Guide to IMMUNOPHARMACOLOGY

Overview presentation for October 2018 meeting

THE UNIVERSITY of EDINBURGH

IMMUNOPHARMACOLOGY: challenges, opportunities and research tools

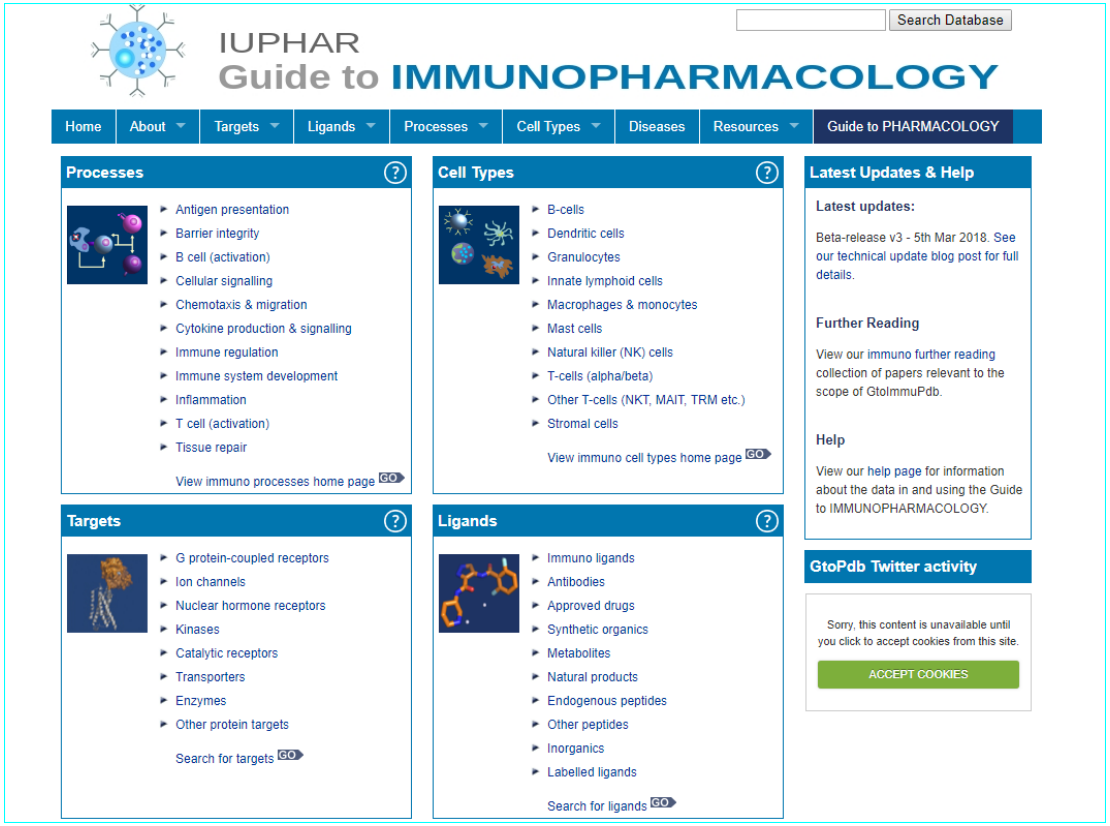
Edinburgh, SCOTLAND

IUPHAR International Union of Basic and Clinical Pharmacology

Individual Team Members:

- Simon Harding
- Chris Southan
- Elena Faccenda
- Joanna Sharman-Soares
- Adam Pawson
- Jamie Davies

http://www.guidetoimmunopharmacology.org/immuno/index.jsp



Development overview

- Extends the existing GtoPdb schema with new immuno-relevant data types e.g. Processes, Cell types, Diseases
- Modification of submission tool to capture and integrate new data
- Extending the web-interface to:
  - Surface new data types within existing GtoPdb resource
  - Provide a unique portal into the new data (GtoImmuPdb view)
  - Extend search mechanisms to encompass new data

Curation sources

- Focussed literature searches
- Pharma companies pipeline disclosures
- Pharma and academic press releases
- Clinical trial registries
- Selected Twitter sources
- INN lists
- Patent documents
- ArchiveX pre-prints (just initiated)

Literature searching

- Most methods we explored worked but had different levels of recall, specificity and efficiency
- Magnitude of the challenge indicated by monthly PubMed alert of: “immunology OR "immune system" AND immunomodulation OR immunosuppression OR immunostimulation OR inflammation” typically returning ~ 5000 hits (good recall)
- Highest specificity was browsing the contents pages of *Journal of Medicinal Chemistry*
- Highest efficiency was via Twitter from selected journals and immunology society feeds and newsletters
- Good specificity during curation of any paper by browsing PubMed “Similar articles” and “Cited by”
- The counter-intuative take home was that only a minority of our curated primary reverences came from what we might classify as the ”immunopharmacolgy” literature (see journal distribution in later slide)

Triage and pre-curation

Benefits of using CUL to triage huge data sources

- On-line collation of relevant references with curatable entities as targets and/or ligands
- Common tags to allow retrieval of combined efforts
- Add pre-curation comments (*e.g*. CIDs, SMILES *etc*. for ligands; Uniprot IDs for new targets)
- Add personal PDFs for full curation
- Repository of useful reviews and Hot Topics as further reading
- System is open and tags can be shared with anyone
- Not restricted to papers (can add any form of text reference)
- Caveats
  - Need to avoid common tags (i.e. use semi-cryptic personal tags)
  - Inability to cross-comment between users (have to duplicate comments and/or other curator adds separate comments)
  - No explicit linking between CUL IDs, DOIs, PubMed IDs and our database references
  - Little active development with Elsevier persistence dependency

Your can see our collections here
http://www.citeulike.org/user/cdsouthan/tag/immpharm
http://www.citeulike.org/user/efaccenda

CUL-tagged papers > further reading

Guide to IMMUNOPHARMACOLOGY - Further Reading

This further reading collection is extracted from an open CiteUlike collection compiled by the curation team http://www.citeulike.org/tag/immpharm. The papers presented are general, not ones we have curated database entries from since those papers are now referenced in the database (with the exception of review articles that include ligand structures). As can be seen these are mostly review articles that are relevant to the scope of the database. We would be pleased to receive recommendations for additions (either to this list or for curation).

Reviews

Impact of oncogenic pathways on evasion of antitumour immune responses.
Spranger S, Gajewski TF. (2018)
Nat. Rev. Cancer, **18** (3): 139-147. [PMID:29326431]

Hitting the Target: How T Cells Detect and Eliminate Tumors.
Zamora AE, Crawford JC, Thomas PG. (2018)
J. Immunol., **200** (2): 392-399. [PMID:29311380]

A Believer's Overview of Cancer Immunosurveillance and Immunotherapy.
Finn OJ. (2018)
J. Immunol., **200** (2): 385-391. [PMID:29311379]

The spectrum of T cell metabolism in health and disease.
Bantug GR, Galluzzi L, Kroemer G, Hess C. (2018)
Nat. Rev. Immunol., **18** (1): 19-34. [PMID:28944771]

Checkpoints in TNF-Induced Cell Death: Implications in Inflammation and Cancer.
Annibaldi A, Meier P. (2017)
Trends in Molecular Medicine, In Press Corrected Proof.

Tag immpharm [more than 800 articles]

Recent papers classified by the tag immpharm. You can also see your immpharm.

