THE CONCISE GUIDE TO PHARMACOLOGY 2015/16: Overview

Stephen PH Alexander1, Eamonn Kelly2, Neil Marrion2, John A Peters3, Helen E Benson4, Elena Faccenda4, Adam J Pawson4, Joanna L Sharman4, Christopher Southan4, O Peter Buneman5, William A Catterall6, John A Cidlowski7, Anthony P Davenport8, Doriano Fabbro9, Grace Fan10, John C McGrath11, Michael Spedding12, Jamie A Davies4 and CGTP Collaborators

1 School of Biomedical Sciences, University of Nottingham Medical School, Nottingham, NG7 2UH, UK
2 School of Physiology and Pharmacology, University of Bristol, Bristol, BS8 1TD, UK
3 Neuroscience Division, Medical Education Institute, Ninewells Hospital and Medical School, University of Dundee, Dundee, DD1 9SY, UK
4 Centre for Integrative Physiology, University of Edinburgh, Edinburgh, EH8 9XD, UK
5 Laboratory for Foundations of Computer Science, School of Informatics, University of Edinburgh, Edinburgh, EH8 9LE, United Kingdom
6 Department of Pharmacology, University of Washington, Seattle, WA 98195-7280, USA
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 The Agnes Irwin School, Rosemont, Pennsylvania, USA
11 School of Life Sciences, University of Glasgow, Glasgow, G12 8QQ, UK
12 Spedding Research Solutions SARL, Le Vésinet 78110, France

Abstract

The Concise Guide to PHARMACOLOGY 2015/16 provides concise overviews of the key properties of over 1750 human drug targets with their pharmacology, plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. The full contents can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.13347/full. This compilation of the major pharmacological targets is divided into eight areas of focus: G protein-coupled receptors, ligand-gated ion channels, voltage-gated ion channels, other 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 Concise Guide is published in landscape format in order to facilitate comparison of related targets. It is a condensed version of material contemporary to late 2015, which is presented in greater detail and constantly updated on the website www.guidetopharmacology.org, superseding data presented in the previous Guides to Receptors & Channels and the Concise Guide to PHARMACOLOGY 2013/14. It is produced in conjunction with NC-IUPHAR and provides the official IUPHAR classification and nomenclature for human drug targets, where appropriate. It consolidates information previously curated and displayed separately in IUPHAR-DB and GRAC and provides a permanent, citable, point-in-time record that will survive database updates.

Table of contents

5729 Overview
5734 Other Protein Targets
5735 Adiponectin receptors
5735 Blood coagulation components
5735 Non-enzymatic BRD containing proteins
5736 Carrier proteins
5737 CD molecules
5738 Methyllysine reader proteins
5739 Cytokines and growth factors
5739 Fatty acid-binding proteins
5741 Sigma receptors
5742 Tubulins
5744 G protein-coupled receptors
5746 Orphan and other 7TM receptors
5746 Class A Orphans
5746 Class C Orphans
5746 Taste 1 receptors
5747 Taste 2 receptors
5750 Other 7TM proteins
5751 S-Hydroxytryptamine receptors
5754 Acetylcholine receptors (muscarinic)
5754 Adenosine receptors
5756 Adhesion Class GPCRs
5756 Adrenoceptors
5757 Angiotensin receptors
5757 Apelin receptor

