene products, wherever possible, with links to HGNC gene nomenclature and UniProt IDs.

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 learning.

## Acknowledgements

We are very grateful to the International Union of Basic and Clinical Pharmacology, the British Pharmacological Society, the Società Italiana di Farmacologia and the Deutsche Gesellschaft für Experimentelle und Klinische Pharmakologie und Toxikologie for financial support for the IUPHAR/BPS Guide to Pharmacology, and to the University of Edinburgh, who host the https://www.guidetopharmacology.org website. We gratefully acknowledge previous funding from IUPHAR and the Wellcome Trust (099156/Z/12/Z) who supported the initiation and expansion of the database.

A major influence on the development of the database was Tony Harmar (1951-2014), who worked with a passion to establish the database curators to ensure a suitably validated dataset.

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 2025/26 and the online database https://www.guidetopharmacology.org.

## Conflict of interest

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

**Family structure**

- Abscisic acid receptor complex
- S8 Adiponectin receptors
- S8 Anti-infective targets
  - Antimalarial targets
    - Aminoacyl-tRNA synthetases
    - Chromatin modifying enzymes (*Plasmodium* spp.)
    - Coenzyme A synthesis pathway enzymes
    - Cyclic nucleotide turnover/signalling (*Plasmodium spp.*)
    - Folate biosynthesis enzymes
    - Haemoglobin degradation pathway enzymes
    - Isoprenoid biosynthesis enzymes
    - Kinases (*Plasmodium* spp.)
    - Nucleoside synthesis and metabolism (*Plasmodium* spp.)
    - Mitochondrial function/Mitochondrial electron flow
    - Other antimalarial targets
    - Peptidases and proteinases (*Plasmodium* spp.)
    - Ribosomal factors (*Plasmodium* spp.)
    - Transporters (*Plasmodium* spp.)
  - Viral protein targets
    - S9 Coronavirus (CoV) proteins
    - Other viral proteins
- S10 Bacterial protein targets
- S11 Aryl hydrocarbon receptor
- Autophagy receptors
- β-catenin destruction complex proteins
- B-cell lymphoma 2 (Bcl-2) protein family
- Bromodomain-containing proteins
- S11 Non-enzymatic BRD containing proteins
- Butyrophilin and butyrophilin-like proteins
- S12 CD molecules
- Chaperone proteins
  - Lipid binding chaperones
- Chitinase-like proteins
- Circadian clock proteins
- Claudins
- COMMD proteins
- Complement system regulators
- Cytolytic pore-forming proteins
- DNA and RNA reader proteins
  - Acylated lysine reader proteins
  - S13 Methyllysine reader proteins
  - N6-methyladenosine readers
- EF-hand domain containing proteins
- S13 Fatty acid-binding proteins
- Gasdermins (GSDM)
- Guanine nucleotide exchange factors (GEFs)
  - Rho GEFs
- Heat shock proteins
- High Mobility Group (HMG) proteins
- Human endogenous retrovirus (HERV) proteins
- Hypoxia-inducible factors
- Immune checkpoint proteins
  - Other immune checkpoint proteins
- Immunoglobulin C1-set domain-containing proteins
- Immunoglobulin C2-set domain-containing proteins
- Immunoglobulin like domain containing proteins
- Immunoglobulins
- Inhibitors of apoptosis (IAP) protein family
- Kelch-like proteins
- Kinesins
- Leucine-rich repeat proteins
- Lipid transfer/lipopolysaccharide binding proteins
- Lymphocyte antigens
- Mitochondrial-associated proteins
- Myosin binding proteins
- Neuropilins and Plexins
- Non-catalytic pattern recognition receptors
  - Absent in melanoma (AIM)-like receptors (ALRs)
  - C-type lectin-like receptors (CLRs)
  - Other pattern recognition receptors
- S15 Notch receptors
- Nuclear export proteins
- Pentraxins
  - Serum pentraxins
- S16 Regulators of G protein Signaling (RGS) proteins
  - S16 RZ family
  - S16 R4 family
  - S17 R7 family
  - S18 R12 family
- Repulsive guidance molecules
- Reticulons and associated proteins
- Ribosomal factors
- Scavenger receptors
- S18 Sialic acid binding Ig like lectins (SIGLECS)
  - S19 CD33-related SIGLECs
  - S20 SIGLECs (conserved)
- S20 Sigma receptors
- Signal regulatory proteins
- Sortilin family proteins
- Synuclein proteins
- Tetraspanins
- Transcription factors
  - Basic helix-loop-helix (BHLH) TFs
  - Basic leucine zipper domain TFs
  - BTB (POZ) domain containing TFs
  - Forkhead box TFs
  - NF-kappa B TF proteins
  - STAT transcription factors
  - T-box transcription factors
  - TEAD (transcriptional enhanced associate domain) transcription factors
  - Zinc finger TFs
- Transcription factor regulators
  - Inhibitors of NF-kappaB (IκB) family proteins
- S21 Transthyretin
- S22 Tubulins
- Tumour-associated antigens
- WD repeat-containing proteins
- Plasmodium multidrug resistance family

# Adiponectin receptors

Other protein targets → Adiponectin receptors

**Overview**: Adiponectin receptors (**provisional nomenclature**, ENSFM00500000270960) respond to the 30kDa 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 [87]. 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 [159]. 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 [141].

| 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 [61].

