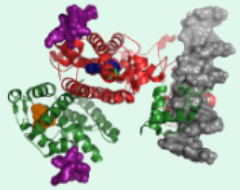
IUPHAR
INTERNATIONAL UNION OF BASIC AND CLINICAL PHARMACOLOGY

IUPHAR/BPS Guide to PHARMACOLOGY



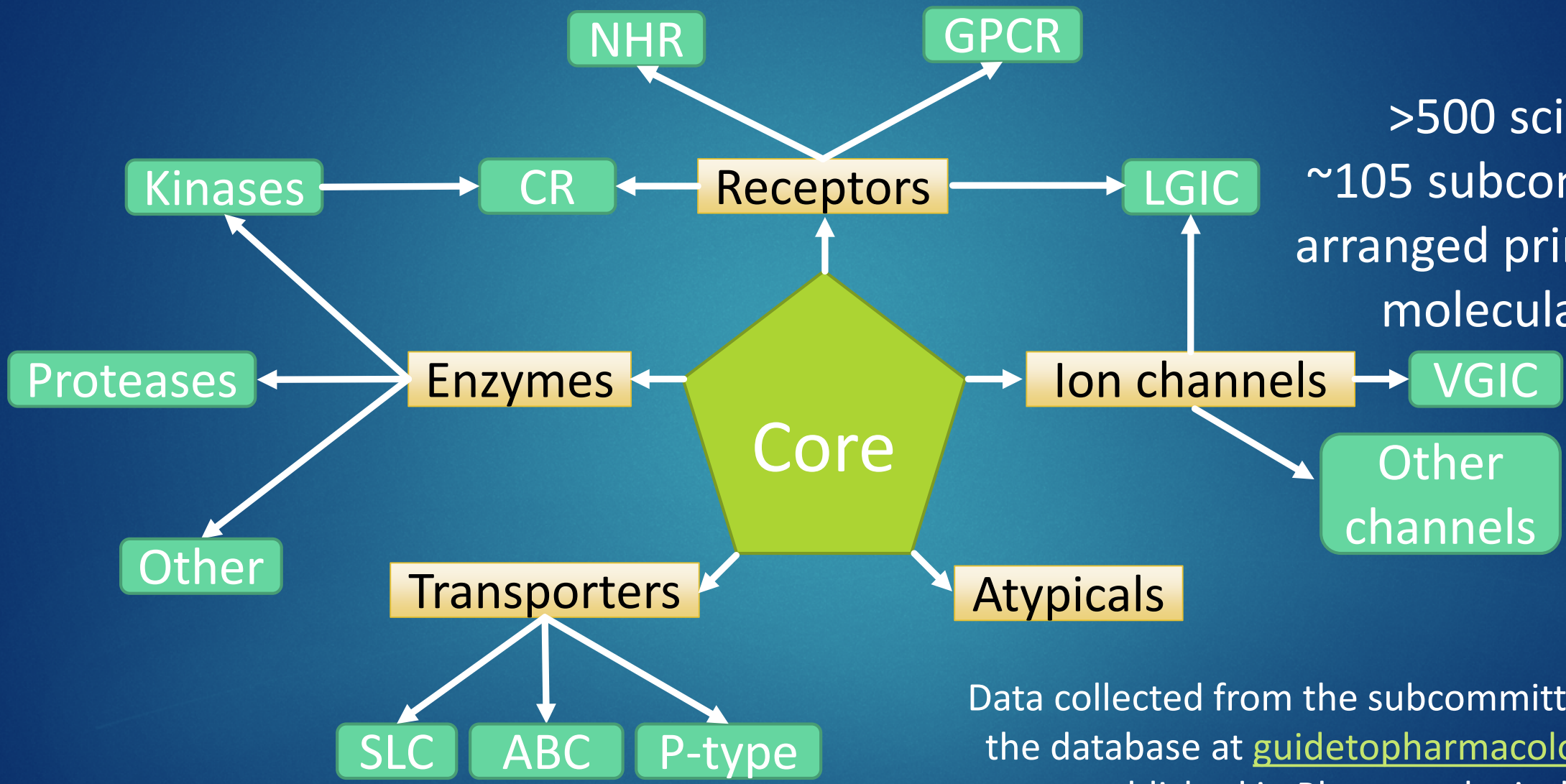
Challenges in identifying receptors for lipid mediators