Searchable database: http://www.guidetopharmacology.org/index.jsp


Searchable database: http://www.guidetopharmacology.org/index.jsp

Overview 5730

5777 Bile acid receptor
5778 Bombesin receptors
5779 Bradykinin receptors
5781 Calcitonin receptors
5783 Calcium-sensing receptors
5784 Cannabinoid receptors
5785 Chemerin receptor
5786 Chemokine receptors
5789 Cholecystokinin receptors
5791 Cholecyctokinin receptors
5792 Class Frizzled GPCRs
5793 Complement peptide receptors
5795 Corticotropin-releasing factor receptors
5796 Dopamine receptors
5798 Endothelin receptors
5799 G protein-coupled estrogen receptor
5800 Formylpeptide receptors
5801 Free fatty acid receptors
5803 GABAB receptors
5804 Galanin receptors
5805 Ghrelin receptor
5806 Glucagon receptor family
5809 Glycoprotein hormone receptors
5810 GPR119
5811 GPR18, GPR55 and GPR119
5812 Histamine receptors
5813 Hydroxycarboxylic acid receptors
5815 Kisspeptin receptor
5816 Leukotriene receptors
5818 Lyrophospholipid (LPA) receptors
5819 Lyrophospholipid (SIP) receptors
5820 Melanin-concentrating hormone receptors
5821 Melanocortin receptors
5822 Melatonin receptors
5823 Metabotropic glutamate receptors
5826 Metulin receptor
5827 Neuropeptide F receptors
5828 Neuropeptide F/neuropeptide AF receptors
5829 Neuropeptide S receptor
5830 Neuropeptide W/neuropeptide B receptors
5831 Neutropins receptors
5832 Neurotensin receptors
5833 Opioid receptors
5835 Orexin receptors
5836 Oxoglutarate receptor
5837 Parathyroid hormone receptors
5838 Platelet-activating factor receptor
5840 Prokineticin receptors
5841 Prolactin-releasing peptide receptor
5842 Prostanoid receptors
5843 Proteinase-activated receptors
5844 QRFP receptors
5845 Relaxin family peptide receptors
5846 Somatostatin receptors
5850 Succinate receptor
5851 Tachykinin receptors
5852 Thyrotropin-releasing hormone receptors
5853 Trace amine receptor
5854 Urotensin receptor
5855 Vasopressin and oxytocin receptors
5856 VIP and PACAP receptors
5870 Ligand-Gated ion Channels
5871 S-HT3 receptors
5873 Acid-sensing (proton-gated) ion channels (ASICs)
5875 Epithelial sodium channels (ENaC)
5877 GABAA receptors
5882 Glycine receptors
5885 Ionotropic glutamate receptors
5889 IP3 receptor
5890 Nicotinic acetylcholine receptors
5896 P2X receptors
5898 Byranoline receptor
5899 ZAC
5904 Voltage-gated ion channels
5905 CatSper and Two-Pore channels
5907 Cyclic nucleotide-regulated channels
5909 Potassium channels
5910 Calcium-activated potassium channels
5912 Inwardly-rectifying potassium channels
5915 Two-P potassium channels
5917 Voltage-gated potassium channels
5920 Transient Receptor Potential channels
5934 Voltage-gated calcium channels
5936 Voltage-gated proton channel
5937 Voltage-gated sodium channels
5942 Other ion channels
5943 Aquaporins
5944 Chloride channels
5945 CIC family
5947 CFTR
5948 Calcium activated chloride channel
5949 Maxi chloride channel
5950 Volume regulated chloride channels
5952 Connexins and Pannexins
5954 Sodium leak channel, non-selective
5956 Nuclear hormone receptors
5958 1A. Thyroid hormone receptors
5959 1B. Retinoid acid receptors
5960 1C. Peroxisome proliferator-activated receptors
5961 1D. Rev-Erb receptors
5962 1F. Retinoic acid-related orphans
5963 1H. Liver X receptor-like receptors
5964 1I. Vitamin D receptor-like receptors
5965 2A. Hepatocyte nuclear factor-4 receptors
5966 2B. Retinoid X receptors
5967 2C. Testicular receptors
5968 2E. Tailless-like receptors
5969 2F. COUP-TF-like receptors
5970 2G. Estrogen-related receptors
5971 4A. Nerve growth factor IB-like receptors
5972 5A. Fushi tarazu F1-like receptors
5973 6A. Germ cell nuclear factor receptors
5974 8B. DAX-like receptors
5975 8D. Steroid hormone receptors
5976 8F. 3. 3-Ketosteroid receptors
5979 Catalytic receptors
5981 Cytokine receptor family
5982 IL-2 receptor family
5983 IL-3 receptor family
5984 IL-6 receptor family
5985 IL-12 receptor family
5986 Interferon receptor family
5987 IL-10 receptor family
5988 Immunoglobulin-like family of IL-1 receptors
5989 IL-17 receptor family
5990 GDNF receptor family
5991 Integrins
5992 Natriuretic peptide receptor family
5993 Pattern recognition receptors
5994 Toll-like receptor family
5995 NOD-like receptor family
5996 Receptor serine/threonine kinase (RSTK) family
5997 Type I receptor serine/threonine kinases
5998 Type II receptor serine/threonine kinases
5999 Type III receptor serine/threonine kinases
6000 Type IV receptors
6001 RSTK functional heteromers
6002 Receptor tyrosine kinases
6004 Type I RTKs: ErbB (epidermal growth factor) receptor family
6005 Type II RTKs: Insulin receptor family
6006 Type III RTKs: PDGFR, CSFR, KIT, FLT3 receptor family
6007 Type IV RTKs: VEGF (vascular endothelial growth factor)
receptor family
6008 Type V RTKs: FGFR (fibroblast growth factor) receptor family
6008 Type VI RTKs: PTK7/CCK4
6009 Type VII RTKs: Neurotrophin receptor/Tbr family
6010 Type VIII RTKs: ROR family
6010 Type IX RTKs: MuSK
6010 Type X RTKs: HGF (hepatocyte growth factor) receptor family
6011 Type XI RTKs: TAM (TYRO3-, AXL- and MER-TK) receptor family
6012 Type XII RTKs: Tie family of angiopoietin receptors
6012 Type XIII RTKs: Ephrin receptor family
6013 Type XIV RTKs: RET
6014 Type XV RTKs: RYK
6015 Type XVII RTKs: LMR family
6016 Type XIX RTKs: Leukocyte tyrosine kinase (LTK) receptor family
6016 Type XX RTKs: STYK1
6017 Receptor tyrosine phosphatases (RTP)
6018 Tumour necrosis factor (TNF) receptor family