Search | Watch | Copy | Export | Sort | Hide Details

✓ Forkhead box transcription factors as context-dependent regulators of lymphocyte homeostasis.
Nature reviews. Immunology (03 September 2018)
by Dietmar M. W. Zaiss, Paul J. Coffer
posted to immpharm immpharm_review by efaccenda keyed Zaiss2018Forkhead on 2018-09-26 14:27:24 ★★★/
■ Abstract ■ Notes ■ Copy ■ My Copy

✓ The emerging role of ADAM metalloproteinases in immunity.
Nature reviews. Immunology (21 September 2018)
by Bart N. Lambrecht, Matthias Vanderkerken, Hamida Hammad
posted to immpharm immpharm_review metalloproteinases by efaccenda keyed Lambrecht2018Emerging on 2018-09-26 14:23:31 ★★★/
■ Abstract ■ Notes ■ Copy ■ My Copy

✓ Anti-IL-23 and Anti-IL-17 Biologic Agents for the Treatment of Immune-Mediated Inflammatory Conditions.
Clinical pharmacology and therapeutics, Vol. 103, No. 1. (January 2018), pp. 88-101
by Jillian Frieder, Dario Kivelevitch, Isabel Haugh, Ian Watson, Alan Menter
posted to il17 immpharm immpharm_review psoriasis by efaccenda keyed Frieder2018AntiIL23 on 2018-09-24 15:38:55 ★★★/
■ Abstract ■ Notes ■ Copy ■ My Copy

✓ Interleukin-17-producing γδ T (γδ 17) cells in inflammatory diseases
Immunology (10 September 2018), doi:10.1111/imm.12993
by Aoi Akitsu, Yoichiro Iwakura
posted to immpharm review by cdsouthan on 2018-09-24 09:26:28 ★★
■ Abstract ■ Copy

Inhibition of neogenin fosters resolution of inflammation and tissue regeneration
The Journal of Clinical Investigation, Vol. 128, No. 10. (September 2018), doi:10.1172/JCI96259
by Martin Schlegel, Andreas Körner, Torsten Kaussen, et al.
posted to immpharm by cdsouthan on 2018-09-22 13:56:51 ★★
■ Abstract ■ Copy

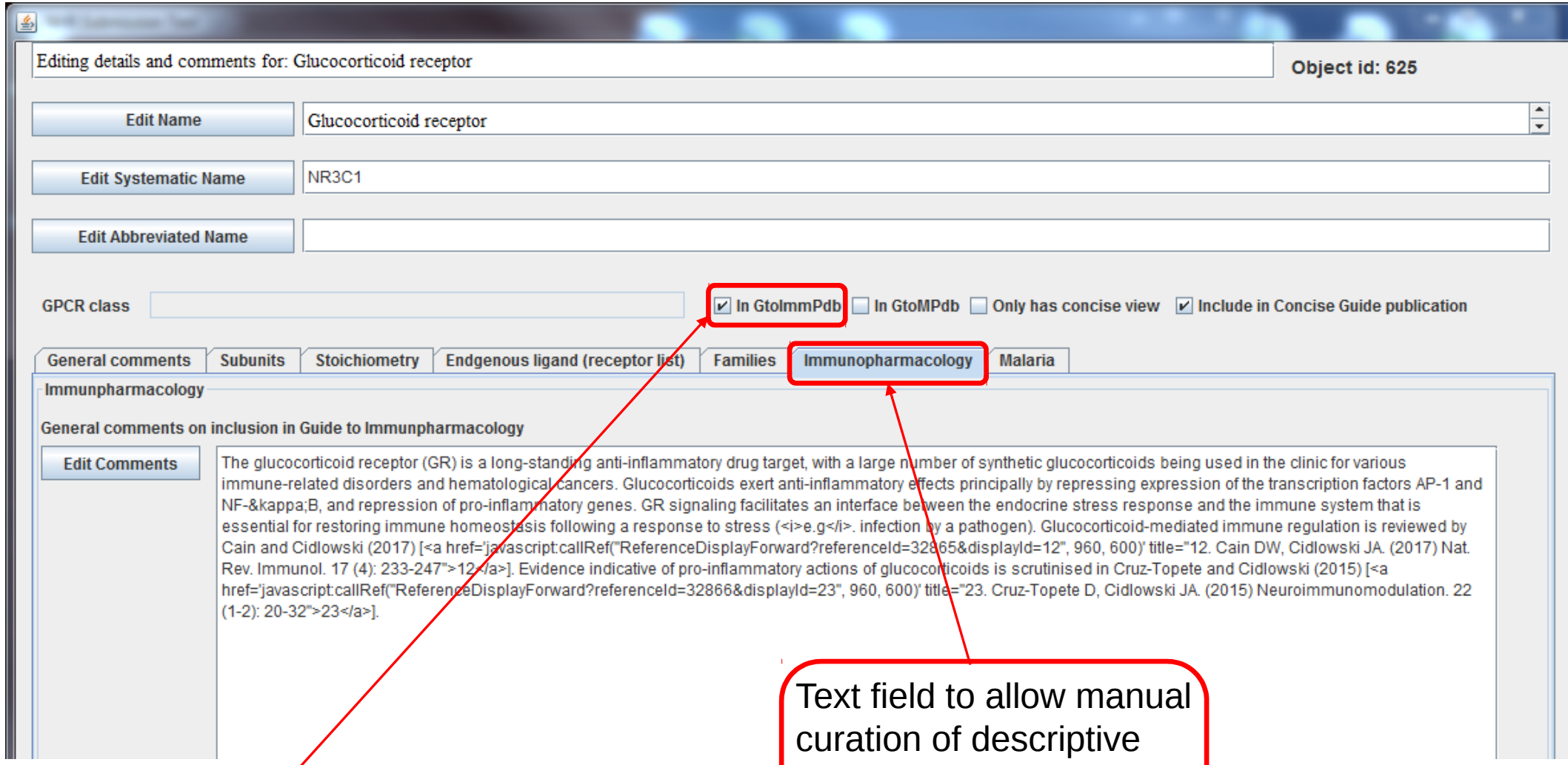
✓ Design, Synthesis, and Biological Evaluation of 3-(Imidazo[1,2- a]pyrazin-3-ylethynyl)-4-isopropyl- N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)benzamide as a Dual Inhibitor of Discoidin Domain Receptors 1 and 2.
Journal of medicinal chemistry, Vol. 61, No. 17. (13 September 2018), pp. 7977-7990
by Zhen Wang, Yali Zhang, Daniel M. Pinkas, et al.
posted to immpharm tobecurated by cdsouthan on 2018-09-21 21:10:52 ★★
■ Abstract ■ Notes ■ Copy

✓ The Chemokine Receptor CCR8 Promotes the Migration of Dendritic Cells into the Lymph Node Parenchyma to Initiate the Allergic Immune Response.
Immunity (28 August 2018)
by Caroline L. Sokol, Ryan B. Camire, Michael C. Jones, Andrew D. Luster
posted to immpharm by cdsouthan on 2018-09-20 08:52:27 ★★
■ Abstract ■ Copy

Design, Synthesis and Characterization of Covalent KDM5 Inhibitors
(September 2018), doi:10.26434/chemrxiv.7072592.v1
by Saleta Vazquez-Rodriguez, Miranda Wright, Catherine Rogers, et al.
posted to curatedlig immpharm kdm5 by cdsouthan on 2018-09-19 08:22:49 ★★
■ Abstract ■ Notes ■ Copy

Shared tags

Target curation (1)



