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The IUPHAR Guide to Immunopharmacology: Connecting Immunology and Pharmacology

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Abbreviations:

BPS - British Pharmacological Society

CANTOS - Canakinumab Anti-inflammatory Thrombosis Outcomes Study

CD - Cluster of Differentiation

CIRT - Cardiovascular Inflammation Reduction Trial

CLL - Chronic lymphocytic leukemia

COX - Cyclooxygenase

CRP - C-reactive protein
CVD - Cardiovascular Disease
FDA - U.S. Food and Drug Administration
GO - Gene Ontology
GolImmuPdb - Guide to Immunopharmacology
GtoPdb - Guide to Pharmacology
HLA-E - Human leukocyte antigen E
IL - Interleukin
INN - International Nonproprietary Names
IRAK - Interleukin-1 receptor-associated kinase
IUIS - International Union of Immunological Science
IUPHAR - International Union of Basic and Clinical Pharmacology
MAS - Macrophage Activation Syndrome
MI - Myocardial Infarction
NAR - Nucleic Acids Research
NC-IUPHAR - Nomenclature Committee of the International Union of Basic and Clinical Pharmacology.
NIH - National Institutes of Health
NLRP3 - NOD-like receptor family 3
NOD - Nucleotide-binding and oligomerization domain
NSAIDs - Nonsteroidal anti-inflammatory drugs
OMIM - Online Mendelian Inheritance in Man
PCSK9 - Proprotein convertase subtilisin/kexin type 9
SID - PubChem Substance Record ID
WHO - World Health Organization

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Summary

Given the critical role that the immune system plays in a multitude of diseases, having a clear understanding of the pharmacology of the immune system is crucial to new drug discovery and development. Here we describe the IUPHAR Guide to IMMUNOPHARMACOLOGY

(GtoImmuPdb), which connects expert-curated pharmacology with key immunological concepts and aims to put pharmacological data into the hands of immunologists. In the pursuit of new therapeutics, pharmacological databases are a vital resource to researchers through providing accurate information on the fundamental science underlying drug action. This extension to the existing IUPHAR/BPS Guide to PHARMACOLOGY supports research into the development of drugs targeted at modulating immune, inflammatory or infectious components of disease. To provide a deeper context for how the resource can support research we show data in GtoImmuPdb relating to a case study on the targeting of vascular inflammation.

Introduction

The immune system has become a major target for new therapeutics, with approximately 20% of new drug approvals in the last five years targeting elements of the immune system (www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products). A high proportion of diseases are also associated with an immune or inflammatory component or process. In particular, chronic age-related diseases such as Alzheimer's disease, atherosclerosis and diabetes have inflammatory components (1–5). The significant roles that inflammation and immune mechanisms play in cardiovascular disease have also made them potential therapeutic targets in its treatment (6). Auto-immunity is a serious problem, for example in multiple sclerosis (7,8), Sjogren's Syndrome (9), inflammatory bowel disease (10,11) and rheumatoid arthritis (12). Such conditions may coexist with depressive disorders (13). There is also much interest in the use of immune therapies, such as the potential exploitation of dendritic cells, to treat cancer (14,15).

The International Union of Basic and Clinical Pharmacology (IUPHAR) and the British Pharmacological Society (BPS) collaborate on the development and maintenance of the Guide to PHARMACOLOGY (GtoPdb, www.guidetopharmacology.org). This database is an expert-curated resource of ligand-activity-target relationships, selected from high-quality pharmacological and medicinal chemistry literature. It has its origins in IUPHAR-DB and the BPS 'Guide to Receptors and Channels', both of which focused on receptors and channels (16–18). The scope of GtoPdb has expanded over the years (19–22) and a Wellcome Trust-funded project has allowed us to address the priority area of immunity, inflammation and infection (23–26). In the course of that project, the database has expanded into the field of immunopharmacology (21).

Well-curated pharmacological databases are an important foundation for research on new therapeutics. In the context of immunopharmacology, although there are good Internet resources that support purely immunological research, for example Immunopaedia (www.immunopaedia.org.za), ImmPort (www.immport.org), ImmGen (www.immgen.org), InnateBD (www.innatedb.com) and IMGT (www.imgt.org), none cover the pharmacology of the immune system. The IUPHAR Guide to Immunopharmacology (GtoImmuPdb; www.guidetoimmunopharmacology.org) has been developed to deliver a knowledge-base that, for the first time, connects immunology with pharmacology (27). It expands the data associated with targets and ligands to cover immunological data types, and enhances access to the pharmacological data through a user-interface tailored to immunologist. GtoImmuPdb puts valuable pharmacological data into an immunological context, and is a resource which enables researchers to easily identify pharmacological agents that can be used experimentally to modulate immune system mechanisms.

The IUPHAR/BPS Guide to Pharmacology

GtoPdb holds data on nearly 3,000 human proteins, with over 1,700 of these ‘targets’ having curated pharmacological interaction data. In total the database has information on over 9,700 ligands, and it contains quantitative data on over 14,000 ligand-target interactions. The selection of content is supported through the expertise of 96 target family subcommittees of the Nomenclature Committee of IUPHAR (NC-IUPHAR), comprised of over 500 scientists worldwide. GtoPdb uses expert human judgement at all stages of curation, in contrast to more automated data and text mining approaches. Curation is not though excluded to only the NC-IUPHAR subcommittees; we also encourage users to make suggestions about content, which when checked often results in appropriate additions or qualifications.

The GtoPdb is a well used and highly cited resource. Our analytics show that the database is accessed by over 22,000 users worldwide each month and they generate a total of more than 118,000 page views. We produce two main biennial publications. The most prominent of these is the Concise Guide to Pharmacology (28) which provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology. The last two editions (2015/16 (29) and 2017/18 (30)) combined have over 2,600 citations. We also produce a biennial publication in Nucleic Acids Research Database Issue, which documents

database and curatorial updates. Our 2016 (20) and 2018 (21) papers have been cited over 1,460 times.

The IUPHAR Guide to Immunopharmacology: Development and curation

In establishing the GtoImmuPdb, NC-IUPHAR expert subcommittees identified targets relevant to immunopharmacology, and they provided detailed curatorial comments on the reasons for their inclusion in the resource. In the 2019.5 database release, 614 targets and 1,232 ligands have been tagged as relevant to immunopharmacology

(www.guidetoimmunopharmacology.org/immuno/immunoHelpPage.jsp#gtoimmupdb_content).