### 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]

# Anti-infective targets

Other protein targets → Anti-infective targets

**Overview**: This is a collection of anti-infective ligand-target interactions.

# Coronavirus (CoV) proteins

Other protein targets → Anti-infective targets → Viral protein targets → Coronavirus (CoV) proteins

**Overview**: Coronaviruses are large, often spherical, enveloped, single-stranded positive-sense RNA viruses, ranging in size from 80-220 nm. Their genomes and protein structures are highly conserved. Three coronaviruses have emerged over the last 20 years as serious human pathogens: SARS-CoV was identified as the causative agent in an outbreak in 2002-2003, Middle East respiratory syndrome (MERS) CoV emerged in 2012 and the novel coronavirus SARS-CoV-2 emerged in 2019-2020. SARS-CoV-2 is the virus responsible for the infectious disease termed COVID-19 (WHO Technical Guidance 2020).

| | | |
|---|---|---|
| Nomenclature | CoV 3C-like (main) protease | CoV Non-structural protein 15 |
| EC number | 3.4.22.69 (SARS-CoV-2) | – |
| Inhibitors | nirmatrelvir ($pK_i$ 9.6) [103] – SARS-CoV-2, bofutrelvir ($pIC_{50}$ 7.3) [30] – SARS-CoV-2 | tipiracil [68] – SARS-CoV-2 |
| Comments | The Mpro enzyme (also known as nsp5 or 3CL protease) cleaves the two polyproteins encoded by the SARS-CoV-2 genome (pp1a and pp1ab) into a range of non-structural proteins (nsp1-11 from pp1a; nsp1-16 from pp1ab). As these component proteins play crucial roles in viral replication, Mpro is considered to be a strong molecular target for drug development. Small molecule Mpro inhibitors would be predicted to reduce viral replication [56, 75, 106]. | Nsp15 (NendoU) is a uridylate-specific endoribonuclease that is essential during the coronavirus lifecycle. The search for inhibitors of SARS-CoV-2 nsp15 that may have antiviral action is ongoing. Two allosteric inhibitors have been reported, FUZS-5 (12200) and LIZA-7 (12199). The docking positions of these compounds within nsp15 have been determined by X-ray crystallography [42]. |

| | | |
|---|---|---|
| Nomenclature | CoV Papain-like protease | CoV RNA-dependent RNA polymerase |
| EC number | 3.4.22.46 (SARS-CoV-2) | – |
| Inhibitors | XR8-23 ($pIC_{50}$ 6.4) [124] – SARS-CoV-2, GRL-0617 ($pIC_{50}$ 5.6–5.6) [33, 101] – SARS-CoV-2 | remdesivir [44] – SARS-CoV-2, remdesivir [44] – SARS-CoV |
| Comments | PL-pro is a domain within coronavirus Nsp3. Its proteolytic activity cleaves three sites in the viral replicase polyprotein (recognition consensus sequence LXGG↓XX) to release the three non-structural proteins Nsp1, Nsp2, and Nsp3 [52]. It has additional non-proteolytic functions as part of the multicomponent replicase-transcriptase complex [125]. | The conservation of RdRP catalytic domain between different RNA viruses endows inhibitors that were designed against other viral pathogens with activity against the SARS coronaviruses. Viral RdRP is the molecular target of nucleotide-based broad-spectrum antiviral compounds like remdesivir, tenofovir and ribavirin [44, 150, 165]. |

| | |
|---|---|
| Nomenclature | CoV Spike glycoprotein |
| Inhibitors | EK-1-C4 (Binding) [158] – SARS-CoV-2 |
| Antibodies | regdanvimab (Binding) ($pK_d$ 10.6) [67] – SARS-CoV-2, casirivimab (Binding) ($pIC_{50}$ 10.2) [50] – SARS-CoV-2 |
| Comments | The spike protein on the surface of CoV particles is central for viral infection of host cells (by binding to ACE2). It is the molecular target of a wide range of clinically approved monoclonal antibodies that reduce infection. At any point in time, the efficacy of these therapeutics is heavily dependent upon spike mutations in the circulating CoV variants. Spike is also the antigen that's exploited for raising anti-CoV immunity by inoculation with either mRNA and/or adenovirus vaccines that induce spike protein expression. |

**Comments**: SARS-CoV-2 causes fewer fatalities than either of its predecessors MERS-CoV and SARS-CoV, but it is far more transmissible [105].

**Further reading on Coronavirus (CoV) proteins**

Alexander SPH *et al.* (2020) A rational roadmap for SARS-CoV-2/COVID-19 pharmacotherapeutic research and development: IUPHAR Review 29. *Br J Pharmacol* **177**: 4942-4966 [PMID:32358833]

Kang C *et al.* (2025) An Evolving Landscape of Small Molecules Targeting SARS-CoV-2: What Are We Awaiting Beyond 3CLpro Inhibitors? *J Med Chem* **68**: 9836-9839 [PMID:40353752]

Kronenberger T *et al.* (2023) COVID-19 therapeutics: Small-molecule drug development targeting SARS-CoV-2 main protease. *Drug Discov Today* **28**: 103579 [PMID:37028502]

Li G *et al.* (2023) Therapeutic strategies for COVID-19: progress and lessons learned. *Nat Rev Drug Discov***22**: 449-475 [PMID:37076602]

Pang X *et al.* (2023) The research progress of SARS-CoV-2 main protease inhibitors from 2020 to 2022. *Eur J Med Chem* **257**: 115491 [PMID:37244162]

# Bacterial protein targets

Other protein targets → Anti-infective targets → Bacterial protein targets

**Overview**: Antimicrobial resistance is recognized by the World Health Organization (WHO) as a major global health threat, and it is estimated that drug-resistant infections contribute to almost 5 million deaths a year [11]. The rapid spread of bacterial strains resistant to available antibacterial medicines is of particular concern, including the 'ESKAPE' pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) that are responsible for many nosocomial infections [110, 140].
Antibacterial compounds act on essential bacterial molecular pathways, resulting in inhibition of growth or death of the microorganisms. These mechanisms of action include: altered DNA replication and structure, cell membrane integrity, and inhibition of cell wall peptidoglycan synthesis, nucleic acid precursor synthesis and protein synthesis.