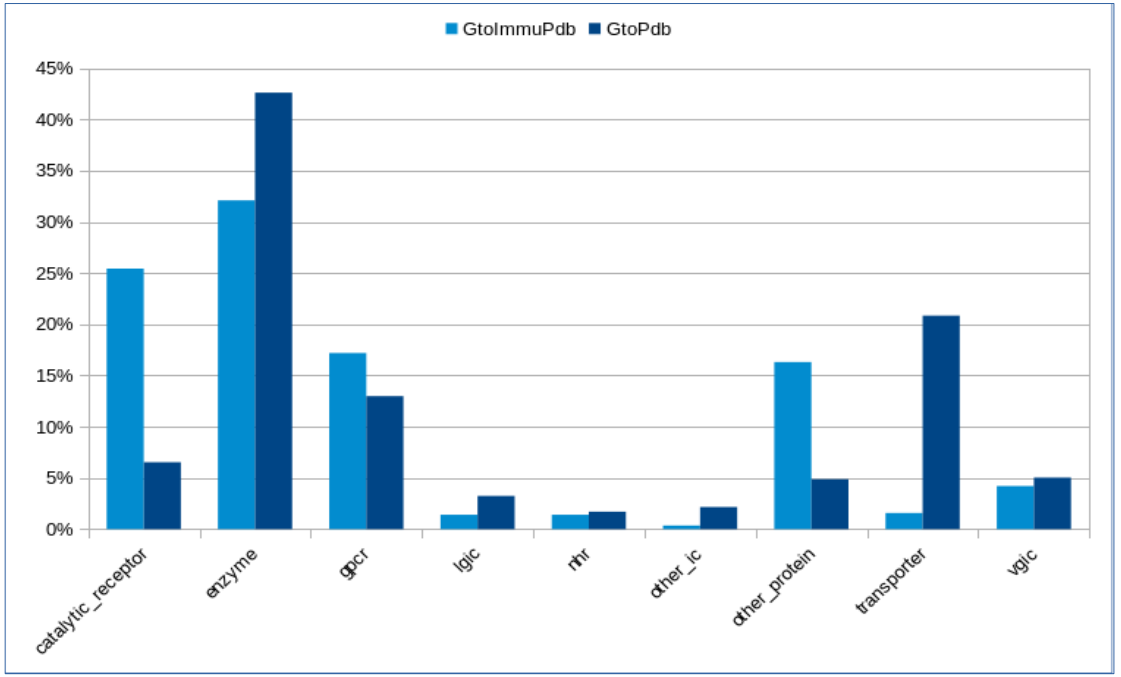
Tag to allow retrieval of all GToImmuPdb targets

Text field to allow manual curation of descriptive information and supporting literature references

Target curation (2)

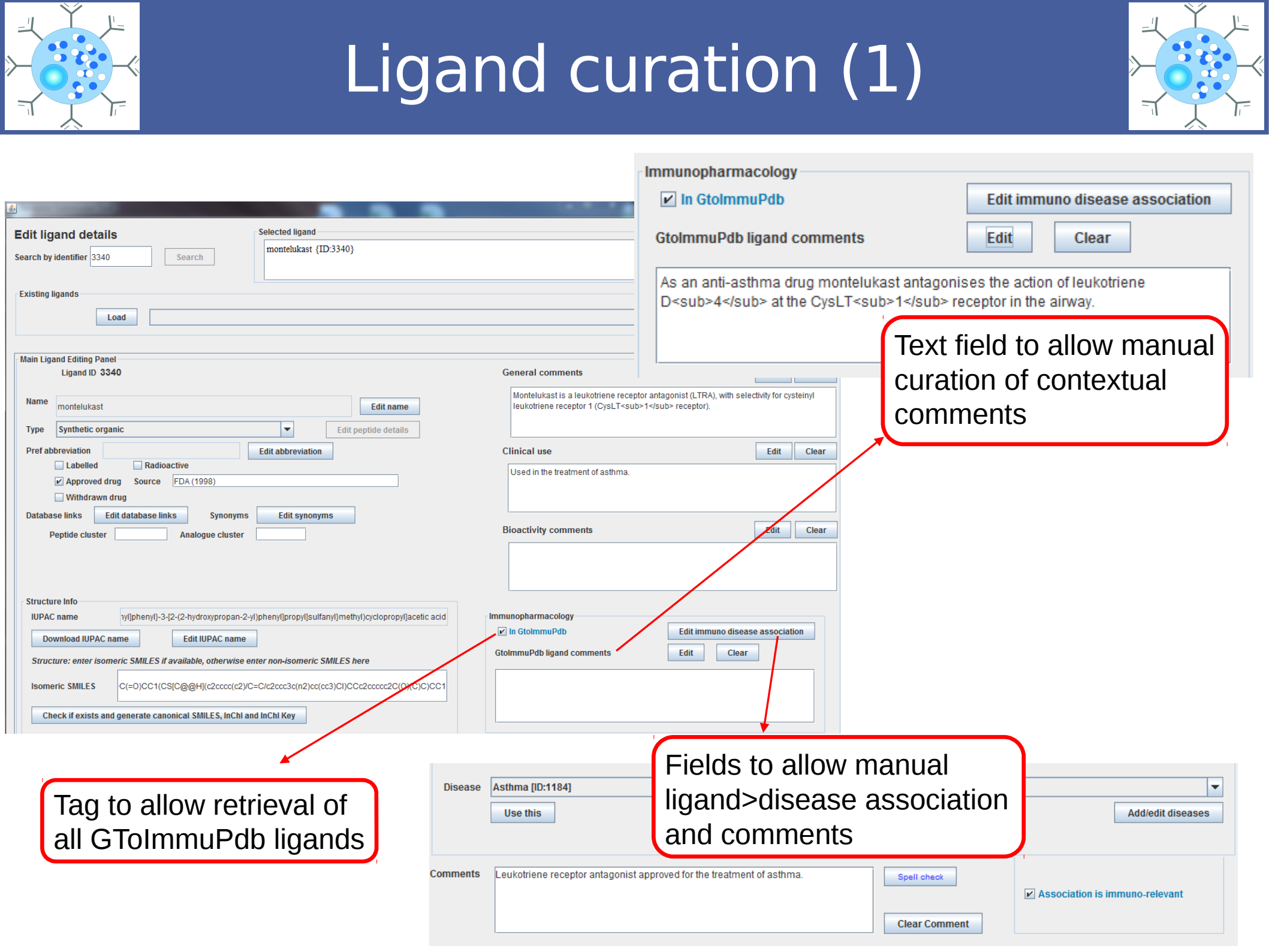
Breakdown of targets tagged in GtoImmuPdb by target class

568 targets in GtoImmuPdb	
Enzymes	183
Catalytic Receptors	145
GPCRs	98
Other Proteins	93
VGICs	24
Transporters	9
NHRs	8
LGICs	8



- Comparing distribution of targets in GtoImmuPdb against all other targets in GtoPdb
- Y-axis shows percentage of targets.
- GtoImmuPdb is over-represented by Catalytic Receptors and Other Protein classes

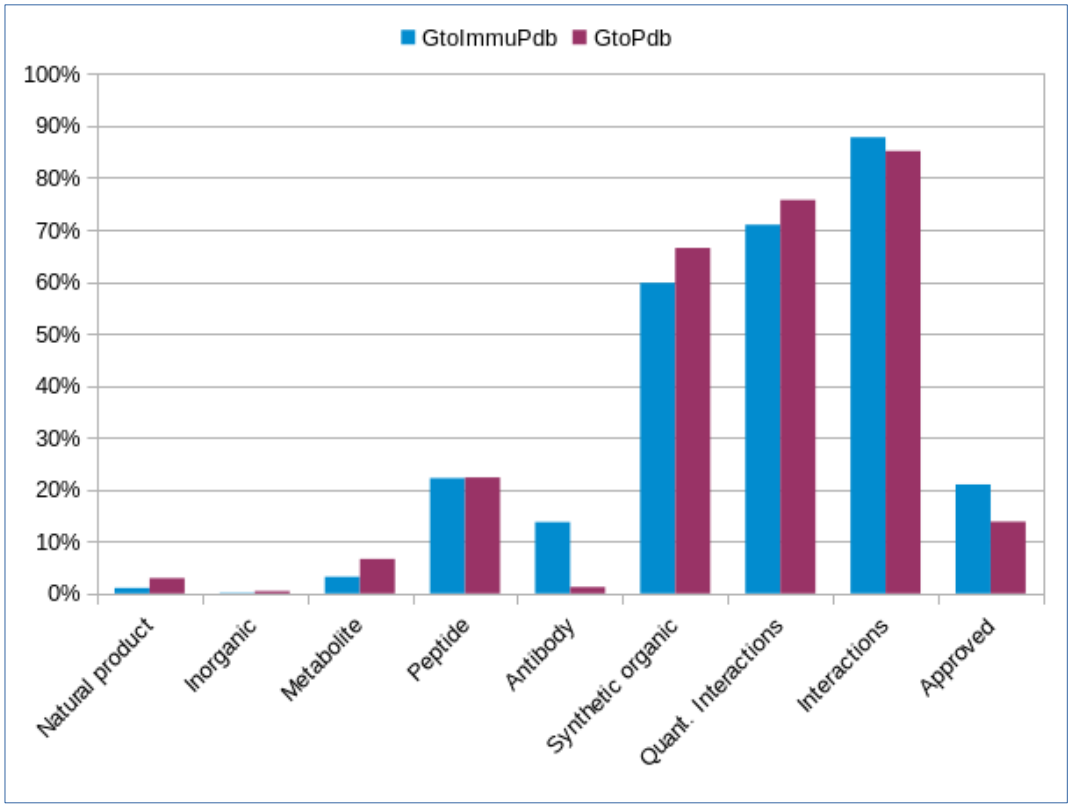
Ligand curation (1)