STEVE ALEXANDER (TWITTER/INSTAGRAM @mqzspa)
UNIVERSITY OF NOTTINGHAM
CHAIR, NOMENCLATURE AND STANDARDS COMMITTEE, IUPHAR

Plan

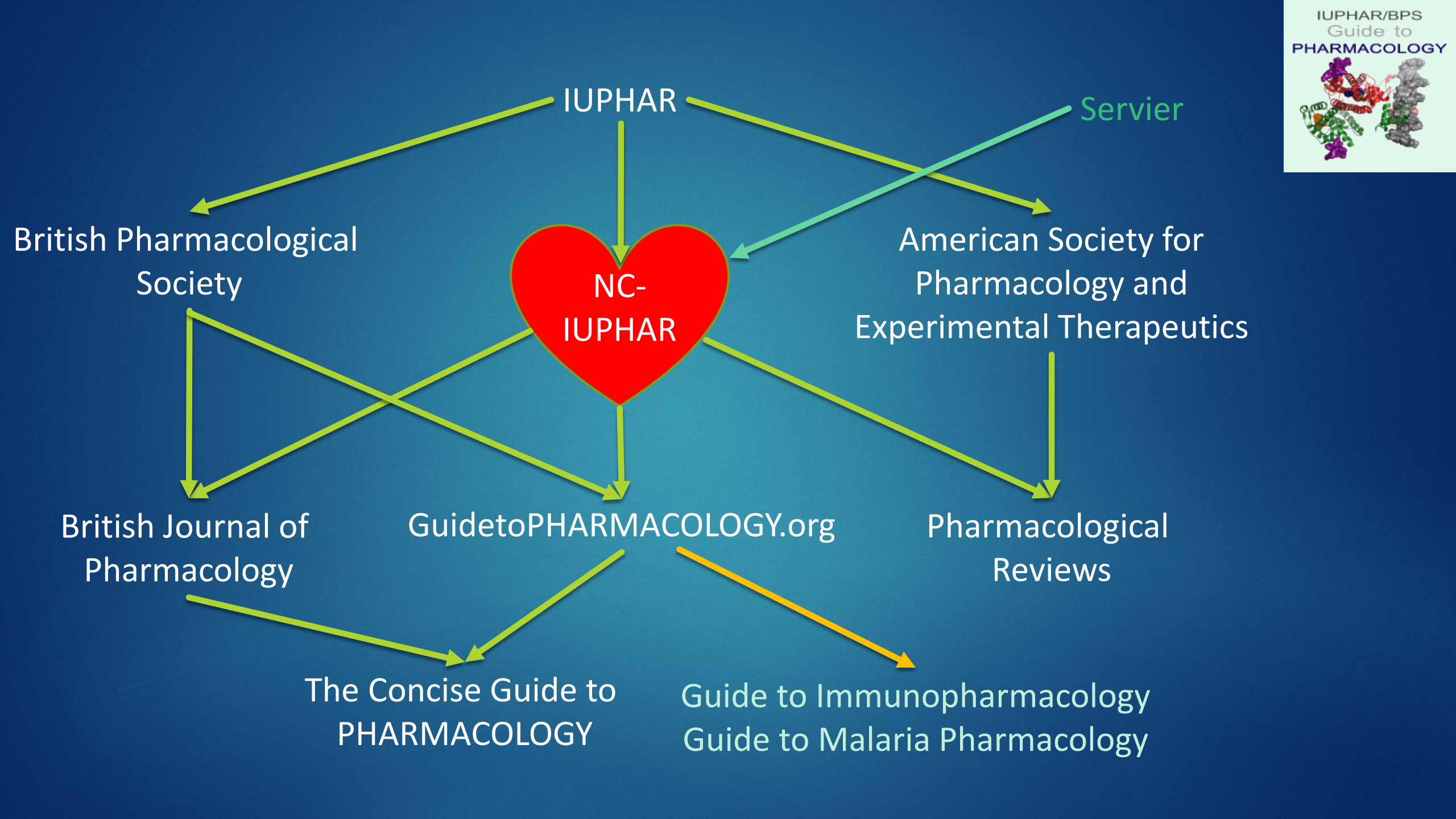
- NC-IUPHAR, guidetopharmacology.org and nomenclature
- GPCR families
- Orphan GPCR
- Challenges for ‘lipid-activated’ orphan GPCR