**Complexes**

| | |
|---|---|
| Nomenclature | DNA gyrase |
| Subunits | DNA gyrase subunit A, DNA gyrase subunit B |
| Comments | DNA gyrase is a type II DNA topoisomerase [38] and one of two enzymes of this subclass found in bacteria, the other being DNA topoisomerase 4. DNA gyrase introduces negative supercoils in closed circular double-stranded DNA in an ATP-dependent manner. This enzyme is the clinically-validated target for a number of antibacterial drug classes, including the aminocoumarins such as novobiocin and fluoroquinolones such as moxifloxacin, levofloxacin, ciprofloxacin and ofloxacin. |

**Subunits**

| | | |
|---|---|---|
| Nomenclature | DNA gyrase subunit A | DNA gyrase subunit B |
| Inhibitors | ofloxacin ($pIC_{50}$ 5.5) [15] – Escherichia coli | novobiocin (Competitive) ($pIC_{50}$ 7.1) [8] – Escherichia coli |
| Comments | DNA gyrase subunit A is comprised of an N-terminal domain (59-64 kDa) involved in DNA cleavage and ligation, and a C-terminal domain (33 kDa) involved in DNA-protein interactions [108]. | DNA gyrase subunit B is comprised of an N-terminal domain (43 kDa) containing the ATPase activity, and a C-terminal domain (47 kDa) involved in interactions with subunit A and DNA. |

| | |
|---|---|
| Nomenclature | polyketide synthase Pks13 |
| Selective inhibitors | TAM16 ($pIC_{50}$ 6.7) [1] – Mycobacterium tuberculosis |

# Aryl hydrocarbon receptor

Other protein targets → Aryl hydrocarbon receptor

**Overview**: The aryl hydrocarbon receptor, highly expressed in the liver and barrier organs, is resident in the cytoplasm bound to the chaperone heat shock protein hsp90. Upon agonist activation, the ligand:aryl hydrocarbon receptor complex migrates to the nucleus and binds the aryl hydrocarbon receptor nuclear translocator (ARNT, P27540, also known as HIF1β). The complex regulates transcription of selected genes through interaction with xenobiotic response elements (XRE). Among the genes regulated by the AHR/ARNT complex are cytochrome P450s, particularly CYP1A1, and the period circadian protein homolog 1 (PER1, O15534). The aryl hydrocarbon receptor is also capable of non-genomic signalling.

| | |
|---|---|
| Nomenclature | Aryl hydrocarbon receptor |
| HGNC, UniProt | *AHR*, P35869 |
| Agonists | indolo[3,2-b]carbazole [19] – Mouse, tapinarof [132], indole-3-carbinol [19] – Mouse, TCDD |
| Antagonists | ezutromid ($pK_d$ 7.3) [155] |

**Further reading on Aryl hydrocarbon receptor**


Bock KW. (2019) Aryl hydrocarbon receptor (AHR): From selected human target genes and crosstalk with transcription factors to multiple AHR functions. *Biochem Pharmacol* **168**: 65-70 [PMID:31228464]

Bock KW. (2020) Aryl hydrocarbon receptor (AHR) functions: Balancing opposing processes including inflammatory reactions. *Biochem Pharmacol* **178**: 114093 [PMID:32535108]

Roman ÁC *et al.* (2018) The aryl hydrocarbon receptor in the crossroad of signalling networks with therapeutic value. *Pharmacol Ther* **185**: 50-63 [PMID:29258844]

Rothhammer V *et al.* (2019) The aryl hydrocarbon receptor: an environmental sensor integrating immune responses in health and disease. *Nat Rev Immunol* **19**: 184-197 [PMID:30718831]

Shi Y *et al.* (2020) The aryl hydrocarbon receptor: An environmental effector in the pathogenesis of fibrosis. *Pharmacol Res* **160**: 105180 [PMID:32877693]

Sládeková L *et al.* (2023) Ligands and agonists of the aryl hydrocarbon receptor AhR: Facts and myths. *Biochem Pharmacol* **213**: 115626 [PMID:37247746]


# 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 lysine acetyltransferase | polybromo 1 | SWI/SNF related BAF chromatin remodeling complex subunit ATPase 4 |
|---|---|---|---|---|---|
| Common abbreviation | – | – | – | – | SMARCA4 |
| HGNC, UniProt | *BAZ2A*, Q9UIF9 | *BAZ2B*, Q9UIF8 | *CREBBP*, Q92793 | *PBRM1*, Q86U86 | *SMARCA4*, P51532 |
| Inhibitors | – | – | inobrodib ($pK_d$ 8.8) [152] | GNE-064 ($pIC_{50}$ 7.7) [142] | GNE-064 ($pIC_{50}$ 8) [142] |
| Selective inhibitors | GSK2801 ($pK_d$ 6.6) [121] | GSK2801 (Binding) ($pK_d$ 6.9) [121] | I-CBP112 ($pK_d$ 6.8) [122] | PFI-3 (Binding) ($pK_d$ 7.3) [123] | PFI-3 (Binding) ($pK_d$ 7.1) [123] |

**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 *et al.* (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 *et al.* (2018) Targeting the cancer epigenome: synergistic therapy with bromodomain inhibitors. *Drug Discov Today* **23**: 76-89 [PMID:28943305]
Spriano F *et al.* (2020) Targeting BET bromodomain proteins in cancer: The example of lymphomas. *Pharmacol Ther* **215**: 107631 [PMID:32693114]
Tang P *et al.* (2021) Targeting Bromodomain and Extraterminal Proteins for Drug Discovery: From Current Progress to Technological Development. *J Med Chem* **64**: 2419-2435 [PMID:33616410]

# 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) |
|---|---|---|---|---|
| HGNC, UniProt | *CD2*, P06729 | *CD3E*, P07766 | *CD6*, P30203 | *MS4A1*, P11836 |
| Antibodies | – | catumaxomab (Binding) [81], muromonab-CD3 (Binding) [43], otelixizumab (Binding) [22] | – | ofatumumab (Binding) (p$K_d$ 9.9) [82], rituximab (Binding) (p$K_d$ 8.5) [135], ibritumomab tiuxetan (Binding), obinutuzumab (Binding) [5, 109], tositumomab (Binding) |

| 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) | – |
| Antibodies | alemtuzumab (Binding) [40, 126] | – | – | ipilimumab (Binding) (p$K_d$ >9) [48], tremelimumab (Binding) (p$K_d$ 8.9) [51] | pembrolizumab (Binding) (p$K_d$~10) [25], nivolumab (Binding) (p$K_d$ 9.1) [49, 71, 73] | – |