Ligand curation (2)

Breakdown of ligands tagged in GtoImmuPdb by type. Includes count of approved drugs

1068 ligands in GtoImmuPdb	
Synthetic Organic	640
Peptides	236
Antibodies	146
Metabolite	34
Natural Products	11
Inorganic	1
Approved Drugs	236



- Comparing distribution of ligands in GtoImmuPdb against all other ligands in GtoPdb
- Y-axis shows percentage of ligands
- GtoImmuPdb is over-represented by Antibodies compared to GtoPdb. It also has a slightly higher proportion of approved drugs

GtoImmuPdb ligands in PubChem

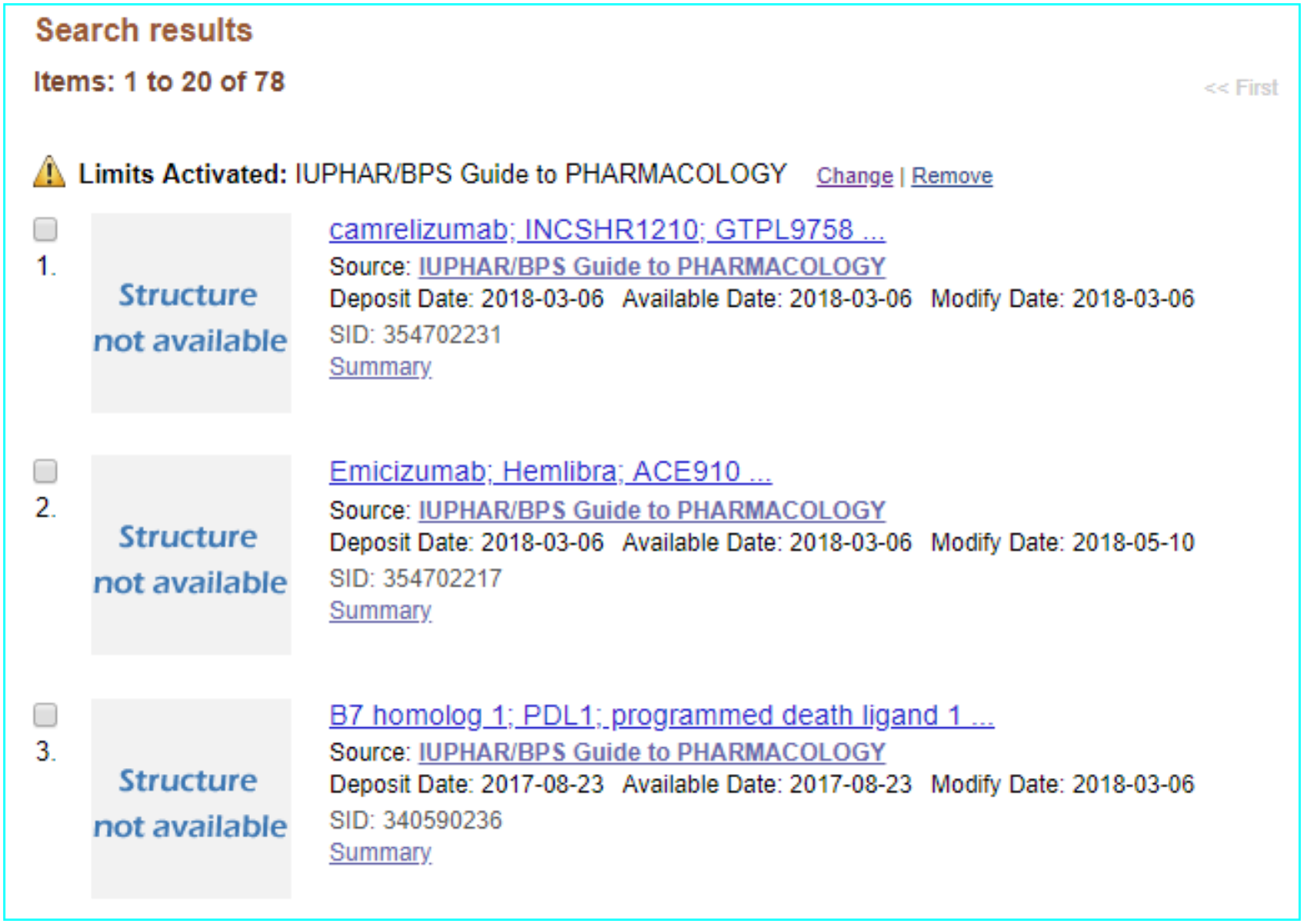
- PubChem is the single most important global resource to surface our GtoImmuPdb ligands
- We have exellent collaborative contacts with the PubChem from our GtoPdb history of submissions for every release
- We have introduced a series of tags that PubChem users can exploit for sub-setting our ligand entries (see stats below)
- Note also our linkages present a ”virtuos cirle” for connectivity between GtoP, PubChem and PubMed, from the references we curate for our ligand entries

- Headline stats associated with GtoPdb releas 2018.4 are as follows:
  - All substances (SIDs) = 9414 (includes antibodies, small proteins and larger peptides)
  - Small-molecule compounds (CIDs) = 7249
  - Approved drugs (human use) = 1480
  - CIDs unique to us as a source = 164
  - Antibodies (clinical) all = 247

- Headline stats associated with GtoImmuPdb
  - All substances (SIDs) = 1064
  - Small-molecule compounds (CIDs) = 687
  - Approved drugs = 259
  - Antibodies = 145
  - Approved antibodies = 78