6024 Enzymes
6028 Protein kinases (EC 2.7.x.x)
6028 Rho kinase
6029 Protein kinase C (PKC)
6029 Alpha subfamily
6029 Delta subfamily
6030 Era subfamily
6030 FRA subfamily
6031 CDK4 subfamily
6031 GSK subfamily
6032 Polo-like kinase (PLK) family
6032 STE7 family
6033 Abi family
6033 Ack family
6034 Janus kinase (Jak) family
6034 Src family
6035 Tec family
6035 RAF family
6036 Peptidases and proteinases
6036 A1: Pepsin
6037 A22: Presenilin
6037 C14: Caspase
6037 M1: Aminopeptidase N
6038 M2: Angiotensin-converting (ACE and ACE2)
6038 M10: Matrix metallopeptidase
6039 M12: Astacin/Adamalysin
6039 M28: Aminopeptidase Y
6040 M19: Membrane dipeptidase
6040 S1: Chymotrypsin
6041 T1: Trypsin
6042 S8: Subtilisin
6042 S9: Prolyl oligopeptidase
6042 Acetylcholine hydrolases
6044 Adenosine turnover
6045 Amino acid hydrolases
6046 L-Ariginase turnover
6047 Arginase
6047 Arginine:glycine amionotransferase
6047 Dimethylarginine dimethylaminohydrolases
6048 Nitric oxide synthases
6048 Carboxylases and dehydrogenases
6049 Carboxylases
6050 Decarboxylases
6052 Catecholamine turnover
6053 Serine palmitoyltransferase
6053 Ceramide turnover
6053 Serine palmitoyltransferase
6056 Ceramide synthase
6057 Sphingolipid Δ4-desaturase
6058 Sphingomyelin synthase
6058 Sphingomyelin phosphodiesterase
6059 Neutral sphingomyelinas coupling factors
6059 Ceramide glucosyltransferase
6060 Acid ceramidase
6060 Neutral ceramidases
6060 Alkaline ceramidases
6061 Ceramide kinase
6061 Alkaline ceramidases
6062 2.1.1-Protein arginine N-methyltransferases
6062 3.5.1.-Histone deacetylases (HDACs)
6063 Cyclic nucleotide turnover
6063 Adenylyl cyclases
6064 Soluble guanylyl cyclase
6065 Exchange protein activated by cyclic AMP (Epac)
6066 Phosphodiesterases, 3',5'-cyclic nucleotide
6067 Cystochrome P450
6069 CYP3 family
6069 CYP2 family
6069 CYP1 family
6070 CYP2 family
6070 CYP3 family
6071 CYP4 family
6070 CYP5, CYP7 and CYP8 families
6072 CYP11, CYP17, CYP19, CYP20 and CYP21 families
6073 CYP24, CYP26 and CYP27 families
6074 CYP39, CYP46 and CYP51 families
6075 Endocannabinoid turnover
6076 Eicosanoid turnover
6077 Cyclooxygenase
6077 Prostaglandin synthases
6077 Prostaglandin synthases
6078 Prostaglandin D2 synthase
6079 Prostaglandin E2 synthase
6079 Lipoxygenases
6080 Leukotriene C4 synthase
6080 Leukotriene D4 synthase
6080 Leukotriene E4 synthase
6081 GABA transporter
6082 Glycerophospholipid turnover
6082 Phosphatidylglycerol transferase
6082 Phosphatidylglycerol transferase
6083 1-phosphatidylinositol 4-kinase family
6083 Phosphatidylglycerol transferase
6084 Phosphatidylglycerol transferase
6085 1-phosphatidylinositol 4,5-bisphosphate 3-kinase family
6085 1-phosphatidylinositol 4,5-bisphosphate 5-kinase family
6085 Phosphatidylglycerol transferase
6085 Type I PIP kinases (1-phosphatidylinositol-4-phosphate 5-kinase family)
6086 Type II PIP kinases (1-phosphatidylinositol-5-phosphate 4-kinase family)
6087 Phosphoinositide-specific phospholipase C
6088 Phospholipase A2
6089 Phosphatidylcholine-specific phospholipase D
6090 Lipid phosphate phosphatases
6091 Haem oxygenase
6092 Hydrogen sulphide synthesis
6093 Hydroxases
6093 Inositol phosphate turnover
6094 Inositol 1,4,5-trisphosphate 3-kinases
6094 Inositol 1,4,5-trisphosphate 5-kinases
6094 Inositol monophosphatase
6095 Lanosterol biosynthesis pathway
6097 Nucleotide synthesis and metabolism
6099 Sphingosine 1-phosphate turnover
6100 Sphingosine kinase
6100 Sphingosine 1-phosphate phosphatase
6101 Sphingosine 1-phosphate lyase
6101 Thyroid hormone turnover
6101 Thyroid hormone turnover
6103 1:14.11.29 2-oxoglutarate oxidoreductases
6103 2.4.2.30 poly(ADP-ribose)polymerase
6104 2.5.1.58 Protein farnesytransferase
6104 3.3.3.15 Peptidyl arginine deiminases (PADI)
6104 Ras subfamily
6105 4.2.1.1 Carboxylate dehydratases
6105 5.99.1.2 DNA Topoisomerases
6110 Transporters
6110 ATP-binding cassette transporter family
6111 ATP-binding cassette transporter family
6111 ATP-binding cassette transporter family
6111 ABCB subfamily
6112 ABCB subfamily
6112 ABCG subfamily
6117 ABCD subfamily of peroxisomal ABC transporters
6118 ABCG subfamily
6119 F-type and V-type ATPases
6119 F-type ATPase
6120 V-type ATPase
6120 V-type ATPase
Overview