Subcommittees of NC-IUPHAR



>500 scientists in ~105 subcommittees arranged primarily by molecular targets

Data collected from the subcommittees update the database at guidetopharmacology.org and are published in Pharmacological Reviews & British Journal of Pharmacology


IUPHAR
Servier
British Pharmacological Society
NC-IUPHAR
American Society for Pharmacology and Experimental Therapeutics
British Journal of Pharmacology
GuidetoPHARMACOLOGY.org
Pharmacological Reviews
The Concise Guide to PHARMACOLOGY
Guide to Immunopharmacology
Guide to Malaria Pharmacology

NC-IUPHAR

- A primary role of the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology is:
  - To provide guidance on the nomenclature of drug targets that is clear, logical and consistent
  - So that the broader scientific community avoids confusion and saves time/energy
- These are published via the IUPHAR/BPS GuidetoPharmacology.org open access online database

IUPHAR/BPS Guide to PHARMACOLOGY

An expert-curated resource of pharmacological targets and the substances that act on them

Home | About | Targets | Ligands | Diseases | Resources | Advanced search | Immuno Portal | Malaria Portal

GtoPdb home page tour

Search GtoPdb

Advanced Search: Targets | Target Pharmacology | Ligands | Chemical Structure

Current Release Version 2024.1 (26th March 2024). Read our release notes blog.

Coronavirus (Covid-19) - view our information page

Quick links

Targets

- G protein-coupled receptors
- Ion channels
- Nuclear hormone receptors
- Kinases
- Catalytic receptors
- Transporters
- Enzymes
- Other protein targets

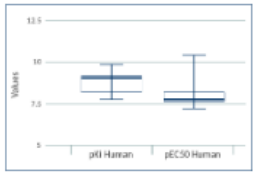
Ligands

- Approved drugs
- Synthetic organics
- Metabolites
- Natural products
- Endogenous peptides
- Other peptides
- Inorganics
- Antibodies
- Labelled ligands

Resources

- Help documentation
- FAQ
- Tutorial
- Download data & reports
- REST web services

Ligand Activity Charts



Use our **interactive ligand activity charts** to compare pharmacology across targets and species.

NAR Database Issue

The IUPHAR/BPS Guide to PHARMACOLOGY in 2024

Now published online!

DOI: 10.1093/nar/gkad944

Our latest NAR paper provides curation updates, info on site usage and connectivity, and discussion on the inclusion of antibacterial compounds through our collaboration with AntibioticDB and GARDP

Immunopharmacology

IUPHAR Guide to IMMUNOPHARMACOLOGY

An immunological access-point to GtoPdb data

Malaria Pharmacology

IUPHAR/MMV Guide to MALARIA PHARMACOLOGY

Optimised access for the malaria research community

Database Reports

GtoP Database Progress Report

View all our past database reports on our **downloads page**. Reports are also accessible, along with database update presentations,

Latest News and Hot Topics in Pharmacology

Database Release 2024.1

A new release, version 2024.1, has been made of the IUPHAR/BPS Guide to Pharmacology database. Released on 26th March 2024 this is the first release of the year. The following blog post gives details of the key content updates and...

Read more ›

3 months ago

BJP Concise Guide to Pharmacology 2023/24 – out now!