Curating GtoImmuPdb data

The first phase of curation involved assessing protein targets and ligands that were already in the GtoPdb for inclusion in the GtoImmuPdb. To extend coverage beyond what was already in GtoPdb, we made use of the Gene Ontology 'biological process' annotations to prioritise targets for curation. We produced a draft list of targets for inclusion in GtoImmuPdb on the basis of both direct involvement in inflammation/immunity, and based on involvement in processes known to be important in inflammation/immunity. Ligands for targets that qualified for GtoImmuPdb were then reviewed and included if there was evidence that their activity has a modulatory effect on inflammation/immune system (e.g. drugs approved to treat inflammatory conditions, or tool compounds used to investigate GtoImmuPdb targets). The selection of content for curation was supported by the NC-IUPHAR subcommittees, who identified key papers and literature reviews. Examples of inclusions identified at this stage are histamine receptors

(www.guidetoimmunopharmacology.org/GRAC/FamilyDisplayForward?familyId=33) (31) and anti-histamine drugs, glucocorticoid receptor

(www.guidetoimmunopharmacology.org/GRAC/ObjectDisplayForward?objectId=625) (32) and anti-inflammatory glucocorticoid drugs, cyclooxygenase (COX) enzymes

(www.guidetoimmunopharmacology.org/GRAC/FamilyDisplayForward?familyId=269) (33) and NSAIDs, and pattern recognition, cytokine and chemokine receptor families. Examples of new content added during this phase include additional families of pattern recognition receptors (34) and immune checkpoint proteins, and ligands and immune checkpoint inhibitors (clinical and investigational) used in immuno-oncology.

Targets and ligands continue to be added to the GtoImmuPdb as new evidence emerges. Ongoing updates are driven by systematic searches of current literature covering immunology and inflammation to identify lead compounds, their molecular targets and pharmacological data. Other useful resources include pharmaceutical companies' declared development programmes and selective patent analysis that can be used to identify pharmacological data in the absence of peer-reviewed publications. Review of clinical trial registries, applications to the World Health Organization (WHO) for new International Nonproprietary Names (INNs; which provides an indication of developments in the immunity/inflammation/immuno-oncology fields), and monitoring new drug approvals can all identify novel ligands, protein targets and molecular mechanisms of action.

Immunological processes and cell types

The data on targets and ligands have been extended by annotating these with immunological data. This means we have made clear connections between immunological processes, cell types and disease, and the targets and ligands already in the database. We have made use of biological ontologies because they provide an organised, hierarchical and controlled vocabulary against which to annotate data. Ontologies also provide unique accession numbers that identify a particular term, and these are valuable in supporting interoperability between data resources. In the context of GtoImmuPdb they are also useful in curating protein targets to different categories and in enabling inferred searching. We have used biological processes from the Gene Ontology (35,36) (geneontology.org) and cell types from the Cell Ontology (37) (<http://obofoundry.org/ontology/cl.html>).

The Gene Ontology is a hierarchical ontology that describes biological processes, including processes that operate in the immune and inflammatory systems (38,39). GtoImmuPdb uses top-level process categories, such as *T cell (activation)* or *Cytokine production and signalling*, underpinned by GO immune and inflammatory process terms. In the case of T cell activation this includes terms such as 'T cell mediated immunity (GO:0002456)' and 'regulation of T cell differentiation (GO:00045580)'.

The Cell Ontology is designed as a structured vocabulary for cell types, from prokaryotes to mammals. In a similar way, GtoImmuPdb uses top-level cell type categories, such as *Mast cells*, due to their relevance in anti-allergic therapies (40), and *Innate lymphoid cells*, reflecting the growing understanding of their role within the innate immune system in the control of tissue

homeostasis, infection, inflammation, metabolic disease, and cancer (41,42). The top-level categories are underpinned by Cell Ontology terms, which in the case of *Mast cells* includes the terms ‘mast cell (CL_0000097)’ and its children, ‘mucosal type mast cell (CL_0000485)’ and ‘connective tissue type mast cell (CL_0000484)’.

Table 1 shows associations between the top-level processes and the number of human immunopharmacological target proteins. The table also shows the number of human target proteins relevant to immunopharmacology associated with the top-level cell types. More details of how data have been curated can be found in our recent publication (21).

The IUPHAR Guide to Immunopharmacology: Accessing the data

The Guide to IMMUNOPHARMACOLOGY portal allows researchers with a primarily immunological background to find pathways, drugs and targets via an interface built around an immunological perspective. Immunological processes, cell types, pathways and diseases are centre-stage, and connect to search functions that prioritise immunologically relevant pharmacological data. This provides rapid access to lists of targets and ligands relevant to immunopharmacology, or allows the viewing of lists of targets and ligands associated with immunological processes, cell types and diseases. In this way, GtoImmuPdb equips immunologists with a means to discover pharmacological agents useful in their research and provides a foundation for developing research into therapeutic modifiers of the immune system.

Navigating the database from a starting point of immunological process of cell type

The database contains nearly 200 targets associated with T cell activation (Table 1). These can be easily accessed via the *processes* panel on the GtoImmuPdb portal (Figure 1a). The targets are organised into sections, one for each target class. Figure 2b shows how some CD molecule targets are displayed in the ‘Other Protein Targets’ section. The GO terms annotated to a target are shown in the third column of figure 1b; summarised curatorial comments are also displayed. In the example of CD28, its role in the activation, proliferation and survival of T cells is indicated. By clicking on the target name, users can view the detailed targets page, which contain the expanded curators’ comments and full pharmacological information on the target.

The annotation of targets to cell types helps highlight useful pharmacological data relevant to immunopharmacology. For example, the role of natural killer cells in anti-tumour immunity is well established (43,44), and the heterodimer CD94/NKG2A is known to have a role in recognition of the main type of HLA class-I molecules and functions as a true checkpoint in NK cell activation (Mariotti et al., 2019). NKG2A (GtoPdb Target 2849; CD159a) is annotated in GtoImmuPdb as being expressed by cells in the natural killer cells category, with the immunopharmacology commentary highlighting its role as an inhibitory checkpoint receptor for HLA-E. The detailed view for CD159a

([www.guidetoimmunopharmacology.org/GRAC/ObjectDisplayForward?](http://www.guidetoimmunopharmacology.org/GRAC/ObjectDisplayForward?objectId=2849#Antibodies)

[objectId=2849#Antibodies](http://www.guidetoimmunopharmacology.org/GRAC/ObjectDisplayForward?objectId=2849#Antibodies)) shows interaction data for the antibody monalizumab

([www.guidetoimmunopharmacology.org/GRAC/LigandDisplayForward?](http://www.guidetoimmunopharmacology.org/GRAC/LigandDisplayForward?tab=summary&ligandId=8323)

[tab=summary&ligandId=8323](http://www.guidetoimmunopharmacology.org/GRAC/LigandDisplayForward?tab=summary&ligandId=8323)), an anti-NKG2A clinical lead molecule that is being developed for solid and haematological cancers (Figure 2).