**Comments**: The endogenous ligands for human PD-1 are programmed cell death 1 ligand 1 (*CD274*, Q9NZQ7) (PD-L1 *aka* CD274) 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 [70]. 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**

Bewersdorf JP *et al*. (2021) Immune checkpoint inhibition in myeloid malignancies: Moving beyond the PD-1/PD-L1 and CTLA-4 pathways. *Blood Rev* **45**: 100709 [PMID:32487480]
Chi Z *et al*. (2021) Transcriptional and epigenetic regulation of PD-1 expression. *Cell Mol Life Sci* **78**: 3239-3246 [PMID:33738533]
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]
Huang MY *et al*. (2021) Combination therapy with PD-1/PD-L1 blockade in non-small cell lung cancer: strategies and mechanisms. *Pharmacol Ther* **219**: 107694 [PMID:32980443]
Peng Z *et al*. (2023) PD-1/PD-L1 immune checkpoint blockade in ovarian cancer: Dilemmas and opportunities. *Drug Discov Today* **28**: 103666 [PMID:37302543]
Vosoughi T *et al*. (2019) CD markers variations in chronic lymphocytic leukemia: New insights into prognosis. *J Cell Physiol* **234**: 19420-19439 [PMID:31049558]

# Methyllysine reader proteins

Other protein targets → DNA and RNA reader proteins → 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 [64] |

**Further reading on Methyllysine reader proteins**

Barghout SH *et al*. (2022) Chemical biology and pharmacology of histone lysine methylation inhibitors. *Biochim Biophys Acta Gene Regul Mech* **1865**: 194840 [PMID:35753676]
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**: 2873-2883 [PMID:31123776]
Li J *et al*. (2019) Understanding histone H3 lysine 36 methylation and its deregulation in disease. *Cell Mol Life Sci* **76**: 2899-2916 [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 [120]) 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 [111] | stearic acid > palmitic acid,oleic acid > linoleic acid > arachidonic acid, α-linolenic acid [111] | stearic acid, oleic acid, palmitic acid > linoleic acid, α-linolenic acid, arachidonic acid [111] | oleic acid, palmitic acid, stearic acid, linoleic acid > α-linolenic acid, arachidonic acid [111] | – |
| Inhibitors | fenofibrate ($pK_i$ 7.6) [26] – Rat, fenofibric acid ($pK_i$ 6.5) [26] – Rat, HTS01037 ($pK_i$ 5.1) [55] – Mouse | – | – | – | compound 13 ($pK_i$ 8.7) [139] |
| Selective inhibitors | – | – | – | HM50316 ($pK_i$ >9) [83] | – |
| Comments | A broader substrate specificity than other FABPs, binding two fatty acids per protein [144]. | Crystal structure of the rat FABP2 [115]. | Crystal structure of the human FABP3 [160]. | – | Crystal structure of the human FABP5 [57]. |

| 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 [166]. | Crystal structure of the human FABP7 [13]. | *In silico* modelling suggests that PMP2/FABP8 can bind both fatty acids and cholesterol [88]. | – | – |

| 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 [112] | – | – | – | – |
| Inhibitors | – | – | – | A1120 ($pIC_{50}$ 7.8) [151] | – | – |

| 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 [29] | tretinoin > alitretinoinstearic acid > palmitic acid, oleic acid, linoleic acid, α-linolenic acid, arachidonic acid [112] | – |

**Comments**: Although not tested at all FABPs, BMS309403 exhibits high affinity for FABP4 (pIC50 ~8.8) compared to FABP3 or FABP5 (pIC50 <6.6) [34, 139]. HTS01037 is reported to interfere with FABP4 action [55]. Ibuprofen displays some selectivity for FABP4 ($pIC_{50}$ 5.5) relative to FABP3 ($pIC_{50}$ 3.5) and FABP5 ($pIC_{50}$ 3.8) [86]. Fenofibric acid displays some selectivity for FABP5 ($pIC_{50}$ 5.5) relative to FABP3 ($pIC_{50}$ 4.5) and FABP4 ($pIC_{50}$ 4.6) [86]. 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]

Nguyen HC *et al.* (2020) Role of the Fatty Acid Binding Proteins in Cardiovascular Diseases: A Systematic Review. *J Clin Med* **9**: [PMID:33105856]

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 Notch signalling pathway is crucial for cell fate decisions during embryogenesis and in fully developed organisms. Notch receptors (4 genes in humans) are single pass transmembrane proteins that interact with membrane-bound endogenous peptide ligands from the Delta/Serrate/LAG-2 (DSL) family. Receptor-ligand engagement can occur in *trans* (between adjacent cells) or *cis* (on the same cell). Notch-ligand complexes formed in *trans* are endocytosed by the ligand-expressing cell, followed by protease-mediated cleavages that free the intracellular fragment of Notch (NICD) to translocate to the nucleus where it participates in the assembly of transcriptional activation complexes. *Cis*-formed complexes are inhibitory in function and act to restrict the spread of Notch activity.

| Nomenclature | notch receptor 1 | notch receptor 2 | notch receptor 3 | notch receptor 4 |
|---|---|---|---|---|
| HGNC, UniProt | *NOTCH1*, P46531 | *NOTCH2*, Q04721 | *NOTCH3*, Q9UM47 | *NOTCH4*, Q99466 |
| Inhibitors | IMR-1 (Binding) (p$K_d$ 5) [12] | – | – | – |
| Endogenous agonists | Jagged2 (*JAG2*) [84] | – | – | – |
| Antibodies | brontictuzumab (Binding) (p$K_d$ 8.4) [45] | tarextumab (Binding) (p$K_d$ >10) [46] | tarextumab (Binding) (p$K_d$ 9.9) [46] | – |
| Comments | Various types of activating and inactivating *NOTCH1* mutations have been reported to be associated with human diseases, for example: aortic valve disease [37, 91], Adams-Oliver syndrome 5 [136], T-cell acute lymphoblastic leukemia (T-ALL) [153], chronic lymphocytic leukemia (CLL) [107] and head and neck squamous cell carcinoma [3, 137]. | – | – | Notch receptor 4 is a potential therapeutic molecular target for triple-negative breast cancer [78, 95]. |

**Comments**: Aberrant Notch signalling is implicated in a number of human hereditary and acquired diseases, including cancers [77, 98, 130, 146], and there is intense pharmaceutical activity being directed towards achieving clinically effective Notch pathway inhibition [32, 92].