The essential guide for those working in the vital search for new drugs A FREE education and research resource What's in it for you? Published as a special issue in the British journal of Pharmacology every 2 years, The Concise Guide...

Read more ›

4 months ago

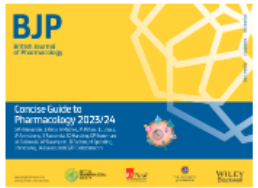
GtoPdb is a Global Core Biodata Resource

The IUPHAR/BPS Guide to Pharmacology is delighted to be named as one of 15 new Global Core Biodata Resources (GCBRs) by the Global Biodata Coalition (GBC). The GBC announced the outcome of its 2023 selection round for GCBRs on 11th...

Read more ›

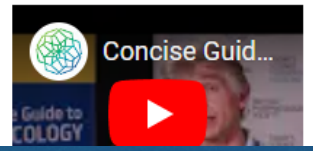
6 months ago

The Concise Guide to PHARMACOLOGY 2023/24



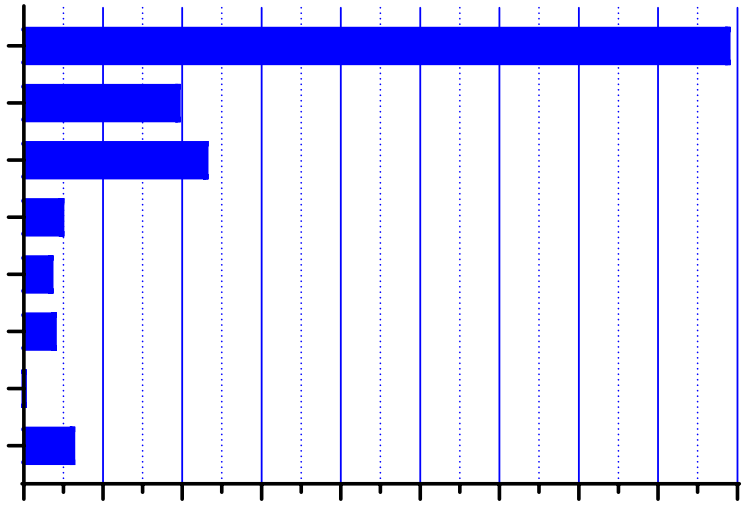
Access the table of contents GO

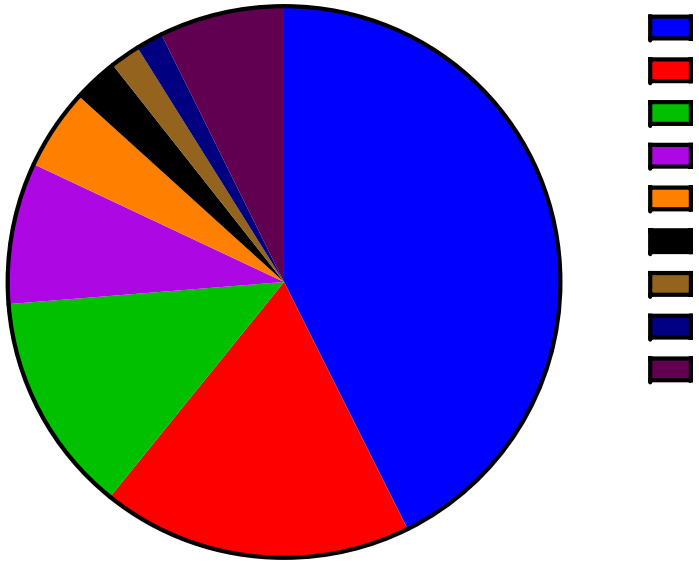
Please see the 5 minute introductory video on the Concise Guide:



"An expert-driven guide to pharmacological targets and the substances that act on them"

GtoPdb content (2024.Q1 release)