Ligand summaries

For ligands, the database contains key information on the biological activity, clinical use, molecular properties, structure and immunopharmacology. This data is displayed on the ligand summary pages which are easily accessed, either from the 'Ligands' menu-bar item, or the Ligands panel on the home page (Figure 3a). Different categories of ligand can be selected from tabs at the top of the page. When navigating from the GtoImmuPdb portal, the lists contain ligands tagged in the database as relevant to immunopharmacology. Selecting a ligand links through to the ligand summary page where data is organised under several tabs (Figure 3b). The 'Immunopharmacology' tab contains curator comments on a compounds relevance to immunopharmacology, as well as listing any disease associations. The 'Summary' tab gives general information about the compound, including if the drug is approved for clinical use and provides a list of trade names (when used clinically), synonyms (such as preclinical names) and International Nonproprietary Names (INNs) so that the drug can be identified and tracked in the literature. The 'Biological Activity' tab as well as displaying tables of the ligand selectivity at targets in the database also provides access to the Ligand Activity Visualisation Tool (Figure 3c). This tool provides box plots summarising all the activity data for a ligand taken from ChEMBL (45) and GtoPdb across multiple species. The 'Clinical data' tab provides information about molecular mechanisms of action and clinical trials together with trial identifying numbers.

Disease summaries

The extension for immunopharmacology has also prioritised the development of pages that give consolidated pharmacological summaries for different diseases. In all, there are over 1,000 diseases in the GtoPdb which have curated associations with targets and/or ligands. The disease lists, accessed from the portal or menu-bar, summarise these (www.guidetoimmunopharmacology.org/GRAC/DiseaseListForward?type=Immuno). As a consequence of our recent curatorial focus on immunological data, diseases with significant immunological aspects, such as asthma, rheumatoid arthritis, inflammatory bowel and psoriasis, show the greatest number associations to targets and/or ligands.

The disease summary pages show targets and ligands associated with a disease and include links to OMIM (46,47) (omim.org), Orphanet (orpha.net) and the Disease Ontology (48) (disease-ontology.org), providing cross-references between the diseases in GtoImmuPdb and other resources (www.guidetoimmunopharmacology.org/GRAC/DiseaseListForward?

[type=Immuno](#)). The pages also detail the bioactivities and clinical uses of relevant ligands. For example, Chronic lymphocytic leukemia (CLL; www.guidetopharmacology.org/GRAC/DiseaseDisplayForward?diseaseId=218) (Figure 4) highlights CD20 as being the molecular target of four antibodies: ofatumumab, veltuzumab, rituximab and obinutuzumab. The summarised view shows these antibodies listed against their molecular target and combines this with detailed disease, clinical use and bioactivity comments (Figure 4). In the case of rituximab, the pages not only explain its role in treating CD20-positive non-Hodgkins lymphoma and chronic lymphocytic leukemia, but highlight its role in several other autoimmune conditions and in the suppression of antibody-mediated organ rejection (49,50).

Immunopaedia

Through the partnership between IUPHAR and the International Union of Immunological Sciences (IUIS) to create standard tools and nomenclature (<https://iuis.org/news/2018-iuis-council-meeting-summary/>), GtoImmuPdb has been working in collaboration with the IUIS resource, Immunopaedia (www.immunopaedia.org.za). Immunopaedia provides materials for teaching and learning immunology, from the basic immune system to advanced immunology and specialised focus areas. They are an official provider for online resources for the IUIS, creating and hosting online courses to educate and support participants before and after immunology conferences world-wide. We have undertaken to provide links from key ligands in GtoImmuPdb to the rich and detailed clinical case studies hosted by Immunopaedia (Figure 5).

Searching, web services and PubChem

The search mechanisms across the website have been extended, such that the new immunological data types are incorporated. The search algorithm itself has been tailored so that when using the Guide to Immunopharmacology URL, results of immunological relevance are upweighted. The immunological relevance of a target or ligand is determined by the amount of immunological data associated with it in the database. Our application programming interface (API) has also been extended to incorporate parameters to retrieve immunopharmacology tagged data. Lists of immuno tagged ligands, www.guidetopharmacology.org/services/ligands?type=immuno.

The GtoPdb maintains strong connectivity with PubChem, the open chemistry database at the National Institutes of Health (NIH) (51). On each database release of GtoPdb we submit our chemical structures to PubChem. As part of this process we include 'Depositor Comments' in the substance (SID) records that we submit to PubChem. These comments, among other things, indicate if a structure is part of GtoImmuPdb and contains any immunopharmacology curatorial comments. Described in more detail in our most recent NAR paper (22), the inclusion

of these comments in our PubChem submissions make it possible to run domain-specific queries related to immunopharmacology when searching via PubChem.

Case study: targeting vascular inflammation

The best way to illustrate the potential usefulness of GtoImmuPdb is through a case study. We have chosen vascular inflammation, because in the last three decades, experimental data have clearly shown the causal role played by immune and inflammatory responses in the initiation and development of atherosclerosis, and in the regulation of plaque instability (6).

Epidemiological studies have also called attention to vascular inflammation. To date, however, there is no immunomodulatory treatment in routine use for prevention of atherosclerosis (52). How might GtoImmuPdb help to change this?

The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS; <http://clinicaltrials.gov/ct2/show/NCT01327846>) (52,53) has been the first large (> 10,000), randomised, double-blind, placebo-controlled trial to target the inflammatory cytokine interleukin IL-1 β (www.guidetoimmunopharmacology.org/GRAC/LigandDisplayForward?tab=biology&ligandId=4974) for secondary prevention (to reduce the number of new or severe cases of the disease) of atherosclerosis. In CANTOS, the human monoclonal antibody canakinumab (www.guidetoimmunopharmacology.org/GRAC/LigandDisplayForward?tab=immuno&ligandId=6773) significantly reduced the rate of a composite endpoint of major cardiovascular events in patients previously affected by myocardial infarction (MI) and who had high levels of C-reactive protein (CRP) (52). The CANTOS trial represents the first clinical evidence that targeting inflammation may be a viable approach in atherosclerosis and it started an important discussion on how to target vascular immune-inflammatory responses in the most efficient way (which might not be by targeting IL-1 β).