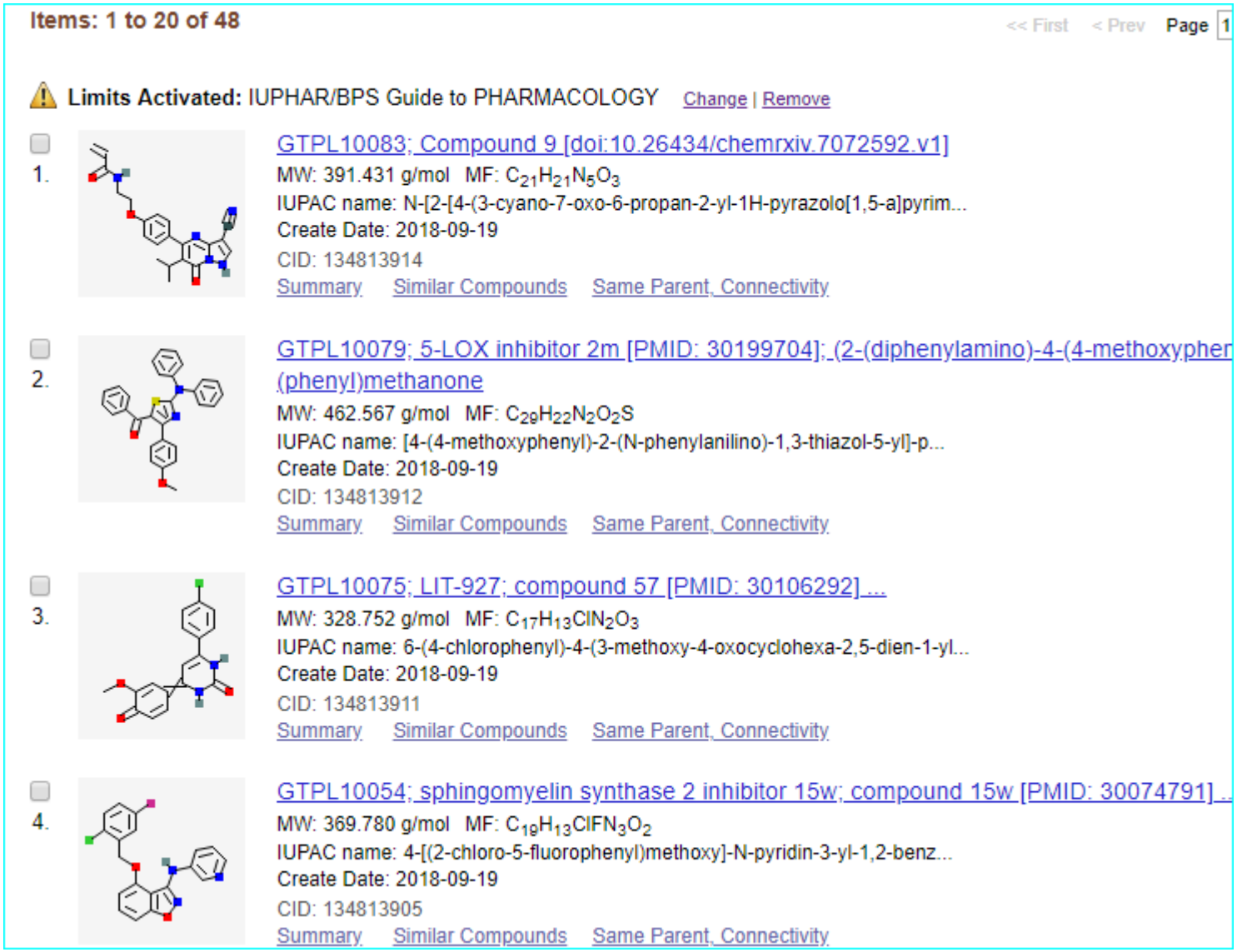
PubChem example (1)

- Substance side query “approved AND antibody AND "IUPHAR/BPS Guide to PHARMACOLOGY"[SourceName]”



PubChem example (2)

- "IUPHAR/BPS Guide to PHARMACOLOGY"[SourceName]" as CIDs from "immunopharmacology, select for unique to us, and sort by date



Items: 1 to 20 of 48 << First < Prev Page 1

Limits Activated: IUPHAR/BPS Guide to PHARMACOLOGY Change | Remove

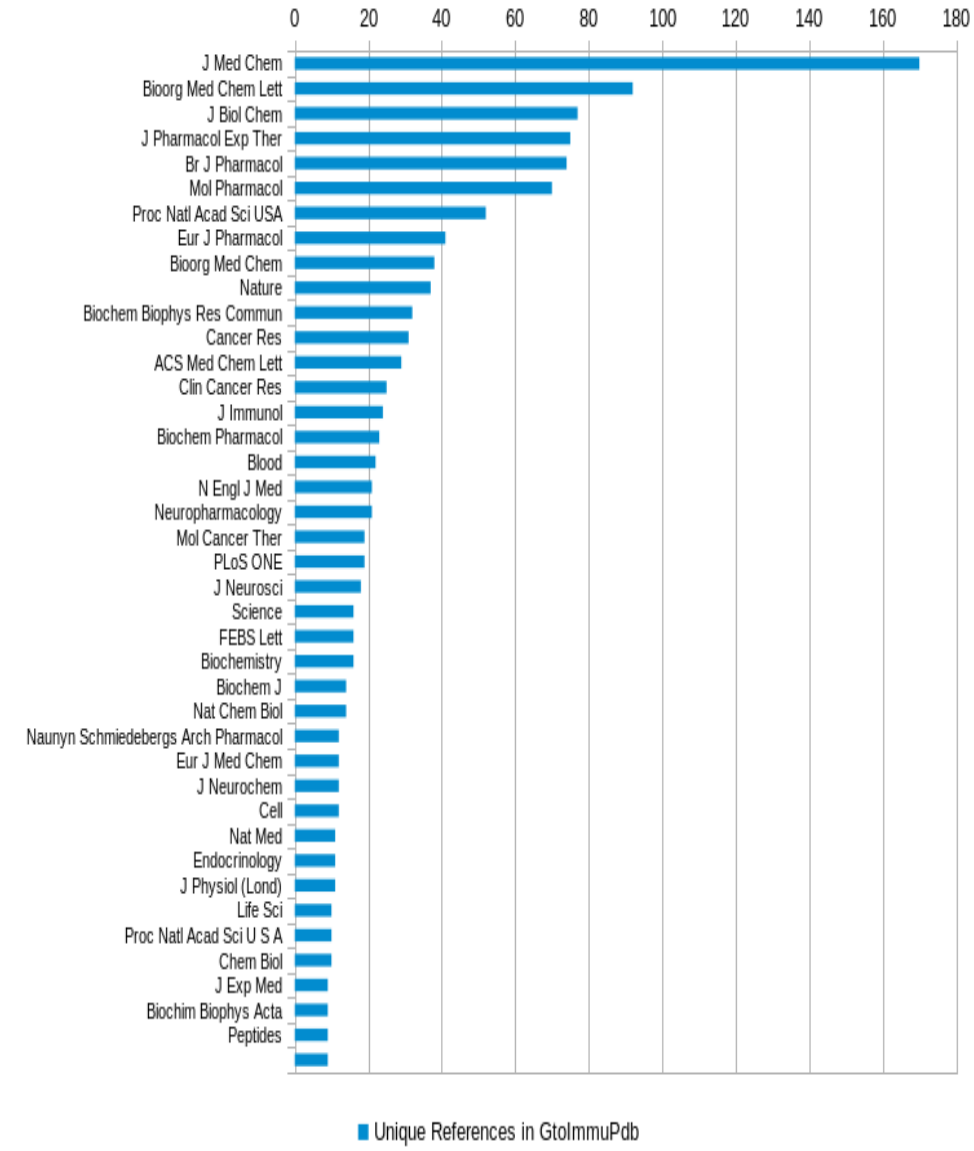
1. GTPL10083; Compound 9 [doi:10.26434/chemrxiv.7072592.v1]
MW: 391.431 g/mol MF: $C_{21}H_{21}N_5O_3$
IUPAC name: N-[2-[4-(3-cyano-7-oxo-6-propan-2-yl-1H-pyrazolo[1,5-a]pyrim...
Create Date: 2018-09-19
CID: 134813914
Summary Similar Compounds Same Parent, Connectivity

