The Concise Guide to Pharmacology 2017/18: Overview

Abstract

The Concise Guide to Pharmacology 2017/18 is the third in a series of biennial publications. This version provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology (where available), 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. Although the Concise Guide represents approximately 400 pages, the material presented is substantially reduced compared to information and links presented on the website.

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

Overview S1

Introduction

In order to allow clarity and consistency in pharmacology, there is a need to define protein targets of pharmacological interest. These targets are G protein-coupled receptors, ligand-gated ion channels, voltage-gated ion channels, transporters, enzymes, and other protein targets. We hope to provide an authoritative consensus on nomenclature, which at least will provide for researchers a state-of-the-art source of accurate, curated information on the background to their work that they will use in the introduction of their Research Papers or Reviews, or in supporting their proposals for funding. The Concise Guide to PHARMACOLOGY, although structural information is available on the online database, the priority for inclusion in the Concise Guide is the presence of quantitative pharmacological data. This is the philosophy of the IUPHAR/BPS Guide to PHARMACOLOGY presented on the online free access database www.guidetopharmacology.org.

Full Contents of Concise Guide

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

Searchable database:

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

Adiponectin receptors

Overview: Adiponectin receptors

Nomenclature: Adipo1 receptor Adipo2 receptor

HGNC, UniProt ADIPOR1, Q96A54 ADIPOR2, Q86V24

Rank order of potency

- C-cadherin (CDH13, P55290) has also been suggested to be a receptor for (hexameric) adiponectin.

Comments: 49

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


No other protein targets

Other Protein Targets

Family Structure

Notch receptors

Pentaxins

Serum pentaxins

Regulators of G protein Signaling (RGS) proteins

R4 family

Repulsive guidance molecules

Reticulons and associated proteins

Ribosomal factors

Sigma receptors

Tubulins

Tumour-associated proteins

WD repeat-containing proteins

Proteolytic enzymes

Protein kinases

Peptidases

Phosphatases

Other protein targets

Heat shock proteins

Immunoglobulins

Inhibitors of apoptosis (IAP) protein family

Kelch-like proteins

Kinesins

Leucine-rich repeat proteins

Lymphocyte antigens

Mitochondrial-associated proteins

Myosin binding proteins

Non-catalytic pattern recognition receptors

Absent in melanoma (AIM)-like receptors (ALRs)

C-type lectin-like receptors (CLRs)

Other pattern recognition receptors

Notch receptors

Pentraxins

Serum pentaxins
Blood coagulation components

Overview: Coagulation is a process mediated by interactions leading to the formation of a gel-like clot in the site of injury. The process involves the conversion of less active precursors into more active forms from proteolysis.

Nomenclature:
- Coagulation factor V: F5, P12259
- Coagulation factor VIII: F8, P00451
- Serpin family C member 1: SERPINC1, P01008

Selective activators:
- Heparin (pKd 7.8)
- Fondaparinux (pKd 7.5)
- Dalteparin
- Danaparoid
- Enoxaparin
- Tinzaparin

Selective inhibitors:
- Drotrecogin alfa

Further reading on Blood coagulation components:
- Girolami A et al. (2017) New clotting disorders that can now light on blood coagulation and may play a role in clinical practice. Thromb Thrombolysis 44:71-75

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

### Non-enzymatic BRD containing proteins

#### Overview

Bromodomain-containing proteins (BRDs) bind to acetylated lysine residues, such as histones, to regulate gene transcription. These proteins are examples of bromodomain-containing proteins for which no crystal structures are available. Research in this area is focused on identifying and validating small molecule inhibitors that target these proteins.

#### Nomenclature

- **Transthyretin (TTR)**
  - HGNC: TTR, P02766
  - Common abbreviation: TTR

#### Further reading on Non-enzymatic BRD containing proteins


#### Carrier proteins

Transferrin (Tf) is a homotetrameric protein that transports iron, copper, and zinc in the plasma and cerebrospinal fluid. Many disease-causing mutations in Tf have been reported, many of which cause complex dissociation and protein mis-assembly and deposition of toxic aggregates. These amyloidogenic mutants are linked to the development of pathological amyloidoses, including familial amyloid polyneuropathy (FAP) and familial amyloid cardiomyopathy (FAC). In old age, non-mutated TTR can also form pathological amyloid fibrils. Pharmacological intervention to reduce or prevent TTR dissociation is being pursued as a therapeutic strategy. To date, one small molecule (tafamidis) has been approved for FAP, and is being evaluated in clinical trials for other TTR amyloidoses.