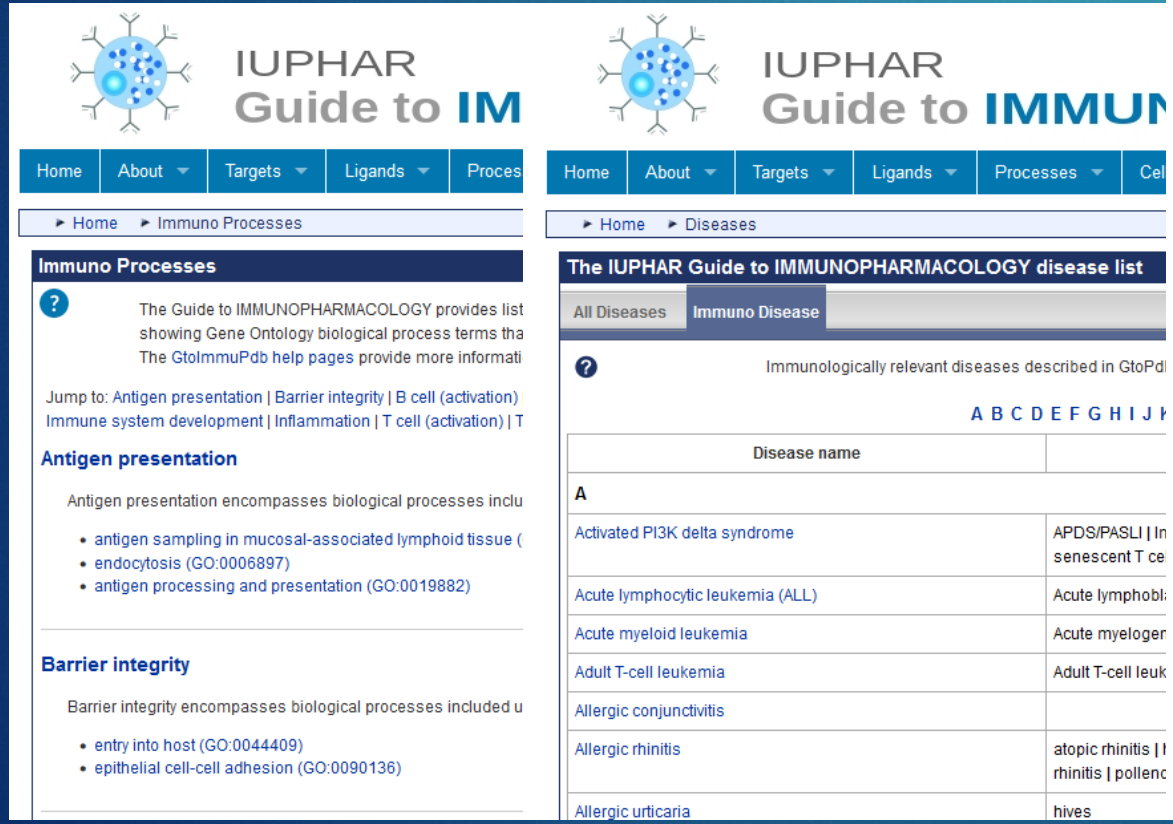
- Highlight ‘Gold Standard’ tools to allow identification of drug targets in complex situations
  - 20 789 curated binding constants
- Major focus on evidence base
  - 45 361 references
- ~ 50 000 engaged sessions/month