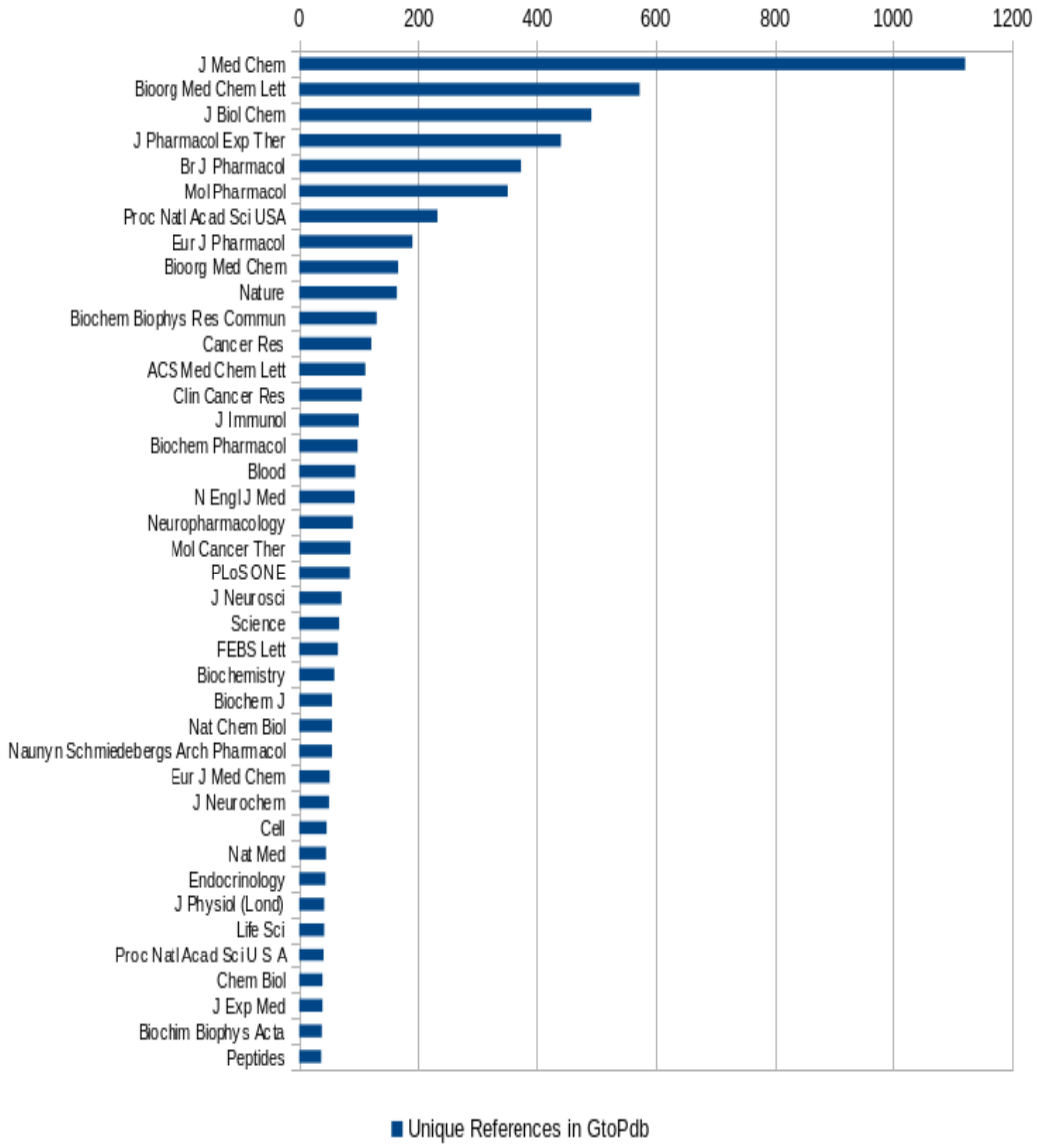
2. GTPL10079; 5-LOX inhibitor 2m [PMID: 30199704]; (2-(diphenylamino)-4-(4-methoxypher
(phenyl)methanone
MW: 462.567 g/mol MF: $C_{29}H_{22}N_2O_2S$
IUPAC name: [4-(4-methoxyphenyl)-2-(N-phenylanilino)-1,3-thiazol-5-yl]-p...
Create Date: 2018-09-19
CID: 134813912
Summary Similar Compounds Same Parent, Connectivity

3. GTPL10075; LIT-927; compound 57 [PMID: 30106292] ...
MW: 328.752 g/mol MF: $C_{17}H_{13}ClN_2O_3$
IUPAC name: 6-(4-chlorophenyl)-4-(3-methoxy-4-oxocyclohexa-2,5-dien-1-yl...
Create Date: 2018-09-19
CID: 134813911
Summary Similar Compounds Same Parent, Connectivity

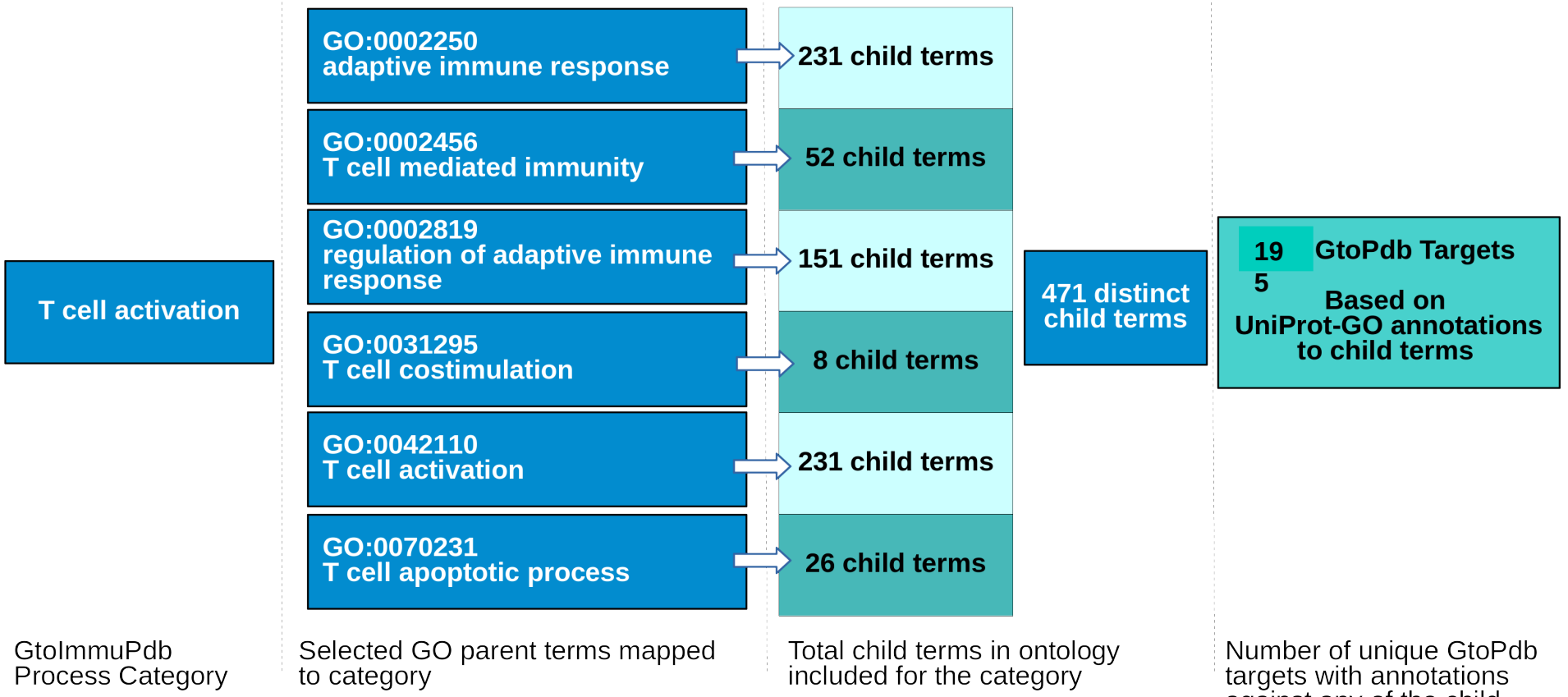
4. GTPL10054; sphingomyelin synthase 2 inhibitor 15w; compound 15w [PMID: 30074791] ...
MW: 369.780 g/mol MF: $C_{19}H_{13}ClFN_3O_2$
IUPAC name: 4-[(2-chloro-5-fluorophenyl)methoxy]-N-pyridin-3-yl-1,2-benz...
Create Date: 2018-09-19
CID: 134813905
Summary Similar Compounds Same Parent, Connectivity

Publication counts





Annotating processes via GO



- Targets associated with top-level immunological process categories
- Parent Gene Ontology (GO) terms mapped to categories
- Auto-curate targets annotated to any of those GO terms (or their children)
- GO annotations downloaded from UniProt
- GO ontology terms obtained from (http://purl.obolibrary.org/obo/go.obo)

Immuno process data (1)