#### Nomenclature

- **Transferrin (Tf)**
  - HGNC: TF, P02766
  - Common abbreviation: Tf

#### Full Contents of Concise Guide:

Overview: Clusters of Differentiation refer to an attempt to catalogue systematically a series of over 300 cell-surface protein-associated immunophenotyping markers of the group having 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 here in are selected members of the family targeted for therapeutic gain.

Nomenclature

- CD2
  - HGNC: P06729
- CD3e
  - HGNC: P07766
- CD20
  - HGNC: P11836
- CD33
  - HGNC: P20138
- CD52
  - HGNC: P31358

Common abbreviations

- SIGLEC-3
- LANTIG2

Selective inhibitors

- Alefacept (Inhibition) \[17,53\]
- Alemtuzumab (Binding) \[24,79\]

Antibodies

- Catumaxomab (Binding) \[43\]
- Muromonab-CD3 (Binding) \[25\]
- Otimizumab (Binding) \[9\]
- Ofatumumab (Binding) (pKd 9.9) \[47\]
- Rituximab (Binding) (pKd 8.5) \[75\]
- Obinutuzumab (Binding) \[3,66\]
- Tositumomab (Binding)
- Lintuzumab (Binding) (pKd ∼10) \[10\]
- Gemtuzumab ozogamicin (Binding) \[7\]

Searchable database:

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

Full Contents of Concise Guide:

Nomenclature

- **CD80**: P33681
- **CD86**: P42081
- **CTLA4**: P16410
- **PDCD1**: Q15116
- **CD300A**: Q9UGN4

**Common abbreviation**

- **CTLA-4 PD-1**

**Antibodies**

- **Ipilimumab** ($pK_d > 9$) [28]
- **Tremelimumab** ($pK_d 8.9$) [30]
- **Pembrolizumab** ($pK_d \sim 10$) [11]
- **Nivolumab** ($pK_d 9.1$) [28, 38, 40]

**Comment**: The endogenous ligand for human PD-1 is programmed death 1 ligand 1 (PD-L1 aka CD274, Q9NZQ7) and programmed death 1 ligand 2 (PD-L2; PDCD1LG2). These ligands are cell surface peptides, normally involved in immune system regulation. Expression of PD-1 by cancer cells induces immune tolerance and evasion of immune system attack. Anti-PD-1 monoclonal antibodies are used to induce immune checkpoint blockade as a therapeutic intervention in cancer. Efficient antibody-dependent immune cell killing of PD-1+ target cells includes immune cell recruitment and recruitment of immune cells to kill PD-1+ tumor cells. These landmarks

**Methyllysine reader proteins**

These proteins bind to methylated proteins, allowing regulation of gene expression.

**Overview**: Methyllysine reader proteins bind to methylated proteins, allowing regulation of gene expression.

**Further reading on CD molecules**


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

Fatty acid-binding proteins

Overview:

These are cytosolic proteins that bind fatty acids. They are involved in various cellular processes, such as lipid metabolism, signaling, and transport across the cell membranes. In some cases, these proteins are also involved in nuclear hormone receptor signaling. The table below lists the human fatty acid-binding proteins, their nomenclature, and some key features:

<table>
<thead>
<tr>
<th>Protein Name</th>
<th>Accession</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>FABP1</td>
<td>P07148</td>
<td></td>
</tr>
<tr>
<td>FABP2</td>
<td>P12104</td>
<td></td>
</tr>
<tr>
<td>FABP3</td>
<td>P05413</td>
<td></td>
</tr>
<tr>
<td>FABP4</td>
<td>P15090</td>
<td></td>
</tr>
</tbody>
</table>

Other protein targets

Fatty acid-binding proteins may interact with other proteins in the process of lipid transport and metabolism. For instance, they can interact with cytosolic fatty acyl coenzyme A (CoA) synthetases, which are involved in the conversion of fatty acids to fatty acyl-CoA esters. This interaction is crucial for the proper metabolism and function of these proteins.

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

Nomenclature

- Retinol binding protein 1: RBP1, P09455
- Retinol binding protein 2: RBP2, P50120
- Retinol binding protein 3: RBP3, P10745
- Retinol binding protein 4: RBP4, P02753
- Retinol binding protein 5: RBP5, P82980
- Retinol binding protein 7: RBP7, Q96R05

Rank order of potency:

- Stearic acid
- Palmitic acid
- Oleic acid
- Linoleic acid
- α-Linolenic acid
- Arachidonic acid

Inhibitors:

- A1120 (pIC50 7.8)
- HTS01037
- Ibuprofen
- Fenofibric acid

Comments:

Although not tested at all FABPs, BMS309403 exhibits high affinity for FABP4 (pIC50 8.8) compared to FABP3 or FABP5 (pIC50 < 6.6). HTS01037 is reported to interfere with FABP4 action. Ibuprofen displays some selectivity for FABP4 (pIC50 5.5) relative to FABP3 (pIC50 3.5) and FABP5 (pIC50 3.8). Fenofibric acid displays some selectivity for FABP5 (pIC50 5.5) relative to FABP3 (pIC50 4.5) and FABP4 (pIC50 4.6).