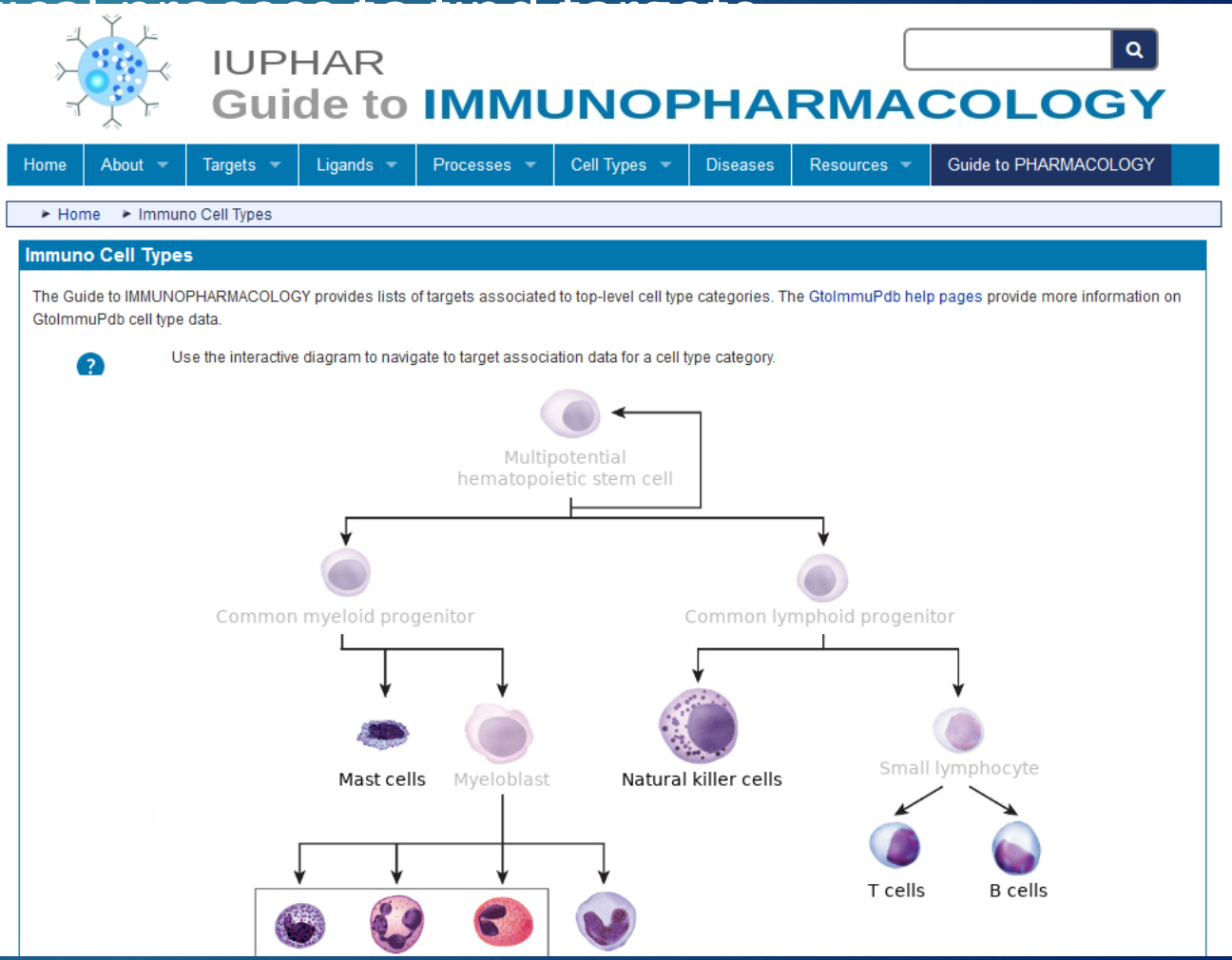
www.guidetoimmunopharmacology.org

- Officially launched in October 2018
- A portal linking GtoPdb targets and ligands to immunological cell types, processes and diseases
- Developed in conjunction with immunologists to include the data types and navigation routes most relevant to immunology
- Immuno-relevant targets and ligands in GtoPdb flagged and annotated with supporting data

Browsing new GtoImmuPdb data types

- Browse by cell type or immunological processes to find targets
- Browse by disease to find targets