Immuno Process Category	GtoPdb Human UniProtKB	GO Annotations
Antigen presentation	178	260
B cell (activation)	156	261
Barrier integrity	47	63
Cellular signalling	480	1177
Chemotaxis & migration	266	491
Cytokine production & signalling	504	1347
Immune regulation	481	1252
Immune system development	240	428
Inflammation	630	1434
T cell (activation)	195	418
Tissue repair	21	21

Immuno process data (2)

Processes auto-curated for the PD-1 checkpoint protein

Immuno Process Associations			
Immuno Process:	T cell (activation)		
GO Annotations:	Associated to 2 GO processes		
	GO:0031295 T cell costimulation	TAS	
	GO:0070234 positive regulation of T cell apoptotic process	IDA	
Immuno Process:	Immune regulation		
GO Annotations:	Associated to 2 GO processes		
	GO:0031295 T cell costimulation	TAS	
	▼ *click arrow to show/hide IEA associations*		
Immuno Process:	Chemotaxis & migration		
GO Annotations:	Associated to 1 GO processes		
	GO:0031295 T cell costimulation	TAS	
Immuno Process:	Cellular signalling		
GO Annotations:	Associated to 1 GO processes		
	GO:0031295 T cell costimulation	TAS	
Immuno Process:	Immune system development		
GO Annotations:	Associated to 1 GO processes, IEA only		
	▼ *click arrow to show/hide IEA associations*		

GO evidence codes

TAS = Traceable Author Statement

IDA = Inferred from Direct Assay

= Inferred from Electronic Annotation; automated- no curatorial judgement

Immuno cell type data(1)

Cell type category	Targets annotated
B cells	47
Dendritic cells	37
Granulocytes	40
Innate lymphoid cells	2
Macrophages & monocytes	53
Mast cells	37
Natural killer cells	22
Other T cells	3
T cells	69
Stromal cells	1

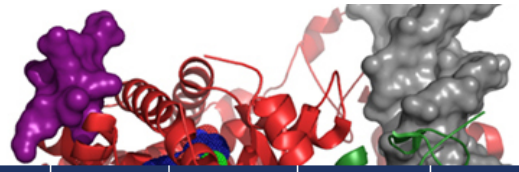
Immuno cell type data (2)

Cell types manually curated as expressing the Orai1 ion channel

Cell Type Associations	
Immuno Cell Type:	Natural killer cells
Cell Ontology Term:	natural killer cell (CL:0000623)
Comment:	Orai1 is expressed by NK cells and is involved in degranulation and NK cell-mediated cytotoxicity.
References:	24
Immuno Cell Type:	Mast cells
Cell Ontology Term:	mast cell (CL:0000097)
Comment:	Orai1 on mast cells is involved in their degranulation, histamine release and cytokine production and in the immediate dermal response to an allergen-IgE interaction (a.k.a. passive cutaneous anaphylaxis).
References:	24
Immuno Cell Type:	T cells
Cell Ontology Term:	regulatory T cell (CL:0000815) T-helper 17 cell (CL:0000899) type I NK T cell (CL:0000921)
Comment:	The Orai1 gene is expressed by a variety of T cell subtypes, some of which are specified here.
References:	24

Disease pages

Developed for GtoImmuPdb but implemented across the wider data set held in the GtoPdb



IUPHAR/BPS Guide to PHARMACOLOGY

Search Database

Home | About | Targets | Ligands | Diseases | Resources | Advanced search | Guide to IMMUNOPHARMACOLOGY Portal

Home ▸ Diseases

The IUPHAR/BPS Guide to PHARMACOLOGY complete disease list

All Diseases | Immuno Disease

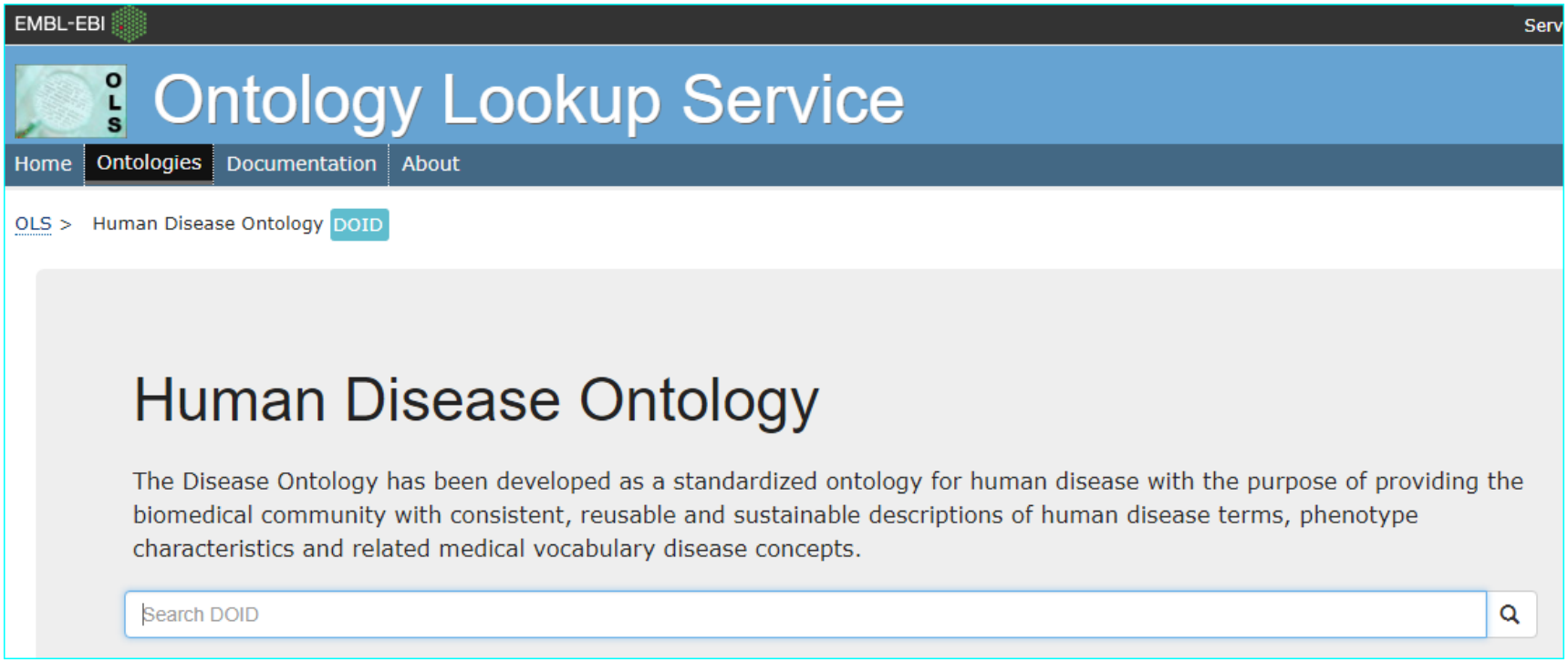
All diseases described in GtoPdb.