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 (http://www.guidetopharmacology.org/). This database is supported by the British Pharmacological Society (BPS), the International Union of Basic and Clinical Pharmacology (IUPHAR), the Wellcome Trust and the University of Edinburgh. 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). 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 2015/16, is the latest snapshot of the database in print form, following on from the Concise Guide to PHARMACOLOGY 2013/14. It contains data drawn from the online database as a rapid overview of the major pharmacological targets. Thus, there are fewer targets presented in the Concise Guide (1761) compared to the online database (2761, as of August 2015). The priority for inclusion in the Concise Guide is the presence of quantitative pharmacological data. This means that often orphan family members are not presented in the Concise Guide (1761) compared to the online database (2761, as of August 2015). The priority for inclusion in the Concise Guide is the presence of quantitative pharmacological data. This means that often orphan family members are not presented in the

Searchable database: http://www.guidetopharmacology.org/index.jsp

Overview 5732
The Concise Guide to PHARMACOLOGY 2015/16 is divided into nine sections, which comprise pharmacological targets of similar structure/function. These are G protein-coupled receptors, ligand-gated ion channels, voltage-gated ion channels, other ion channels, catalytic receptors, nuclear hormone receptors, enzymes, transporters and other protein targets. A new aspect of the Concise Guide 2015/16 is that each of these sections contains a complete listing of the families available for inspection on the online database, identifying those families reported in the Concise Guide by their page numbers. 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:


A dedication

This Edition of the Concise Guide to PHARMACOLOGY is dedicated to Tony Harmar (1951-2014). Tony was a friend and colleague, who was involved with IUPHAR for over 15 years and worked on the IUPHAR database for over a decade at Edinburgh, working hard to establish the curators as a team of highly informed and informative individuals imbued with Tony’s passion and dogged determination to focus on high-quality data input, ensuring high-quality data output. With time and the resources of the BPS and Wellcome Trust, combined with the expertise of the NC-IUPHAR committee members mentioned above, Tony established the online database at [http://www.guidetopharmacology.org/](http://www.guidetopharmacology.org/) as the exceptional resource it is today.

Acknowledgements

We are extremely grateful for the financial contributions from the British Pharmacological Society, the International Union of Basic and Clinical Pharmacology, the Wellcome Trust (099156/Z/12/Z), which support the website and the University of Edinburgh, who host the guidetopharmacology.org website. 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 2015/16 and the online database www.GuideToPHARMACOLOGY.org

Conflict of interest

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

© 2015 The Authors. British Journal of Pharmacology published by John Wiley & Sons Ltd on behalf of The British Pharmacological Society. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
Other Protein Targets