**Further reading on Notch receptors**

Fabbro D *et al.* (2020) Notch Inhibition in Cancer: Challenges and Opportunities. *Chimia (Aarau)* **74**: 779-783 [PMID:33115560]

Moore G *et al.* (2020) Top Notch Targeting Strategies in Cancer: A Detailed Overview of Recent Insights and Current Perspectives. *Cells* **9**: [PMID:32575680]

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**: Regulator of G protein Signaling, or RGS, proteins serve an important regulatory role in signaling mediated by G protein-coupled receptors (GPCRs). They all share a common RGS domain that directly interacts with active, GTP-bound Gα subunits of heterotrimeric G proteins. RGS proteins stabilize the transition state for GTP hydrolysis on Gα and thus induce a conformational change in the Gα subunit that accelerates GTP hydrolysis, thereby effectively turning off signaling cascades mediated by GPCRs. This GTPase accelerating protein (GAP) activity is the canonical mechanism of action for RGS proteins, although many also possess additional functions and domains. RGS proteins are divided into four families, R4, R7, R12 and RZ based on sequence homology, domain structure as well as specificity towards Gα subunits. For reviews on RGS proteins and their potential as therapeutic targets, see *e.g.* [7, 58, 97, 114, 127, 128, 129, 161, 164].

# 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. 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 [80] which is a site of palmitoylation and could serve functions in membrane targeting, protein stability or aid protein-protein interactions [4, 80]. 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 GAP activity for $G\alpha_z$, a function that resulted in the name of the family [41, 89, 147, 156]. 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**: The R4 family of RGS proteins is the largest family of RGS proteins with 10 members. Each of the R4 family members contain only small N- and C-termini apart from the RGS domain. The N-terminal amphipathic helix present in most R4 family members serves an important function in membrane association and can directly bind phospholipids. In contrast to the RGS domain, which is well conserved among members of the R4 family of RGS proteins, the N- and C-termini vary, enabling specificity of non-GAP functions. Despite the non-complex structure of these proteins, several R4 family RGS proteins have been shown to possess additional functions apart from acting as GAPs at activated Gα subunits [18, 116].

| 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) [145], CCG-50014 ($pIC_{50}$ 7.5) [20, 145], CCG-203920 ($pIC_{50}$ 7.3) [145] |

| 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 |

**Further reading on R4 family**

Xie Z *et al.* (2016) R4 Regulator of G Protein Signaling (RGS) Proteins in Inflammation and Immunity. *AAPS J* **18**: 294-304 [PMID:26597290]

# R7 family

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

**Overview**: The members of the R7 family of RGS proteins [9] are more complex structures than the R4 family and are closely related to the *C. elegans* homologues EGL-10 and EAT-16 that were identified in the early stage of RGS protein research [47, 72]. Apart from the RGS domain, several additional domains are present in these proteins that mediate protein-protein interactions, sub-cellular localization and protein stability. All R7 family members form obligatory dimers with Gβ5 through the G-γ like (GGL) domain and the disheveled-EGL10-Pleckstrin homology (DEP) domain [131]. The DEP and DEP helical extension domain interact with R7 binding protein (R7BP) or RGS9 anchoring protein (R9AP; in retina) that serves as a plasma membrane anchoring mechanism [54, 65].

| 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 consisting 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, the sequence homology the RGS10 RGS domain clearly places it in the R12 family [76]. 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 $G\alpha_{i3}$ [69, 127]. 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 [118, 133, 134].

| | | | |
|---|---|---|---|
| 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 |
| Inhibitors | – | Z55627844 ($pIC_{50}$ 4.7) [2] | Z55627844 ($pIC_{50}$ 5.4) [2] |

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


Alqinyah M *et al.* (2018) Regulating the regulators: Epigenetic, transcriptional, and post-translational regulation of RGS proteins. *Cell Signal* **42**: 77-87 [PMID:29042285]

Fuentes N *et al.* (2021) RGS proteins, GRKs, and beta-arrestins modulate G protein-mediated signaling pathways in asthma. *Pharmacol Ther* **223**: 107818 [PMID:33600853]

Neubig RR *et al.* (2002) Regulators of G-protein signalling as new central nervous system drug targets. *Nat Rev Drug Discov* **1**: 187-97 [PMID:12120503]

Sethakorn N *et al.* (2010) Non-canonical functions of RGS proteins. *Cell Signal* **22**: 1274-81 [PMID:20363320]

Sjögren B. (2017) The evolution of regulators of G protein signalling proteins as drug targets - 20 years in the making: IUPHAR Review 21. *Br J Pharmacol* **174**: 427-437 [PMID:28098342]

Sjögren B *et al.* (2010) Thinking outside of the "RGS box": new approaches to therapeutic targeting of regulators of G protein signaling. *Mol Pharmacol* **78**: 550-7 [PMID:20664002]


# Sialic acid binding Ig like lectins (SIGLECS)

Other protein targets → Sialic acid binding Ig like lectins (SIGLECS)

**Overview**: SIGLECs are a family of type I transmembrane proteins (15 in humans) that are predominantly expressed by hemopoietic cells and they play critical roles in immune cell signalling and discrimination of self and nonself. The receptors differ in their specificity for sialic acid containing ligands. SIGLECs act as checkpoints in immune responses in human diseases including cancer, asthma, allergy, neurodegeneration, and autoimmune diseases and are being investigated as therapeutic targets [21, 31, 39].