The CANTOS was followed by the Cardiovascular Inflammation Reduction Trial (CIRT; <http://clinicaltrials.gov/ct2/show/NCT01594333>) (53,54). In CIRT, treatment with low-dose methotrexate failed to reduce cardiovascular event rates in patients with previous multi-vessel coronary artery disease or MI also affected by metabolic syndrome or type 2 diabetes (54). It should be noted that despite comorbidities, CIRT patients had normal CRP levels and therefore had not been selected on the basis of residual inflammatory risk. Given that high levels of CRP are associated with an increased risk of cardiovascular events, this may help to explain the

difference between the CANTOS and CIRT results. In fact, in *post hoc* observations within CANTOS, patients with the largest reduction in IL-6 and CRP in response to IL-1 β inhibition (55) showed the greatest reduction in cardiovascular mortality, while methotrexate had no effect on circulating inflammatory mediators in CIRT. It is worth noting that typing the name of a clinical trial into the main search box on GtoImmuPdb returns a list of ligands involved in the trial, where this data has been curated.

We have learned to a great extent from both trials, but we still have a long way to go before anti-inflammatory therapies may become standard care in the treatment of cardiovascular disease (CVD) (56).

Canakinumab is an expensive agent and it is very unlikely that it will be used in CVD prevention. Several further directions may be investigated, and the first clear opportunity is represented by the targeting of mediators that sit either just above or below IL-1 β . More recent analysis from the CANTOS trial revealed that there remains substantial residual inflammatory risk related to both IL-18 and IL-6 after IL-1 β inhibition (57). Therefore, targeting IL-18 or IL-6 signalling (58), could be a way forward. These presents us with several questions - can we find a good way to target IL-18, IL-6? Can GtoImmuPdb help in finding a good way to modulate either of these molecules?

Accessing ligand summaries for IL-6 and IL-18

To access information about IL-6 in GtoImmuPdb, go to the portal and type 'IL-6' into the database search at the top of any page. IL-6 is the top-hit from this search and clicking on the ligand name links through to its ligand summary page. Ligand summary pages can also be accessed by browsing via the 'Ligand' menu-bar item, either via 'Ligand List' (alphabetical) (Figure 1), or 'Ligand Families', which has several groupings of ligands, including one for Interleukins, where IL-6 can be found (Figure 6).

Information on IL-6 is contained under several tabs on the ligand summary page (Figure 7). Figure 7a shows information under the immunopharmacology tab, highlighting its pro- and anti-inflammatory effects and indicating its role in the treatment of rheumatoid arthritis. Figure 7b shows biological activity data, which lists ligands with which IL-6 interacts, including binding affinity data and indications of whether the ligands are approved drugs, as is the case for siltuximab. As a starting point when considering a way to potentially target IL-6, this pharmacological data and immunological context is helpful, particularly as it shows that IL-6 is

already a validated drug target. A primary target of three ligands which include the approved drug siltuximab.

Similarly, information on IL-18 can be accessed in the same way. Figure 8 shows some of the highlights from the IL-18 ligand summary page, including tadekinig alfa, a peptide ligand, that binds to and inhibits the pro-inflammatory activity of IL-18 and has U.S. Food and Drug Administration (FDA) orphan drug designation for the treatment of macrophage activation syndrome (MAS). This is useful pharmacological information and context for further investigation of targeting IL-18.

Accessing immunopharmacology data for NLRP3 and PCSK9

Targeting NLRP3 inflammasome inhibitors that can inhibit both IL-1 β and IL-18 (59), may also present a viable way forward. In this regard using GtoImmuPdb to view the detailed target page for NLRP3 may be helpful. It is possible to use the direct search to find NLRP3, but it can also be found by browsing through the Catalytic Receptors targets, where NLRP3 (34) is found under the Pattern Recognition receptors and NOD-like receptor subfamilies. Figure 9 shows inhibitors and immunopharmacology comments from the NLRP3 detailed target page. Two of the three ligands, CY-09 and MCC950, have quantitative interaction data for NLRP3 and all three are indicated as having relevance to immunopharmacology. CY-09 and MCC950 (www.guidetoimmunopharmacology.org/GRAC/LigandDisplayForward?tab=immuno&ligandId=10057#immuno) is shown to have significant therapeutic effects in NLRP3-driven diseases (60), MCC950 (www.guidetoimmunopharmacology.org/GRAC/LigandDisplayForward?tab=immuno&ligandId=8228#immuno) has the potential to block NLRP3 induced-events and there is evidence that dapansutrole (www.guidetoimmunopharmacology.org/GRAC/LigandDisplayForward?tab=immuno&ligandId=10056) is a clinical lead for autoinflammatory disease and heart failure.

A further translational direction may be the development of a novel combination of lipid-lowering and anti-inflammatory treatments by design of monoclonal antibodies that could simultaneously inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9) (Figure 11) and either IL-1 β or IL-6. Figure 11 shows inhibitor data from the GtoImmuPdb for PCSK9, showing three monoclonal antibodies with quantitative interaction data for PCSK9. Both evolocumab and alirocumab are approved drugs, and bococizumab is being evaluated in Phase III clinical trials.

Another alternative in targeting the IL-1 β pathway could be targeting the IL-1 receptor itself, or modulating signal transduction downstream of the activated receptors such as members of the Interleukin-1 receptor-associated kinase (IRAK) family. In GtoImmuPdb, details for the IL-1 receptor (www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1905) show that it is already targeted by the antagonist peptide mimic anakira (www.guidetopharmacology.org/GRAC/LigandDisplayForward?tab=clinical&ligandId=6972). For IRAK4, the target detail page shows 11 inhibitors (www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2045&familyId=579&familyType=ENZYME#Inhibitors), 6 of which are selective, including the Pfizer compound (PF-06650833; www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=9667) which is a clinical lead for Rheumatoid arthritis, demonstrating that IRAK4 is a druggable target in the pathway.

The testing of new drugs should move in parallel with the identification of better biomarkers for patient stratification, the development of novel molecular imaging modalities for diagnosis and monitoring of vascular inflammation, as well as novel drug-delivery systems for selective *in situ* targeting of vascular immune pathways and consequent reduced risk of systemic immunosuppression (61).

Concluding Remarks

The recent appreciation that most chronic diseases include immune aspects, and that modulation of immunity can have a profound effect on disease progression or resolution, makes the immune system a critical target for new therapies. The historically small overlap between immunological and pharmacological research communities has probably hindered rapid development of immunologically-relevant therapeutics. The IUPHAR Guide to IMMUNOPHARMACOLOGY database and search tools provide a partial solution to this problem, allowing researchers with an immunological training to use search terms framed in the concepts of immunology to find pharmacological information and tools relevant to them. In this way, the database should accelerate discovery and development of new strategies against chronic disease.