Family structure

- Adiponectin receptors
- B-cell lymphoma 2 (Bcl-2) protein family
- Bromodomain-containing proteins
- Non-enzymatic BRD containing proteins
- Carrier proteins
- CD molecules
- Chromatin-interacting transcriptional repressors
- Methyllysine reader proteins
- Circadian clock proteins
- Cytokines and growth factors
- EF-hand domain containing
- Fatty acid-binding proteins
- Heat shock proteins
- Immunoglobulins
- Inhibitors of apoptosis (IAP) protein family
- Kelch-like proteins
- Kinesins
- Mitochondrial-associated proteins
- Notch receptors
- Pentatans
- Regulators of G protein signaling (RGS) proteins
- R4 family
- R7 family
- R12 family
- Ribosomal factors
- Reticulons
- Sigma receptors
- Tubulins
- Tumour-associated proteins
- WD repeat-containing proteins
- R4 family
- R7 family
- R12 family
- Ribosomal factors
- Reticulons
- Sigma receptors
- Tubulins
- Tumour-associated proteins
- WD repeat-containing proteins

Adiponectin receptors

Overview: Adiponectin receptors (provisional nomenclature, ENSFM0000000270960) 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 [49]. 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 [86]. Signalling through these receptors appears to avoid G proteins. Adiponectin receptors appear rather to stimulate protein phosphorylation via AMP-activated protein kinase and MAP kinase pathways [86], possibly through the protein partner APPL1 (adaptor protein, phosphotyrosine interaction, PH domain and leucine zipper containing 1, Q9UKG1 [52]). The adiponectin receptors are a class of proteins (along with membrane progesterin receptors), which contain seven sequences of aliphatic amino acids reminiscent of GPCRs, but which are structurally and functionally distinct from that class of receptor.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Adipo1 receptor</th>
<th>Adipo2 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>ADIPO1, Q96A54</td>
<td>ADIPO2, Q86V24</td>
</tr>
</tbody>
</table>

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 [35].

Searchable database: http://www.guidetopharmacology.org/index.jsp
Further Reading


Blood coagulation components

Other protein targets → Blood coagulation components

Overview: Coagulation as a pathophysiologial 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 targeted by agents in current clinical usage.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>coagulation factor V (proaccelerin, labile factor)</th>
<th>coagulation factor VIII, procoagulant component</th>
<th>serpin peptidase inhibitor, clade C (antithrombin), member 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>F5, P12259</td>
<td>F8, P00451</td>
<td>SERPINC1, P01008</td>
</tr>
<tr>
<td>Selective activators</td>
<td>–</td>
<td>–</td>
<td>heparin (pKd 7.8) [25], fondaparinux (pKd 7.5) [65], dalteparin [34], danaparoid [15, 58], enoxaparin [17], tinzaparin [19]</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>drotrecogin alfa (Inhibition) [40, 41]</td>
<td>drotrecogin alfa (Inhibition) [40, 41]</td>
<td>–</td>
</tr>
</tbody>
</table>

Further Reading


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.

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

Carrier proteins

Overview: 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 [66]. These amyloidogenic mutants are linked to the development of pathological amyloidoses, including familial amyloid polyneuropathy (FAP) [1, 13], familial amyloid cardiomyopathy (FAC) [37], amyloidotic vitreous opacities, carpal tunnel syndrome [57] and others. In old age, non-mutated TTR can also form pathological amyloid fibrils [85]. 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.

Further Reading

## 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 is not possible in the Guide to PHARMACOLOGY; listed herein are selected members of the family targeted for therapeutic gain.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>CD2</th>
<th>CD3e molecule, epsilon (CD3-TCR complex)</th>
<th>CD20 (membrane-spanning 4-domains, subfamily A, member 1)</th>
<th>CD33</th>
<th>CD52</th>
<th>CD80</th>
<th>CD86</th>
<th>cytotoxic T-lymphocyte-associated protein 4 (CD152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common abbreviation</td>
<td>CD2, P06729</td>
<td>CD3E, P07766</td>
<td>MS4A1, P11836</td>
<td>CD33, P20138</td>
<td>CD52, P31358</td>
<td>CD80, P33681</td>
<td>CD86, P42081</td>
<td>CTLA-4 (CD152)</td>
</tr>
<tr>
<td>HGNC, UniProt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CTLA4, P16410</td>
</tr>
<tr>
<td>Selective inhibitors</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>alectacept (Inhibition) [56, 89]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Antibodies</td>
<td>–</td>
<td>catumaxomab (Binding) [46], muromonab-CD3 (Binding) [24], otezolizumab (Binding) [7]</td>
<td>ofatumumab (Binding) (pKd 9.9) [47], rituximab (Binding) (pKd 8.5) [78], ibritumomab tiuxetan (Binding), obinutuzumab (Binding) [2, 68], tositumomab (Binding)</td>
<td>lintuzumab (Binding) (pKd ~10) [8], gemtuzumab ozogamicin (Binding) [6]</td>
<td>alemtuzumab (Binding) [22]</td>
<td>–</td>
<td>–</td>
<td>ipilimumab (Binding) (pKd &gt; 9) [28], tremelimumab (Binding) (pKd 8.9) [30]</td>
</tr>
</tbody>
</table>