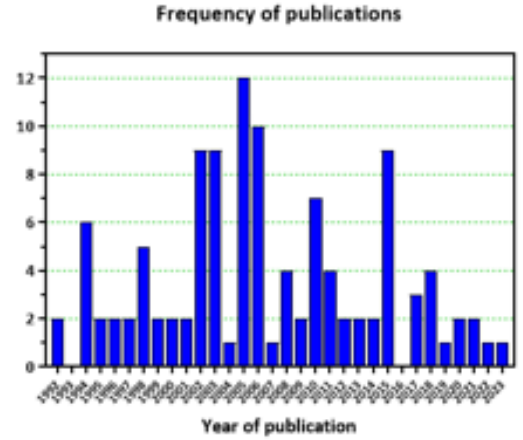


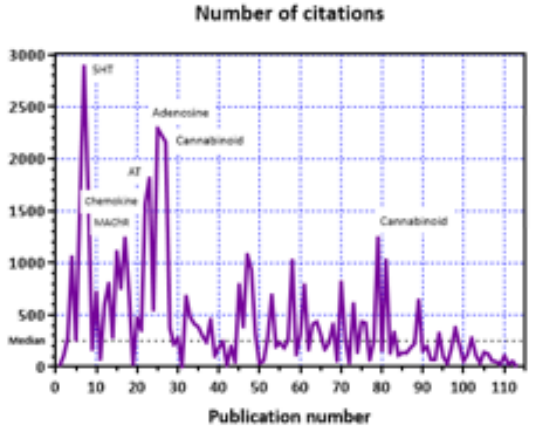


Publications and Impact

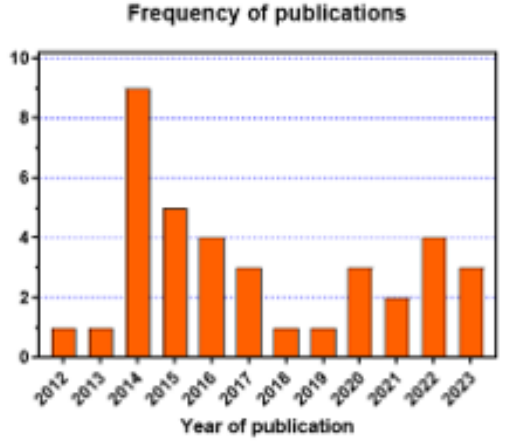
NC-IUPHAR and GtoPdb outputs on 2024-04-05