Multiple pseudogenes for the FABPs have been identified in the human genome.

Further reading on Fatty acid-binding proteins:


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

The canonical Notch signalling pathway has four type I transmembrane Notch receptors (Notch1-4) and five ligands (DLL1, 2 and 3, and Jagged 1-2). Each member of this highly conserved receptor family plays a unique role in cell-fate determination during embryogenesis, differentiation, tissue patterning, proliferation and cell death [2]. As the Notch ligands are also membrane bound, cells have to be in close proximity for receptor-ligand interactions to occur. Cleavage of the intracellular domain (ICD) of activated Notch receptors by \( \gamma \)-secretase is required for downstream signalling and Notch-induced transcriptional modulation [18, 57, 71, 89]. This is why \( \gamma \)-secretase inhibitors can be used to downregulate Notch signalling and explains their anti-cancer action. One such small molecule is RO4929097 [47], although development of this compound has been terminated following an unsuccessful Phase II single agent clinical trial in metastatic colorectal cancer [78].

Aberrant Notch signalling is implicated in a number of human cancers [41, 59, 74, 85]. Pharmaceutical inhibitors of Notch signalling such as demcizumab and tarextumab are being actively investigated as novel anti-cancer agents [64].

**Nomenclature**

<table>
<thead>
<tr>
<th>Notch 1</th>
<th>Notch 2</th>
<th>Notch 3</th>
<th>Notch 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>NOTCH1, P46531</td>
<td>NOTCH2, Q04721</td>
<td>NOTCH3, Q9UM47</td>
</tr>
</tbody>
</table>

Comments Various types of activating and inactivating NOTCH1 mutations have been reported to be associated with human diseases, for example: aortic valve disease [23, 52], Adams-Oliver syndrome 5 [76], T-cell acute lymphoblastic leukemia (T-ALL) [87], chronic lymphocytic leukemia (CLL) and head and neck squamous cell carcinoma [1, 77].

Notch 4 is a potential therapeutic molecular target for triple-negative breast cancer [42, 55].

Further reading on Notch receptors


**Regulators of G protein Signalling (RGS) proteins**

Regulators of G protein signalling (RGS) proteins increase the deactivation rate of G protein signalling pathways through enhancing the GTPase activity of the G protein alpha subunit. Interactions through protein:protein interactions of many RGS proteins have been described. The 20 RGS proteins are commonly divided into five families (R4, R7, R12 and RZ) based on sequence and domain homology. Described here is RGS4 for which a number of pharmacological inhibitors have been described.

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; the crystal structure of the sigma1 receptor suggests a trimeric structure featuring 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

Selective agonists

PRE-084

(+)-SKF 10.047

Selective antagonists

NE-100

BD-1047 (pIC50 7.4) [51]

Labelled ligands

[3H]pentazocine (Agonist)

[3H]-dio-tolylguanidine (Agonist)

Comments:

(-)-pentazocine also shows activity at opioid receptors. The sigma2 receptor has recently been reported to be TMEM97 [92], a TMP4 partner of NPC1, the Niemann-Pick C1 protein.

Further reading on Sigma receptors


Searchable database:

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

Sigma receptors S14

Full Contents of Concise Guide:

Tubulins

Overview:

Tubulins are a family of intracellular proteins most commonly associated with microtubules, part of the cytoskeleton. They are essential for the assembly and maintenance of microtubules, which are important for many cellular processes including cell division, transport, and shape.

Other protein targets → Tubulins

Tubulins are a family of intracellular proteins most commonly associated with microtubules, part of the cytoskeleton. They are essential for the assembly and maintenance of microtubules, which are important for many cellular processes including cell division, transport, and shape.

Inhibitors –
- vinblastine (pIC\textsubscript{50} 9), vincristine, eribulin (pIC\textsubscript{50} 8.2) [58], paclitaxel (pEC\textsubscript{50} 8.1) [61], colchicine (pIC\textsubscript{50} 8) [13], cabazitaxel, docetaxel, ixabepilone, combretastatin A4 (pIC\textsubscript{50} 8.2) [22]

Further reading on Tubulins


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


Other protein targets → Tubulins

Tubulins S15
References