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SDH designed and developed the database and wrote the manuscript. CS, EF & AP curated the GtoImmuPdb database. PM made a significant contribution to the writing of the manuscript, in particular the case study. SPHA & APD had input on writing the manuscript and as grant holder had roles in the planning of the project. DF contributed to GtoImmuPdb in curation of protein kinases. FLS contributed to GtoImmuPdb in curation of cellular targets, pathways and monoclonal antibodies. MS as grant holder had roles in the planning of the project. JAD contributed to the writing of the manuscript and is the principal investigator of the database development and curation team at the University of Edinburgh.

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Conflict of Interest

There are no conflicts of interest to declare.

Tables and Figures

Process	Annotated Human Targets	Cell Type	Annotated Human Targets
Barrier integrity	49	B cells	51
Inflammation	633	Dendritic cells	41
Antigen presentation	142	Granulocytes	46
T cell (activation)	196	Innate lymphoid cells	6
B cell (activation)	161	Macrophages	56
Immune regulation	503	Mast cells	39

Tissue repair	19	Natural killer cells	26
Immune system development	251	Other T cells	3
Cytokine production & signalling	504	Stromal cells	1
Chemotaxis & migration	256	T cells	76
Cellular signalling	476		

Table 1. GtoImmuPdb Process and Cell Type categories and the number of human proteins associated with each group.

The screenshot shows the IUPHAR Guide to Immunopharmacology website. The 'Processes' panel on the left has 'T cell activation' selected. Below it, the 'Targets Associated to Immuno Processes - T cell activation' table is displayed. A callout box highlights the CD28 target, showing its name links, immunopharmacology comments, and associated GO biological process terms.

CD molecule	Target name links to detailed view	Immunopharmacology comments	Associated GO biological process terms
CD28 (CD molecules)	<ul style="list-style-type: none"> negative regulation of T cell proliferation (GO:0042102) IDA regulation of T cell proliferation (GO:0042110) IGI negative thymic T cell selection (GO:0045066) IEA regulatory T cell differentiation (GO:0045066) IDA regulation of regulatory T cell differentiation (GO:0045589) IEA positive regulation of alpha-beta T cell proliferation (GO:0046641) IEA positive regulation of isotype switching to IgG isotypes (GO:0048304) IEA 	<p>CD28 is expressed on the surface of T cells and is required for the co-stimulatory signal essential for the activation, proliferation and survival of T cells, and Th2 cell development. CD28 acts in concert with the T cell receptor to stimulate cytokine release (promotes IL-2 production). CD28 binds the B7 proteins CD80 and CD86 on the surface of antigen presenting cells to effect a co-stimulatory signal to T cells. In contrast, CTLA-4 delivers a co-inhibitory signal via CD80/CD86 [6] ...</p>	<ul style="list-style-type: none"> adaptive immune response (GO:0002250) IEA T cell differentiation (GO:0030217) IDA T cell costimulation (GO:0031295) IEA positive regulation of T cell proliferation (GO:0042102) IMP T cell activation (GO:0042110) NAS positive thymic T cell selection (GO:0045059) IEA negative thymic T cell selection (GO:0045066) IEA positive regulation of alpha-beta T cell proliferation (GO:0046641) IEA
CD300a (CD molecules)	<ul style="list-style-type: none"> negative regulation of NK T cell activation (GO:0051134) IDA 	<p>CD300a is a member of the CD300 family of leucocyte surface receptors [44] ...</p>	
CD3e (CD molecules)	<ul style="list-style-type: none"> adaptive immune response (GO:0002250) IEA T cell differentiation (GO:0030217) IDA T cell costimulation (GO:0031295) IEA positive regulation of T cell proliferation (GO:0042102) IMP T cell activation (GO:0042110) NAS positive thymic T cell selection (GO:0045059) IEA negative thymic T cell selection (GO:0045066) IEA positive regulation of alpha-beta T cell proliferation (GO:0046641) IEA 	<p>CD3e is a subunit of the T cell receptor (TCR)-CD3 complex that mediates T cell receptor signal transduction in response to antigen detection. The TCR complex contains a CD3γ chain (CD3γ), a CD3δ chain (CD3δ), and two CD3ε chains (CD3ε), plus the TCR (that can be αβ, or αβ type in the subsets of T cells named after the TCR they express) and the ζ-chain (zeta-chain).</p> <p>CD3e plays a crucial role in T cell development, highlighted by the discovery that defects in CD3e cause severe immunodeficiency [91,334] ...</p>	
CD4 (CD molecules)	<ul style="list-style-type: none"> adaptive immune response (GO:0002250) IEA T cell differentiation (GO:0030217) IDA helper T cell enhancement of adaptive immune response (GO:0038397) IEA positive regulation of T cell proliferation (GO:0042102) IEA T cell activation (GO:0042110) IEA T cell selection (GO:0045059) IDA regulation of T cell activation (GO:0050863) IDA 	<p>CD4 is being targeted for clinical utility in inflammatory diseases like rheumatoid arthritis (RA), neoplasms derived from T helper cells (T cell lymphomas and related malignancies), and for anti-HIV potential. Depending on the design of CD4 targeting antibodies, they can produce immunosuppressive effects via activation of Tregs and induction of tolerance, block HIV binding to CD4 to prevent HIV infection, or induce depletion of CD4+ T cells by apoptosis, ADCC, or CDC [192,365] ...</p>	

Figure 1. Browsing for targets associated with an immunological process. A. The GtoImmuPdb portal is shown in (A), with the Processes panel linking to lists of targets associated with T cell activation (B). Under the 'Other Proteins' section (C) CD molecule targets are listed, and in the example of CD28, curatorial comments indicate its role in the activation, proliferation and survival of T cells.

The screenshot displays the IUPHAR Guide to IMMUNOPHARMACOLOGY interface. The navigation path is: Home > About > Targets > Ligands > Processes > Cell Types > Diseases > Resources. Under 'Cell Types', 'Natural killer (NK) cells' is selected, leading to a list of targets including CD159a. A detailed view for CD159a is shown, listing associated antibodies like monalizumab. The detailed view includes a table with the following data:

Antibody	Sp.	Action	Value	Parameter	Reference
monalizumab	Hs	Binding	-10.6	pK _d	1

Below the table, the 'Immunopharmacology Comments' section states: "NKG2A (KLRC1; CD159a) acts as an inhibitory checkpoint receptor for HLA-E. NKG2A forms functional heterodimers with CD94 (KLRD1) to form a human leukocyte antigen E (HLA-E) recognition complex on a subset of natural killer (NK) cells and cytotoxic T cells. NKG2A/CD94/HLA-E binding suppresses immune vigilance, and overexpression of HLA-E is used by cancer cells to evade immune recognition and destruction [2,5-7]. As a result NKG2A is being investigated as a molecular target for the development of novel cancer immunotherapeutics." It also mentions that novel anti-NKG2A monoclonals like Innate Pharma's antibody monalizumab block NKG2A/CD94 activation.