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

Nomenclature: programmed cell death 1 (CD279)

Common abbreviation: PD-1

HGNC, UniProt: PDCD1, Q15116

Antibodies: pembrolizumab (Binding) (pKd ~10) [9], nivolumab (Binding) (pKd 9.1) [29, 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. Many types of cancer cells evolve mechanisms to evade control and elimination by the immune system. Such mechanisms can include inhibition of so-called ‘immune checkpoints’, which would normally be involved in the maintenance of immune homeostasis. An increasingly important area of clinical oncology research is the development of new agents which impede these evasion techniques, thereby switching immune vigilance back on, and effecting immune destruction of cancer cells. Three molecular targets of checkpoint inhibitors which are being extensively pursued are cytotoxic T-lymphocyte antigen 4 (CTLA4), programmed cell death 1 (PD-1), and programmed cell death ligand 1 (PD-L1). Using antibody-based therapies targeting these pathways, clinical responses have been reported in various tumour types, including melanoma, renal cell carcinoma [64] and non-small cell lung cancer [39, 51]. pembrolizumab is the first-in-class, anti-PD-1 antibody to be approved by the US FDA, with ongoing clinical trials for nivolumab (e.g. NCT01673867, NCT01721746) and pidilizumab (NCT02077959, NCT01952769).

Methyllysine reader proteins

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

Nomenclature: l(3)mbt-like 3 (Drosophila)

HGNC, UniProt: L3MBTL3, Q96JM7

Selective agonists: UNC1215 (pKd 6.9) [38]

Further Reading


Cytokines and growth factors

Overview: cytokines and growth factors are a group of small proteins released from cells, which act upon the same cell or neighbouring cells, often with a role in immune regulation and/or proliferation. Listed herein are examples of cytokines and growth factors targeted for therapeutic benefit.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>interleukin 1, beta</th>
<th>tumor necrosis factor</th>
<th>vascular endothelial growth factor A</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>IL1B, P01584</td>
<td>TNF, P01375</td>
<td>VEGFA, P15692</td>
</tr>
<tr>
<td>Antagonists</td>
<td>–</td>
<td>etanercept (Inhibition) [18, 23]</td>
<td>aflibercept (Inhibition) [10, 11, 82]</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>–</td>
<td>pegaptanib (Inhibition) [26, 61]</td>
<td>pegaptanib (Inhibition) [26, 61]</td>
</tr>
<tr>
<td>Antibodies</td>
<td>gevokizumab (Binding) (pK shut 12.5) [36, 53, 71], canakinumab (Binding) (pK shut 10.5) [27], rilonacept (Binding) [32, 55]</td>
<td>golimumab (Inhibition) (pIC 50 10.7) [77], infliximab (Inhibition) (pK shut 8.7) [44], adalimumab (Inhibition) (pK shut &gt;8) [75], certolizumab pegol (Inhibition) [60]</td>
<td>ranibizumab (Inhibition) (pK shut ~9.8) [3], bevacizumab (Inhibition) (pIC 50 8–8.3) [3]</td>
</tr>
</tbody>
</table>