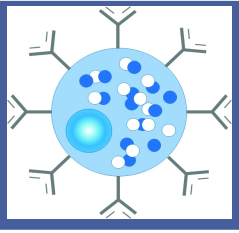
A B C D E F G H I J K L M N O P Q R S T U V W X Y

Disease name	Synonyms	Targets	Ligands
A			Back to top
ABCD syndrome		1	0
Abdominal obesity-metabolic syndrome 1; AOMS1	Metabolic syndrome X	2	0
Abdominal obesity-metabolic syndrome 3; AOMS3		1	0
Abnormal pregnancies		1	0
Absence epilepsy	early onset absence epilepsy	2	0
Acatalasemia	acatalasia | catalase deficiency | Takahara disease	1	0
Acetyl-CoA acetyltransferase-2 deficiency; ACAT2D		1	0
Achondroplasia		1	0
Achromatopsia 2; ACHM2	Achromatopsia	1	0
Achromatopsia 3; ACHM3	Achromatopsia	1	0
Acne inversa, familial, 3; ACNINV3	Hidradenitis suppurativa	1	0
Acne vulgaris	adult acne	0	1
Acrodermatitis enteropathica		1	0
Acrodysostosis 1 with or without hormone resistance; ACRDYS 1	Acrodysostosis | Acrodysostosis with multiple hormone resistance	1	0
Acromegaly		1	0
Acromesomelia and painful neuropathy	acromesomelic dysplasia | neuropathy	1	0
Activated PI3K delta syndrome	APDS/PASLI | Immunodeficiency 14 | p110 delta activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency	1	3

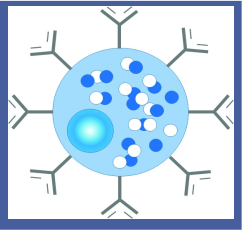
Disease data

	Disease Associations	Targets/Ligands	Diseases
Targets	55	37	29
Ligands	708	401	103





Annotated diseases



Disease Associations to Targets and Ligands: Disease with most associations			
Disease	**Targets**	**Disease**	**Ligands**
Rheumatoid arthritis	11	Rheumatoid arthritis	125
Asthma	6	Asthma	77
Osteoarthritis	5	Psoriasis	56
Acute myeloid leukemia	3	Chronic obstructive pulmonary disease	42
Psoriasis	2	Crohn's disease	26
Irritable bowel syndrome	2	Osteoarthritis	25
Acute lymphocytic leukemia (ALL)	2	Systemic lupus erythematosus	23
Behcet syndrome	2	Ulcerative colitis	21
Multiple sclerosis	2	Psoriatic arthritis	16
		Atopic dermatitis	15
		Dermatitis	14
		Ankylosing spondylitis	14
		Allergic rhinitis	13
		Relapsing-remitting multiple sclerosis	12
		Chronic lymphocytic leukemia	11
		Allergic urticaria	9
		Allergic conjunctivitis	8
		Inflammatory bowel disease 1; IBD1	8
		Graft versus host disease	7
		non-Hodgkin lymphoma	7

GtoImmuPdb growth (1)

	May 2016	Oct 2016	Mar 2017	June 2017	Nov 2017	Jan 2018	Mar 2018	Apr 2018	Sep 2018
Targets	54	99	406	448	475	493	509	523	568
Ligands	79	195	553	776	856	910	920	985	1068
Ligands associated to disease	0	0	219	324	342	349	362	386	401
Targets associated to disease	0	0	11	22	24	24	25	35	37
Targets associated to processes	0	401	448	828	884	928	941	941	979
Targets associated to cell types	0	0	86	105	106	109	116	117	147

We retrospectively GToImmuPdb-tagged 488 existing GToPdb targets and 594 existing ligands

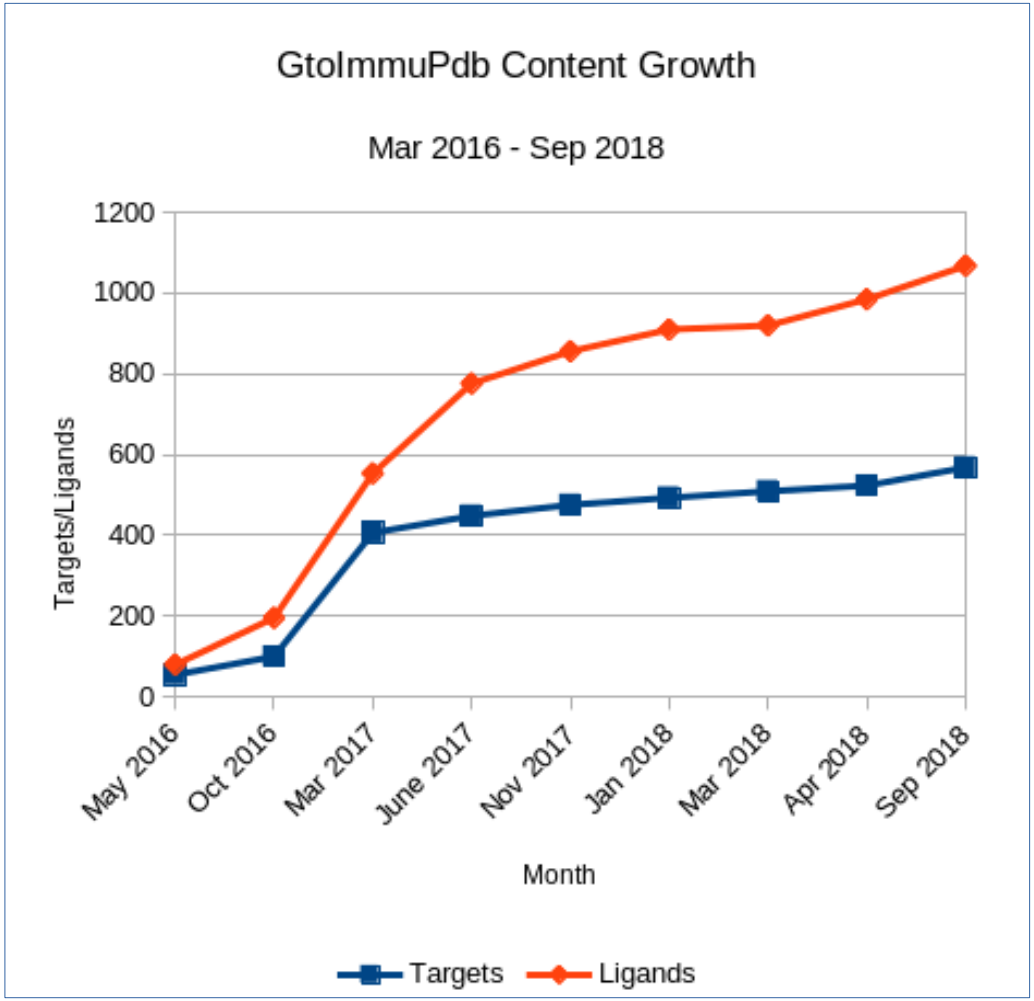
GtoImmuPdb growth

17% of existing (pre-2015) GToP targets were retrospectively tagged for GToImmuPdb.

Since 2015, the percentage of new targets added and tagged for GToImmuPdb is ~60% (80 out of the 129 added)

For ligands, 7.2% of pre-2015 entries were retrospectively GToImmuPdb-tagged, this has increased to 40% of new ligands (475 out of 1205 added).

These figures illustrate the shift in focus to 'immuno' relevant data.



Achievements and plans

- Achievements outlined in external slides, posters, database report and NAR paper (PMID: 29149325)
- Good progress leading up to beta release
- Need to broaden feedback
- Need more committee (and other expert) inputs for
  - Triaging “Further Reading” for the birds eye picture
  - More dot-joining on “big themes” (e.g. athero, AD, depression)
  - Check false-negatives (i.e. do we have a “coverage gap”)
- Engage with key wet labs (e.g. for ligand testing in new systems)
- Continue getting the word out (e.g. papers and press release)
- Explore crowd-source options (e.g. call for papers)

Technical issues and challenges

- Assessing publication quality in immunopharmacology is even more difficult than for general pharmacology
- Ditto for the “reproducibility crisis” w.r.t. to ligand quantitative activity
- As ever, the rate of blinding for pharma development candidates is ~40% (i.e. no name-to-structure)
- We do not curate without a defined molecular structure for ligands (even if we have to dig out an antibody sequence from a patent)
- Difficult for users to differentiate where the target has different (or even the same) ligands published in both immunopharmacolgy and other therapeutic contexts
- Diseases that are mechanistically “grey” but potentially large (e.g. fibrosis as immunological causality?)
- Single-cell expression data will eventually split our cell hierachies

Sustainability and resourcing

- Our 2015 Wellcome Trust Grant for the Guide to Immunopharmacology expires at the end of October 2018
- This reduces the project headcount in Edinburgh by three positions
- GtoImmuPdb can be sustained and moderately expanded after Oct but at ~50% less capacity than when initiated
- Implications and options need to be considered