The 'Cell Type Associations' section lists: Immuno Cell Type: Natural killer cells; Cell Ontology Term: natural killer cell (CL:0000623).

The 'Immuno Process Associations' section lists: Immuno Process: Immune regulation; GO Annotations: Associated to 1 GO processes (GO:0050776 regulation of immune response); TAS.

Figure 2. Pharmacological data associated with an immunological cell type. The example shows linking from the portal via the cell type category of 'Natural killer (NK) cells'. The resulting list of targets associated with NK cells includes CD159a. Selecting the link through to the detailed view page shows CD159a interaction with the antibody monalizumab, an anti-NKG2A clinical lead for haematological cancer.

A. IUPHAR Guide to IMMUNOPHARMACOLOGY

Search Database

Home About Targets Ligands Processes Cell Types Diseases Resources Guide to

Ligand list

The IUPHAR Guide to IMMUNOPHARMACOLOGY Ligand families Ligand list

Approved WHO Syn. organic Ligand search Endo, peptide Other peptide Inorganic Antibody Labelled

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

A

852A
A286982
A438079
abatcept
abedterol
ADGn-169H

B.

dupilumab

Ligand id: 7574

Name: dupilumab

Summary Biological activity Clinical data References Immunopharmacology

View interactive charts of activity data from GtoPdb and ChEMBL (where available)

Bioactivity Comments

Affinity data in the table below is taken from patent US7608693 [2], using antibody clone H4H098P as a representative becoming dupilumab is not reported.

Selectivity at catalytic receptors

Key to terms and symbols

Target	Sp.	Type	Action	Value
Interleukin-4 receptor subunit α	Hs	Antibody	Binding	11.1

C.

dupilumab [Ligand id: 7574] activity data from GtoPdb

Click here for a description of the charts and data table

Please tell us if you are using this feature and what you think!

Interleukin-4 receptor subunit α in Human [GtoPdb: 1697] [UniProtKB: P24394]

Interleukin-4 receptor subunit α

Values

12.5
10
7.5
5
2.5
0
-2.5

pk1d Human pKi Human pIC50 Human pEC50 Human

DB	Assay description	Assay Type	Standard value	Standard parameter	Original value	Original units	Original parameter	Reference
GtoPdb	Value derived from an ELISA-based solution competition assay.	-	11.06	pIC50	0.01	nM	IC50	US7608693. Cytokine specific immunoglobulin for use in diagnosis, prevention and treatment of cell proliferative, inflammatory, allergic, respiratory, autoimmune and astrotic disorders. (2009)

Figure 3. Ligand summary pages. A. List of ligands are accessed from the menu bar. B. clicking on a ligand name links to the ligand summary page, here showing dupilumab. Data is presented under several tabs, including one specific to immunopharmacology. Users can link through to the ligand activity visualisation tool (C), to compare activities across species.

CD20 (membrane-spanning 4-domains, subfamily A, member 1)																	
Comments:	CD20 is the molecular target of the CLL therapeutics ofatumumab and obinutuzumab.																
Ligand interactions:	<table border="1"> <thead> <tr> <th>Ligand</th> <th></th> <th>Comments</th> </tr> </thead> <tbody> <tr> <td>ofatumumab</td> <td>  </td> <td>Approved drug for some CLL patients.</td> </tr> <tr> <td>veltuzumab</td> <td> </td> <td>FDA and EMA orphan drug for CLL.</td> </tr> <tr> <td>rituximab</td> <td>  </td> <td>An anti-CD20 therapy approved for CLL and non-Hodgkins lymphoma.</td> </tr> <tr> <td>obinutuzumab</td> <td>  </td> <td>Approved for use in combination with chemotherapy in patients who have received no prior therapy.</td> </tr> </tbody> </table>		Ligand		Comments	ofatumumab	  	Approved drug for some CLL patients.	veltuzumab	 	FDA and EMA orphan drug for CLL.	rituximab	  	An anti-CD20 therapy approved for CLL and non-Hodgkins lymphoma.	obinutuzumab	  	Approved for use in combination with chemotherapy in patients who have received no prior therapy.
Ligand		Comments															
ofatumumab	  	Approved drug for some CLL patients.															
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obinutuzumab	  	Approved for use in combination with chemotherapy in patients who have received no prior therapy.															

Ligands		
<p>Key to terms and symbols Click ligand name to view ligand summary Click column headers to sort</p>		
Ligand	References	Clinical and Disease comments
ofatumumab	 	▼
veltuzumab		▼
idelalisib	 	▼
rituximab	 	▲
<p>Immuno Disease Comments: An anti-CD20 therapy approved for CLL and non-Hodgkins lymphoma. Clinical Use: Used to treat CD20-positive non-Hodgkins lymphoma, chronic lymphocytic leukemia, and several autoimmune conditions (severe active, DMARD/TNF inhibitor-refractory rheumatoid arthritis; severe, active granulomatosis with polyangiitis (Wegener's, GPA); microscopic polyangiitis (MPA)). Rituximab is also used to suppress antibody-mediated rejection in living-donor kidney recipients prior to an ABO-incompatible transplant [9,18]. A modified formulation containing rituximab + human hyaluronidase (Rituxan Hycela) that can be delivered subcutaneously (the original rituximab only formulation has to be administered intravenously) was FDA approved in June 2017 for the treatment of previously untreated and relapsed or refractory follicular lymphoma, previously untreated diffuse large B-cell lymphoma (DLBCL), and previously untreated and previously treated chronic lymphocytic leukemia (CLL). In June 2018, the FDA approved the use of rituximab as a much needed treatment for the potentially life-threatening skin disease pemphigus vulgaris (PV), for use in adult patients with moderate to severe disease. EMA approval for the treatment of PV patients followed in March 2019. View clinical data Bioactivity Comments: The patents covering rituximab do not contain any data regarding antibody-antigen affinity [2-3], but a dissociation constant is provided by Stein et al (2004) [24]. View biological activity</p>		
ibrutinib	 	▼
obinutuzumab	 	▼
milatuzumab		▼
zanubrutinib		▼
otlertuzumab	 4	▼
venetoclax	  7	▼
...