# CD33-related SIGLECs

Other protein targets → Sialic acid binding Ig like lectins (SIGLECS) → CD33-related SIGLECs

**Overview**: CD33-related SIGLECs (3, 5, 6, 7, 8, 9, 10, 11, 12, 14, and 16) are more broadly expressed in myeloid and lymphoid tissues and cells than the conserved SIGLECs. The structurally and functionally related SIGLECs 7 and 9 from this subfamily [163] have been implicated in myeloid cell-mediated modulation in cancer [14, 16, 62, 113, 143, 148], making these proteins novel therapeutic targets to enhance antitumour immunity (cancer immunotherapy).

| Nomenclature | CD33 | sialic acid binding Ig like lectin 6 | sialic acid binding Ig like lectin 8 | sialic acid binding Ig like lectin 10 |
|---|---|---|---|---|
| Common abbreviation | SIGLEC3 | – | SIGLEC8 | SIGLEC10 |
| HGNC, UniProt | *CD33*, P20138 | *SIGLEC6*, O43699 | *SIGLEC8*, Q9NYZ4 | *SIGLEC10*, Q96LC7 |
| Selective agonists | – | – | – | MK-7110 [162] |
| Antibodies | lintuzumab (Binding) ($pK_d$~10) [24], gemtuzumab ozogamicin (Binding) [17] | – | – | – |
| Comments | – | SIGLEC6 binds sialyl-TN glycans and leptin. It was considered as a therapeutic target for the treatment of eosinophil- and mast cell-mediated inflammation [74, 99, 117]. However, development of the anti-SIGLEC6 monoclonal antibody AK006 was discontinued at phase 1 due to lack of efficacy in patients with moderate-to-severe chronic spontaneous urticaria. | – | – |

**Further reading on CD33-related SIGLECs**

Boelaars K *et al.* (2024) Targeting myeloid cells for cancer immunotherapy: Siglec-7/9/10/15 and their ligands. *Trends Cancer* **10**: 230-241 [PMID:38160071]

# SIGLECs (conserved)

Other protein targets → Sialic acid binding Ig like lectins (SIGLECS) → SIGLECs (conserved)

**Overview**: This subfamily of 4 SIGLECs share conserved sequence homology. SIGLEC15 from this group has been implicated in myeloid cell-mediated modulation in cancer making it a novel therapeutic target to enhance antitumour immunity (cancer immunotherapy) [36, 60, 93, 149, 157].

| | | |
|---|---|---|
| Nomenclature | CD22 | sialic acid binding Ig like lectin 15 |
| Common abbreviation | SIGLEC2 | SIGLEC15 |
| HGNC, UniProt | *CD22*, P20273 | *SIGLEC15*, Q6ZMC9 |
| Comments | – | An anti-SIGLEC15 monoclonal antibody has been used experimentally to establish the therapeutic anti-cancer potential of targeting this receptor on tumour-associated macrophages [53, 148]. |

# 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 [119] 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 [79] – Guinea pig |
| Selective agonists | PRE-084 [138], (+)-SKF 10.047 | – |
| Antagonists | – | SM 21 ($pIC_{50}$ 7.2) [85] |
| Selective antagonists | NE-100 ($pIC_{50}$ 8.4) [100], BD-1047 ($pIC_{50}$ 7.4) [90] | – |
| Labelled ligands | [$^3$H]pentazocine (Agonist)` | [$^3$H]-di-o-tolylguanidine (Agonist) |
| Comments | – | The sigma2 receptor has been reported to be TMEM97 [6], 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 [6], a 4TM protein partner of NPC1, the Niemann-Pick C1 protein, a 13TM cholesterol-binding protein.

**Further reading on Sigma receptors**

Chu UB *et al*. (2016) Biochemical Pharmacology of the Sigma-1 Receptor. *Mol Pharmacol* **89**: 142-53 [PMID:26560551]

Herrando-Grabulosa M *et al*. (2021) Sigma 1 receptor as a therapeutic target for amyotrophic lateral sclerosis. *Br J Pharmacol* **178**: 1336-1352 [PMID:32761823]

Sambo DO *et al*. (2018) The sigma-1 receptor as a regulator of dopamine neurotransmission: A potential therapeutic target for methamphetamine addiction. *Pharmacol Ther* **186**: 152-167 [PMID:29360540]

Schmidt HR *et al*. (2019) The Molecular Function of σ Receptors: Past, Present, and Future. *Trends Pharmacol Sci* **40**: 636-654 [PMID:31387763]

Su TP *et al*. (2016) The Sigma-1 Receptor as a Pluripotent Modulator in Living Systems. *Trends Pharmacol Sci* **37**: 262-278 [PMID:26869505]

Vavers E *et al*. (2019) Allosteric Modulators of Sigma-1 Receptor: A Review. *Front Pharmacol* **10**: 223 [PMID:30941035]

# Transthyretin

Other protein targets → Transthyretin

**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 [104]. These amyloidogenic mutants are linked to the development of pathological amyloidoses, including familial amyloid polyneuropathy (FAP) [10, 28], familial amyloid cardiomyopathy (FAC) [63], amyloidotic vitreous opacities, carpal tunnel syndrome [94] and others. In old age, non-mutated TTR can also form pathological amyloid fibrils [154]. Pharmacological intervention to reduce or prevent TTR dissociation is being pursued as a therapeutic 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 |
| Ligands | tafamidis (Binding) (p$K_d$ 8.7) [23] |

**Comments**: Excess production and accumulation of TTR causes hereditary transthyretin-mediated amyloidosis. Two novel drugs are now approved to combat this disease: inotersen (Tegsedi®) [66] and patisiran (Onpattro®) [59]. Both of these drugs act to reduce the amount of TTR protein (both wild type and mutant) produced in the liver, but by slightly different mechanisms. Inotersen is an antisense oligonucleotide inhibitor of TTR synthesis, whereas patisiran is a double-stranded small interfering RNA (which targets a conserved sequence in the 3′ UTR of mutant and wild-type TTR mRNA). Inotersen is administered subcutaneously, and patisiran is delivered by intravenous infusion in a lipid nanoparticle formulation.