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 [76]) or for interaction with metabolic enzymes. Although sequence homology is limited, crystallographic studies suggest conserved 3D structures across the group of binding proteins.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>fatty acid binding protein 1, liver</th>
<th>fatty acid binding protein 2, intestinal</th>
<th>fatty acid binding protein 3, muscle and heart</th>
<th>fatty acid binding protein 4, adipocyte</th>
<th>fatty acid binding protein 5 (psoriasis-associated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>FABP1, P07148</td>
<td>FABP2, P12104</td>
<td>FABP3, P05413</td>
<td>FABP4, P15090</td>
<td>FABP5, Q01469</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>stearic acid, oleic acid &gt; palmitic acid, linoleic acid &gt; arachidonic acid, α-linolenic acid [69]</td>
<td>stearic acid &gt; palmitic acid, oleic acid &gt; linoleic acid &gt; arachidonic acid, α-linolenic acid [69]</td>
<td>stearic acid, oleic acid, palmitic acid &gt; linoleic acid, α-linolenic acid, arachidonic acid [69]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Comments</td>
<td>A broader substrate specificity than other FABPs, binding two fatty acids per protein [83]</td>
<td>Crystal structure of the rat FABP2 [74]</td>
<td>Crystal structure of the human FABP3 [87]</td>
<td>–</td>
<td>Crystal structure of the human FABP5 [33]</td>
</tr>
<tr>
<td>Nomenclature</td>
<td>fatty acid binding protein 6, ileal</td>
<td>fatty acid binding protein 7, brain</td>
<td>peripheral myelin protein 2</td>
<td>fatty acid binding protein 9, testis</td>
<td>fatty acid binding protein 12</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------------------</td>
<td>------------------------------------</td>
<td>---------------------------</td>
<td>-------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>HGNC, UniProt</td>
<td>FABP6, P51161</td>
<td>FABP7, O15540</td>
<td>PMP2, P02689</td>
<td>FABP9, Q0Z758</td>
<td>FABP12, A6NFH5</td>
</tr>
<tr>
<td>Comments</td>
<td>Able to transport bile acids [88].</td>
<td>Crystal structure of the human FABP7 [4].</td>
<td>In silico modelling suggests that FABP8 can bind both fatty acids and cholesterol [50].</td>
<td>– – –</td>
<td>– – –</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>retinol binding protein 1, cellular</th>
<th>retinol binding protein 2, cellular</th>
<th>retinol binding protein 3, interstitial</th>
<th>retinol binding protein 4, plasma</th>
<th>retinol binding protein 5, cellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>RBP1, P09455</td>
<td>RBP2, P50120</td>
<td>RBP3, P10745</td>
<td>RBP4, P02753</td>
<td>RBPS, P82980</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>–</td>
<td>stearic acid &gt; palmitic acid, oleic acid, linoleic acid, α-linolenic acid, arachidonic acid [70]</td>
<td>– – –</td>
<td>– – –</td>
<td>– – –</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>retinol binding protein 7, cellular</th>
<th>retinaldehyde binding protein 1</th>
<th>cellular retinoic acid binding protein 1</th>
<th>cellular retinoic acid binding protein 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>RBP7, Q96R05</td>
<td>RLBP1, P12271</td>
<td>CRABP1, P29762</td>
<td>CRABP2, P29373</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>–</td>
<td>11-cis-retinal, 11-cis-retinol &gt; 9-cis-retinal, 13-cis-retinal, 13-cis-retinol, all-trans-retinol, retinol [14]</td>
<td>tretinoin &gt; alitretinoin stearic acid &gt; palmitic acid, oleic acid, linoleic acid, α-linolenic acid, arachidonic acid [70]</td>
<td>– – –</td>
</tr>
</tbody>
</table>

Comments: Although not tested at all FABPs, BMS309403 exhibits high affinity for FABP4 (pIC50 8.8) compared to FABP3 or FABP5 (pIC50 – 6.6) [20, 81]. HTS01037 is reported to interfere with FABP4 action [31]. Multiple pseudogenes for the FABPs have been identified in the human genome.

Further Reading
Schroeder F et al. (2008) Role of fatty acid binding proteins and long chain fatty acids in modulating nuclear receptors and gene transcription. Lipids 43: 1-17 [PMID:17882463]

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
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. A wide range of compounds, ranging from psychoactive agents to antihistamines, have been observed to bind to these sites, which appear to be intracellular.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>sigma non-opioid intracellular receptor 1</th>
<th>α2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>SIGMAR1, Q99720</td>
<td></td>
</tr>
<tr>
<td>Agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Sub)family-selective agonists</td>
<td>(RS)-PPCC (pKᵢ 8.8) [67]</td>
<td></td>
</tr>
<tr>
<td>Selective agonists</td>
<td>PRE-084 (pIC₅₀ 7.4) [80], (+)-SK&amp;F10047</td>
<td></td>
</tr>
<tr>
<td>Antagonists</td>
<td>(-)-pentazocine</td>
<td></td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>NE-100 (pIC₅₀ 8.4) [62], BD-1047 (pIC₅₀ 7.4) [54]</td>
<td></td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[³H]pentazocine (Agonist)</td>
<td>[³H]-di-o-tolyguanidine (Agonist)</td>
</tr>
<tr>
<td>Comments</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments: (-)-pentazocine also shows activity at opioid receptors.