Figure 4. An example disease summary page illustrating Chronic lymphocytic leukemia (www.guidetopharmacology.org/GRAC/DiseaseDisplayForward?diseaseId=218). Four antibodies are highlighted, all of which are therapeutics for CLL, that target CD20. The ligands section provides extended curatorial commentary on the clinical use and bioactivity of the compounds.

rituximab

Ligand Id: 6780

Name: rituximab

View more information in the IUPHAR Pharmacology Education Project: rituximab

Summary Biological activity Clinical data References **Immunopharmacology**

Immunopharmacology Comments

Rituximab is the first biological agent to show positive effects on biological and clinical disease parameters in Sjögren's syndrome [

Disease	X-Refs	Comment
Chronic lymphocytic leukemia	Disease Ontology: DOID:1040 OMIM: 151400 Orphanet: ORPHA67038	An anti-CD20 therapy approved for CLL and non-Hodgk
Rheumatoid arthritis	Disease Ontology: DOID:7148 OMIM: 180300	An anti-CD20 therapy approved for RA.
Pemphigus	Disease Ontology: DOID:9182	Rituximab is the first biologic therapy approved for pemphigus (PV), and represents the first major PV therapeutic advance in 60 years.

Immunopaedia Case Studies Links

[My eyes cross at twilight](#)

[A 7 year old with severe muscle weakness and difficulty walking](#)

[A case of lymphadenopathy and night sweats](#) →

[My head hurts and I cannot speak?](#)

Immunopaedia > Clinical Cases > Malignancies > A case of lymphadenopathy and night sweats

A case of lymphadenopathy and night sweats

Patient Presentation History Differential Diagnosis Examination Investigations Discussion

Treatment Final Outcome References Evaluation - Questions & answers MCQ

Treatment

ART was commenced

Chemotherapy: CHOP (cyclophosphamide, daunorubicin, vincristine and prednisone) and rituximab (anti CD20 monoclonal antibody)

Although not used to treat the patient in this case study new drugs that target IL-6 have been developed and are being tested in patients with MCD.

- **Tocilizumab** (Actemra®), is a monoclonal antibody that blocks the action of IL-6 by binding to its receptor on lymphocytes. Currently approved for treatment of rheumatoid arthritis in the United States, there has been some success in its off label use in patients with MCD.
- **Siltuximab**, also a monoclonal antibody, targets IL-6 itself. This drug has been approved by the FDA and EMA for treatment of MCD.

Figure 5. Example of ligand summary page links to relevant Immunopaedia clinical case studies. The illustrated link shows that the antibody rituximab was used in the chemotherapy treatment of a case of lymphadenopathy.

The screenshot shows the IUPHAR Guide to IMMUNOPHARMACOLOGY website. The main navigation bar includes Home, About, Targets, Ligands, Processes, Cell Types, Diseases, Resources, and Guide to PHARMACOLOGY. The Ligands menu is expanded, showing options for Ligand list, Ligand families, and Ligand search. The Ligand families section is active, displaying a list of families with 'Interleukins' highlighted in blue. An arrow points from the 'Interleukins' link in the list to the 'Interleukins' group page. This page has a sub-menu with 'Ligands' selected, showing a list of interleukins (IL-1d, IL-1B, IL-2, IL-3, IL-4, IL-5, IL-6) with 'IL-6' highlighted in blue. An arrow points from the 'IL-6' link to its detailed summary page. A blue callout box with the text 'Links to detail ligand summary page for IL-6 (Figure 7)' points to the 'More detailed page' link for IL-6.

IUPHAR Guide to IMMUNOPHARMACOLOGY

Home About Targets Ligands Processes Cell Types Diseases Resources Guide to PHARMACOLOGY

Home Ligands Ligand families Ligand list Ligand families Ligand search

GtoImmuPdb View ON Toggle CGTP status Expand all nodes Collapse all nodes

Families that contain ligands of relevance to immunopharmacology are highlighted in blue

- Ligand families
 - Activin and Inhibin
 - Antimalarial ligands
 - Bone morphogenetic proteins
 - CD molecules (ligands)
 - Chemokines
 - Complement components and ligands
 - Ephrins
 - Fibroblast growth factor (FGF) family ligands
 - Galectins
 - Glycoprotein hormones
 - Immune checkpoint regulators
 - Interferons
 - Interleukins
 - Neuropeptides
 - Non-steroidal anti-inflammatory ligands
 - Tumor necrosis factor superfamily ligands
 - Vascular endothelial growth factor (VEGF) family
 - Wnt family ligands

Interleukins

GtoImmuPdb View ON Toggle CGTP status Expand all sections Collapse all sections

Ligands

Ligands of relevance to immunopharmacology are highlighted in blue

- [IL-1d](#) (Sp: Human) Show summary » More detailed page [EIO](#)
- [IL-1B](#) (Sp: Human) Show summary » More detailed page [EIO](#)
- [IL-2](#) (Sp: Human) Show summary » More detailed page [EIO](#)
- [IL-3](#) (Sp: Human) Show summary » More detailed page [EIO](#)
- [IL-4](#) (Sp: Human) Show summary » More detailed page [EIO](#)
- [IL-5](#) (Sp: Human) Show summary » More detailed page [EIO](#)
- [IL-6](#) (Sp: Human) « Hide summary More detailed page [EIO](#)

Ligand Id	4998
Name	IL-6
Synonyms	B-cell stimulatory factor 2 CTL differentiation factor hybridoma growth factor
Genes	<i>IL6</i> (Hs)
UniProtKB AC	P05231 (Hs)

Links to detail ligand summary page for IL-6 (Figure 7)

Figure 6. Illustrates accessing ligand summary data using IL-6 as an example. Browsing via the menu bar for ligand families, selecting the Interleukins group, opens the link through to the Interleukins group. Users can then link through from these points to the IL-6 ligand summary page (Figure 7).

A.

Summary Biological activity References Structure **Immunopharmacology**

Immunopharmacology tab of IL-6 highlighting its pro- and anti-inflammatory effects and its role in treatment of rheumatoid arthritis.

Immunopharmacology Comments

IL-6 signalling in monocytes and macrophages is pro-inflammatory. It is produced by these cell types in response to infection and traumatic tissue injury. In contrast, the IL-6 produced by exercising muscle produces an anti-inflammatory effect. Antibodies and other agents that inhibit the IL-6 signalling pathway are in development as immunomodulators for the treatment of rheumatoid arthritis (RA), and other inflammatory and autoimmune diseases [3]. The mAb siltuximab is already approved. Investigational agents include sirukumab, clazakizumab, olamkicept, gerilimzumab (an anti-IL-6 mAb with a high potency and long half-life, which has the potential to support low and infrequent dosing- beginning Phase 2 trial NCT02795299 for methotrexate or TNF- α antagonist resistant RA), and olokizumab [10] (CDP6038) a RA Phase 2 clinical candidate [5,12].