**Further reading on Transthyretin**

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]

Bezerra F *et al*. (2020) Modulation of the Mechanisms Driving Transthyretin Amyloidosis. *Front Mol Neurosci***13**: 592644 [PMID:33362465]

Dohrn MF *et al*. (2021) Targeting transthyretin - Mechanism-based treatment approaches and future perspectives in hereditary amyloidosis. *J Neurochem* **156**: 802-818 [PMID:33155274]

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

Griffin JM *et al*. (2021) Transthyretin cardiac amyloidosis: A treatable form of heart failure with a preserved ejection fraction. *Trends Cardiovasc Med* **31**: 59-66 [PMID:31889610]

# 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) [96], paclitaxel (Mitotic cell cycle arrest in A431 cells) ($pEC_{50}$ 8.1) [102], colchicine ($pIC_{50}$ 8) [27], cabazitaxel, docetaxel, ixabepilone, vincristine | combretastatin A4 ($pIC_{50}$ 8.2) [35] | – | – |

### Further reading on Tubulins


Arnst KE *et al.* (2019) Current advances of tubulin inhibitors as dual acting small molecules for cancer therapy. *Med Res Rev* **39**: 1398-1426 [PMID:30746734]

Boiarska Z *et al.* (2021) Microtubule-targeting agents and neurodegeneration. *Drug Discov Today* **26**: 604-615 [PMID:33279455]

Eshun-Wilson L *et al.* (2019) Effects of α-tubulin acetylation on microtubule structure and stability. *Proc Natl Acad Sci USA* **116**: 10366-10371 [PMID:31072936]

Magiera MM *et al.* (2018) Tubulin Posttranslational Modifications and Emerging Links to Human Disease. *Cell* **173**: 1323-1327 [PMID:29856952]

Penna LS *et al.* (2017) Anti-mitotic agents: Are they emerging molecules for cancer treatment? *Pharmacol Ther* **173**: 67-82 [PMID:28174095]

Zhang YF *et al.* (2023) Tubulin degradation: Principles, agents, and applications. *Bioorg Chem* **139**: 106684 [PMID:37356337]