Further Reading

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.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>tubulin, alpha 1a</th>
<th>tubulin, alpha 4a</th>
<th>tubulin, beta class I</th>
<th>tubulin, beta 3 class III</th>
<th>tubulin, beta 4B class IVb</th>
<th>tubulin, beta 8 class VIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>TUBA1A, Q71U36</td>
<td>TUBA4A, P68366</td>
<td>TUBB, P07437</td>
<td>TUBB3, Q13509</td>
<td>TUBB4B, P68371</td>
<td>TUBB8, Q3ZCM7</td>
</tr>
<tr>
<td>Inhibitors</td>
<td>–</td>
<td>–</td>
<td>eribulin (pIC_50 8.2) [59], paclitaxel (Mitotic cell cycle arrest in A431 cells) (pEC_50 8.1) [63], colchicine (pIC_50 8) [12], cabazitaxel, docetaxel, ixabepilone</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>(Sub)family-selective inhibitors</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Inhibitors**
- vinblastine (pIC\_50 9), vincristine
- eribulin (pIC\_50 8.2) [59], paclitaxel (Mitotic cell cycle arrest in A431 cells) (pEC\_50 8.1) [63], colchicine (pIC\_50 8) [12], cabazitaxel, docetaxel, ixabepilone

**Further Reading**


**Searchable database**: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

References

1. ANDRADE C. (1952) [12978172]
2. Alduain W et al. (2011) [21378274]
4. Balendiran GK et al. (2000) [10854433]
5. Berardi F et al. (1996) [8568804]
7. Bolt S et al. (1993) [8436176]
8. Caron PC et al. (1992) [1458463]
10. Chang AA et al. (2013) [24144450]
11. Chu QS. (2009) [19236257]
12. Cifuentes M et al. (2006) [16504507]
14. Crabj JW et al. (1998) [9541407]
15. Czirakj MJ et al. (1993) [8137606]
16. El-Charaby E et al. (2012) [22992146]
17. Eriksson BI et al. (1995) [7667822]
18. Feldman M et al. (1998) [9865320]
19. Friedel HA et al. (1994) [7528134]
20. Furuhashi M et al. (2007) [17554340]
21. Garcia-Calvo M et al. (2005) [13928087]
22. Giralad L et al. (1998) [9593475]
23. Goldenberg MM. (1999) [10090426]
25. Gotti R et al. (2013) [23598032]
29. Hall RD et al. (2013) [23302904]
31. Hertzlag AV et al. (2009) [19754198]
32. Hoffman HM et al. (2008) [18668355]
33. Hohof CF et al. (1999) [10493790]
34. Holmer E et al. (1986) [3744129]
35. Hug C et al. (2004) [15210937]
36. Issafar H et al. (2014) [21494526]
37. Jacobson DR et al. (1997) [9017939]
38. James LI et al. (2013) [23292653]
39. Johnson DB et al. (2014) [25096781]
40. Kania S et al. (2001) [11742121]
41. Kapur S et al. (2001) [11463021]
42. Kline J et al. (2010) [21154117]
45. Lever JR et al. (2006) [16463398]
46. Linke R et al. (2010) [20190561]
48. Mach RH et al. (1999) [10096443]
49. Maeda K et al. (1996) [8619847]
50. Majava V et al. (2010) [20421974]
51. Malas S et al. (2014) [24969320]
52. Mao X et al. (2006) [16622416]
54. Matsumoto RR et al. (1995) [8566908]
55. McDermott MF. (2009) [19649332]
57. Murakami K et al. (1999) [10403814]
58. Nakase J et al. (2009) [19938784]
59. Narayan S et al. (2011) [21324687]
60. Nesbit A et al. (2007) [17636564]
61. Nimjee SM et al. (2005) [15600527]
62. Okuyama S et al. (1993) [7901723]
63. Ouyang X et al. (2006) [16777187]
64. Pal SK et al. (2014) [24892254]
65. Paolucci F et al. (2002) [12383040]
66. Penchala SC et al. (2013) [23716704]
67. Prezavento O et al. (2007) [17328523]
68. Reslan L et al. (2013) [23537278]
69. Richieri GV et al. (1994) [7929039]
70. Richieri GV et al. (2000) [10852718]
71. Recll MK et al. (2010) [20410301]
74. Sacchettini JC et al. (1989) [2671390]
76. Schroeder F et al. (2008) [17882463]
77. Shealy DJ et al. (2010) [20519961]
78. Stein R et al. (2004) [15102696]
80. Su TP et al. (1991) [1658302]
81. Sulsky R et al. (2007) [17502136]
82. Tang PA et al. (2013) [24179482]
83. Thompson J et al. (1997) [9054409]
84. Vicente Rabaneda EF et al. (2013) [23899231]
85. Westmark P et al. (1990) [2320592]
86. Yamauchi T et al. (2003) [12802337]
87. Young AC et al. (1994) [7922029]
88. Zwickert BL et al. (2013) [23603607]