There is evidence to suggest that IL-6 in the cerebrospinal fluid may be linked to the emergence of depressive symptoms that are often associated with systemic inflammation [2]. Additional evidence showing that treatment with anti-IL-6 antibodies (sirukumab or siltuximab) reduces depressive symptoms in patients being given these agents as therapy for inflammatory diseases, supports this proposed mechanism in depression [11].

Immunopharmacology Disease

Disease	X-Refs	Comment	References
Rheumatoid arthritis	Disease Ontology: DOID:7148 OMIM: 180300	IL-6 is known to drive arthritic inflammation and bone destruction in RA. mAbs against both the IL-6 ligand and its receptor (IL-6R) are now approved for use in the clinic, and accumulating evidence suggests that targeting of IL-6 can be the best treatment option for RA. In light of this, development of new monoclonal antibodies targeting the IL-6/IL-6R pathway is continuing.	

B.

Selectivity at catalytic receptors

Key to terms and symbols Click column headers to sort

Target	Sp.	Type	Action	Value	Parameter	Reference
Interleukin-6 receptor, α subunit	Hs	Agonist	Agonist	9.4	pK_d	8
Interleukin-6 receptor	Hs	Agonist	Agonist	9.4	pK_d	8

Other ligands which bind to or alter the activity of this ligand

Key to terms and symbols Click column headers to sort

Ligand	Sp.	Type	Action	Value	Parameter	Reference
sirukumab	Hs	Antibody	Binding	13.4	pK_d	1
clazakizumab	Hs	Antibody	Binding	>10.3		
siltuximab	Hs	Antibody	Binding	10.2		
olamkicept	Hs	None	Binding	8.4		

Biological activity data lists the binding affinity data of ligands that interaction with IL-6, this includes the approved drug siltuximab

Figure 7. Highlights from the IL-6 ligand summary page

(www.guidetoimmunopharmacology.org/GRAC/LigandDisplayForward?ligandId=4998).

Curator's comments (A) are shown under the immunopharmacology tab and indicate links with rheumatoid arthritis. Parts of the biological activity tab (B), show ligands that interact with IL-6, including the approved drug siltuximab.

Natural/Endogenous Targets

Target
Interleukin-18 receptor

Biological activity data for IL-18, and below, immunopharmacology comments

Selectivity at catalytic receptors

Key to terms and symbols Click column headers to sort

Target	Sp.	Type	Action
Interleukin-18 receptor 	Hs	Agonist	Agonist

Other ligands which bind to or alter the activity of this ligand

Key to terms and symbols Click column headers to sort

Ligand	Sp.	Type	Action	Value	Parameter	Reference
NSC80734 	Hs	Antagonist	Binding	6.4	pK _i	1
tadekinig alfa 	Hs	Antagonist	Binding	-	-	4

Immunopharmacology Comments

Chronic, elevated production of free (mature) IL-18 has been identified as a driver of macrophage activation syndrome (MAS), a life-threatening systemic inflammatory disorder that occurs in patients with rheumatic disease [2-3]. In particular, MAS is a severe complication in children with systemic juvenile idiopathic arthritis, for which there are currently limited treatment options [4]. Epithelial NLR4 inflammasome hyperactivity appears to be the source of the excessively high IL-18 production in MAS. One next generation biologic treatment for MAS is tadekinig alfa, a recombinant human IL-18 binding protein, which is proposed to mop up the free circulating IL-18 to reduce its inflammatory effect on macrophages.

Figure 8. Showing the biological activity and immunopharmacology data from the IL-18 ligand summary page (www.guidetoimmunopharmacology.org/GRAC/LigandDisplayForward?ligandId=4983). Interaction with the tadekinig alfa peptide is highlighted, which plays a role in reducing the inflammatory effect of IL-18.

Inhibitors

Key to terms and symbols View all chemical structures Click column headers to sort

Ligand	Sp.	Action	Value	Parameter	Reference
CY-09  	Hs	Inhibition	6.3	pK _d	5
MCC950 	Hs	Inhibition	>8.0	pI _{C₅₀}	2
dapansutril  	Hs	Inhibition	-	-	8

Immunopharmacology Comments

NLRP3 is a component of the NLRP3 inflammasome, a protein complex which activates caspase-1, and plays an important role in the regulation of inflammation and apoptosis (pyroptosis). Drug-like NLRP3 inhibitors are under investigation as novel therapeutics for the treatment of autoinflammatory diseases and neuroinflammation, as an alternative to anti-IL-1 therapies such as rilonacept, anakinra and canakinumab [1,6]. The potential of pharmacological modulation of the NLRP3 inflammasome as a mechanism to treat inflammatory diseases is reviewed by Mangan *et al.* (2018) [7].

Figure 9. Inhibitors and immunopharmacology data from the detailed target page for NLRP3 (www.guidetoimmunopharmacology.org/GRAC/ObjectDisplayForward?objectId=1770#Inhibitors). Immunopharmacology comments highlight its role in the regulation of inflammation. Both CY-09 and MCC950 have quantitative interaction data and these are marked with the immuno-icon, showing they have relevance to immunopharmacology.

Inhibitors						
Key to terms and symbols						Click column headers to sort
Ligand	Sp.	Action	Value	Parameter	Reference	
bococizumab	Hs	Inhibition	10.0	pK _d	6	▼
evolocumab	Hs	Inhibition	9.7	pK _d	5	▼
alirocumab	Hs	Inhibition	9.4	pK _d	14	▼

Immuno Process Associations	
Immuno Process:	Antigen presentation
GO Annotations:	Associated to 4 GO processes
	GO:0002092 positive regulation of receptor internalization IDA
	GO:0034383 low-density lipoprotein particle clearance TAS
	GO:1905598 negative regulation of low-density lipoprotein receptor activity IDA
	GO:1905601 negative regulation of receptor-mediated endocytosis IDA
	involved in cholesterol transport

PCSK9 GtoImmuPdb target detail page, showing inhibitors and associations with antigen presentation GO biological processes

Figure 10. Inhibitors and immunopharmacology data from the detailed target page for PCSK9 (www.guidetoimmunopharmacology.org/GRAC/ObjectDisplayForward?objectId=2388#Inhibitors).

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