# References


1. Aggarwal A *et al.* (2017) [28669536]
2. Agogo-Mawuli PS *et al.* (2025) [40667230]
3. Agrawal N *et al.* (2011) [21798897]
4. Ajit SK *et al.* (2007) [17126529]
5. Alduaij W *et al.* (2011) [21378274]
6. Alon A *et al.* (2017) [28559337]
7. Alqinyah M *et al.* (2018) [29042285]
8. Alt S *et al.* (2011) [21693461]
9. Anderson GR *et al.* (2009) [19521673]
10. Andrade C. (1952) [12978172]
11. Antimicrobial Resistance Collaborators. (2022) [35065702]
12. Astudillo L *et al.* (2016) [27197169]
13. Balendiran GK *et al.* (2000) [10854433]
14. Barkal AA *et al.* (2019) [31367043]
15. Barnard FM *et al.* (2001) [11408214]
16. Beatson R *et al.* (2016) [27595232]
17. Bernstein ID. (2000) [10720144]
18. Bernstein LS *et al.* (2000) [10764749]
19. Bjeldanes LF *et al.* (1991) [1658785]
20. Blazer LL *et al.* (2011) [21329361]
21. Boelaars K *et al.* (2024) [38160071]
22. Bolt S *et al.* (1993) [8436176]
23. Bulawa CE *et al.* (2012) [22645360]
24. Caron PC *et al.* (1992) [1458463]
25. Carven GJ *et al.* (2010) Patent number: US20100266617.
26. Chuang S *et al.* (2008) [18533710]
27. Cifuentes M *et al.* (2006) [16504507]
28. Coelho T. (1996) [8894411]
29. Crabb JW *et al.* (1998) [9541407]
30. Dai W *et al.* (2020) [32321856]
31. Duan S *et al.* (2020) [31986070]
32. Fabbro D *et al.* (2020) [33115560]
33. Freitas BT *et al.* (2020) [32428392]
34. Furuhashi M *et al.* (2007) [17554340]
35. Gangjee A *et al.* (2013) [23895532]
36. Gao HY *et al.* (2024) [38169162]
37. Garg V *et al.* (2005) [16025100]
38. Gellert M *et al.* (1976) [186775]
39. Gibbons A. (2020) [32732402]
40. Ginaldi L *et al.* (1998) [9593475]
41. Glick JL *et al.* (1998) [9748279]
42. Godoy AS *et al.* (2023) [37115000]
43. Goldstein G. (1987) [3105134]
44. Gordon CJ *et al.* (2020) [32284326]
45. Gurney Al *et al.* (2014) Patent number: US20140011271A1.
46. Gurney AL *et al.* (2012) Patent number: US8226943 B2.
47. Hajdu-Cronin YM *et al.* (1999) [10421631]
48. Halk EL *et al.* (2001) Patent number: WO2001014424.
49. Hall RD *et al.* (2013) [23302904]
50. Hansen J *et al.* (2020) [32540901]
51. Hanson DC *et al.* (2004) Patent number: US6682736 B1.
52. Harcourt BH *et al.* (2004) [15564471]
53. He F *et al.* (2021) [34988324]
54. Hepler JR. (2005) [16046666]
55. Hertzel AV *et al.* (2009) [19754198]
56. Hilgenfeld R. (2014) [25039866]
57. Hohoff C *et al.* (1999) [10493790]
58. Hollinger S *et al.* (2002) [12223533]
59. Hoy SM. (2018) [30251172]
60. Huang Z *et al.* (2024) [38072971]
61. Hug C *et al.* (2004) [15210937]
62. Ibarlucea-Benitez I *et al.* (2021) [34155121]
63. Jacobson DR *et al.* (1997) [9017939]
64. James LI *et al.* (2013) [23292653]
65. Jayaraman M *et al.* (2009) [19042037]
66. Keam SJ. (2018) [30120737]
67. Kim C *et al.* (2021) [33436577]
68. Kim Y *et al.* (2021) [33564093]
69. Kimple RJ *et al.* (2001) [11387333]
70. Klement JD *et al.* (2023) [36917954]
71. Kline J *et al.* (2010) [21154117]
72. Koelle MR *et al.* (1996) [8548815]
73. Korman AJ *et al.* (2006) Patent number: WO2006121168.
74. Korver W *et al.* (2024) [38186079]
75. La Monica G *et al.* (2022) [36169610]
76. Lee JK *et al.* (2015) [26123306]
77. Lefort K *et al.* (2007) [17344417]
78. Lehmann BD *et al.* (2015) [25993190]
79. Lever JR *et al.* (2006) [16463398]
80. Linder ME *et al.* (2007) [17183362]
81. Linke R *et al.* (2010) [20190561]
82. Liu Q. (2013) Patent number: WO2013007052.
83. Liu X *et al.* (2011) [21481589]
84. Luo B *et al.* (1997) [9315665]
85. Mach RH *et al.* (1999) [10096443]
86. Machbub B *et al.* (1988) [24248795]
87. Maeda K *et al.* (1996) [8619847]
88. Majava V *et al.* (2010) [20421974]
89. Mao H *et al.* (2004) [15096504]
90. Matsumoto RR *et al.* (1995) [8566098]
91. McBride KL *et al.* (2008) [18593716]
92. Moore G *et al.* (2020) [32575680]
93. Moreira RS *et al.* (2023) [37843557]
94. Murakami K *et al.* (1999) [10403814]
95. Nagamatsu I *et al.* (2014) [24403446]
96. Narayan S *et al.* (2011) [21324687]
97. Neubig RR *et al.* (2002) [12120503]
98. Ntziachristos P *et al.* (2014) [24651013]
99. O'Sullivan JA *et al.* (2023) [37413923]
100. Okuyama S *et al.* (1993) [7901723]
101. Osipiuk J *et al.* (2021) [33531496]
102. Ouyang X *et al.* (2006) [16377187]
103. Owen DR *et al.* (2021) [34726479]
104. Penchala SC *et al.* (2013) [23716704]
105. Petersen E *et al.* (2020) [32628905]
106. Pillaiyar T *et al.* (2016) [26878082]
107. Puente XS *et al.* (2011) [21642962]
108. Reece RJ *et al.* (1989) [2555327]
109. Reslan L *et al.* (2014) [23537278]
110. Rice LB. (2008) [18419525]
111. Richieri GV *et al.* (1994) [7929039]
112. Richieri GV *et al.* (2000) [10852718]
113. Rodriguez E *et al.* (2021) [33627655]
114. Ross EM *et al.* (2000) [10966476]
115. Sacchettini JC *et al.* (1989) [2671390]
116. Saitoh O *et al.* (2001) [11087736]
117. Schanin J *et al.* (2022) [36369358]
118. Schiff ML *et al.* (2000) [11130074]
119. Schmidt HR *et al.* (2016) [27042935]
120. Schroeder F *et al.* (2008) [17882463]
121. SGC. thesgc.org. Accessed on 03/03/2015. Modified on 04/08/2023.
122. SGC. thesgc.org. Accessed on 04/08/2023.
123. SGC. thesgc.org. Accessed on 10/11/2014. Modified on 04/08/2023.
124. Shen Z *et al.* (2022) [34665619]
125. Shin D *et al.* (2020) [32726803]
126. Shitara K *et al.* (2011) Patent number: US7923538 B2.
127. Siderovski DP *et al.* (2005) [15951850]
128. Sjögren B. (2011) [21907914]
129. Sjögren B *et al.* (2010) [20691960]
130. Sjölund J *et al.* (2008) [18079963]
131. Slepak VZ. (2009) [20374716]
132. Smith SH *et al.* (2017) [28595996]
133. Snow BE *et al.* (2002) [11771424]
134. Snow BE *et al.* (1998) [9651375]
135. Stein R *et al.* (2004) [15102696]
136. Stittrich AB *et al.* (2014) [25132448]
137. Stransky N *et al.* (2011) [21798893]
138. Su TP *et al.* (1991) [1658302]
139. Sulsky R *et al.* (2007) [17502136]
140. Tacconelli E *et al.* (2018) [29276051]
141. Tanabe H *et al.* (2015) [25855295]
142. Taylor AM *et al.* (2022) [35930799]
143. Theruvath J *et al.* (2022) [35027753]
144. Thompson J *et al.* (1997) [9054409]
145. Turner EM *et al.* (2012) [22368763]
146. Vilimas T *et al.* (2007) [17173050]
147. Wang J *et al.* (1998) [9748280]
148. Wang J *et al.* (2019) [30833750]
149. Wang J *et al.* (2023) [37325664]
150. Wang Y *et al.* (2021) [32633831]
151. Wang Y *et al.* (2014) [24835984]
152. Welti J *et al.* (2021) [33431496]
153. Weng AP *et al.* (2004) [15472075]
154. Westermark P *et al.* (1981) [7016817]
155. Wilkinson IVL *et al.* (2020) [31755636]
156. Wong YH *et al.* (1992) [1347957]
157. Wu Q *et al.* (2023) [37955317]
158. Xia S *et al.* (2020) [32231345]
159. Yamauchi T *et al.* (2003) [12802337]
160. Young AC *et al.* (1994) [7922029]
161. Zhang P *et al.* (2011) [21778436]
162. Zheng X *et al.* (2013) Patent number: US20130231464A1.
163. Zheng Y *et al.* (2020) [32322597]
164. Zhong H *et al.* (2001) [11356902]
165. Zhu W *et al.* (2020) [32660307]
166. Zwicker BL *et al.* (2013) [23603607]