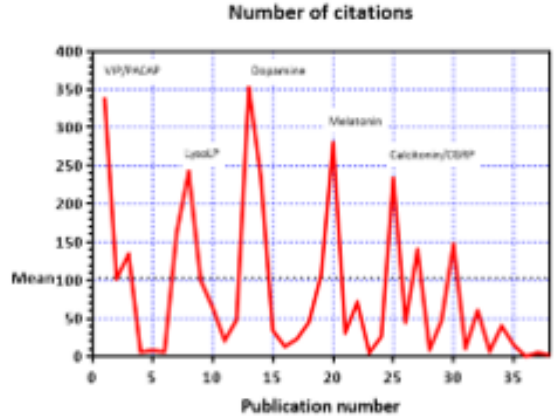
Pharmacological Reviews



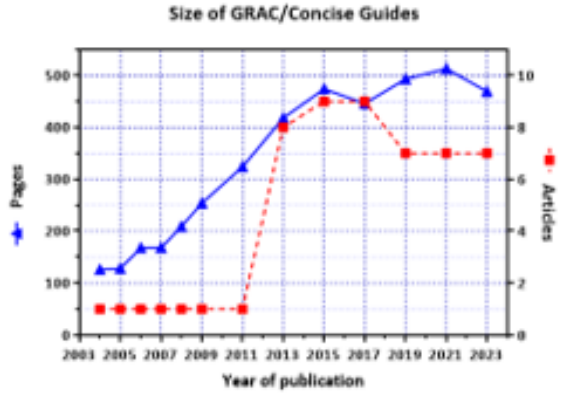


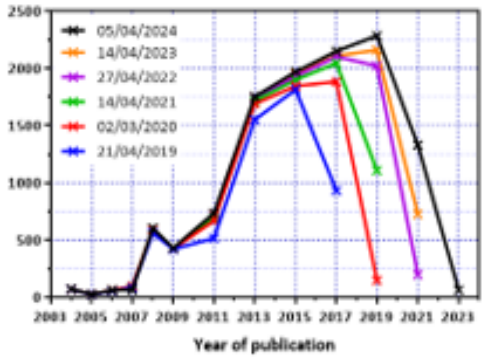
British Journal of Pharmacology



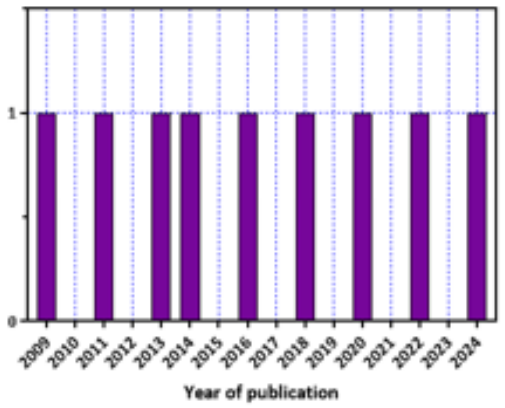


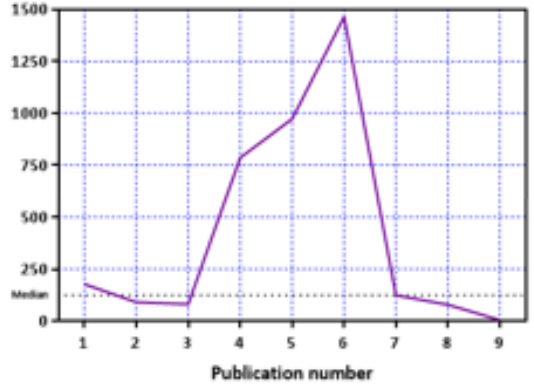
Concise Guides to Pharmacology





Nucleic Acids Research





Receptor nomenclature

- Subcommittees of NC-IUPHAR consider the nomenclature for specific receptors and families of receptors, with an aim to reflect the endogenous, ‘canonical’ ligand and to align subfamilies of receptors responding to the same endogenous ligand
- Sometimes this has been straightforward and sometimes not
  - Chemokines are divided by structure into four subclasses by the number and arrangement of four conserved cysteines.
    - CC with 0 aa between the first two cysteines
    - CXC with 1 aa between the first two cysteines
    - CX3C with 3 aa between the first two cysteines
    - C chemokines have only the second and fourth cysteines found in other chemokines
  - G protein-coupled chemokine receptors are named acccording to the class of chemokines bound
  - ACKR are Atypical ChemoKine Receptors with an apparent scavenger role

GPCR families and orphans

GPCR families

- Non-mammalian GPCR families
  - Fungal and cAMP receptors
- 811 human genes generating 808 proteins
  - 728 Family A GPCR
    - 407 odorant, 288 rhodopsin, 27 Taste 2, 5 pheromone, 1 ocular albinism
  - 47 Family B GPCR
    - 24 adhesion, 16 secretin, 7 LN-TM7
  - 22 Family C GPCR
    - Glutamate
  - 11 Family F GPCR
    - Frizzled

Orphan GPCR

- NC-IUPHAR has identified 193 non-sensory Family A GPCR with an endogenous, canonical ligand
  - Divided into 57 families
- 19 Family A GPCR have no pharmacology/putative endogenous ligands
- 15 Family A GPCR have close ties to existing NC-IUPHAR subcommittees
  - For example, GPR18, GPR55 and GPR119 are ‘foster’ GPCR of the cannabinoid subcommittee, because of the similarity of their putative endogenous ligands with the endocannabinoids
- 51 Family A GPCR are being evaluated for potential deorphanization

Checklist points 1-4

The crux

What is/are the suggested putative endogenous agonist/s?

Reproducibility

Has the activity of this putative agonist been reproduced in the same signalling paradigm by a fully independent lab?

Has the receptor been included in a published major screening program and with what outcome?

Physiology

Is the potency of the putative agonist consistent with a physiological function?

Are there plausible mechanisms for the putative agonist to reach bioactive concentrations in tissues expressing the receptor?

Is the ligand:receptor pairing physiologically feasible?

Binding

Has binding of the putative agonist to the receptor been demonstrated?

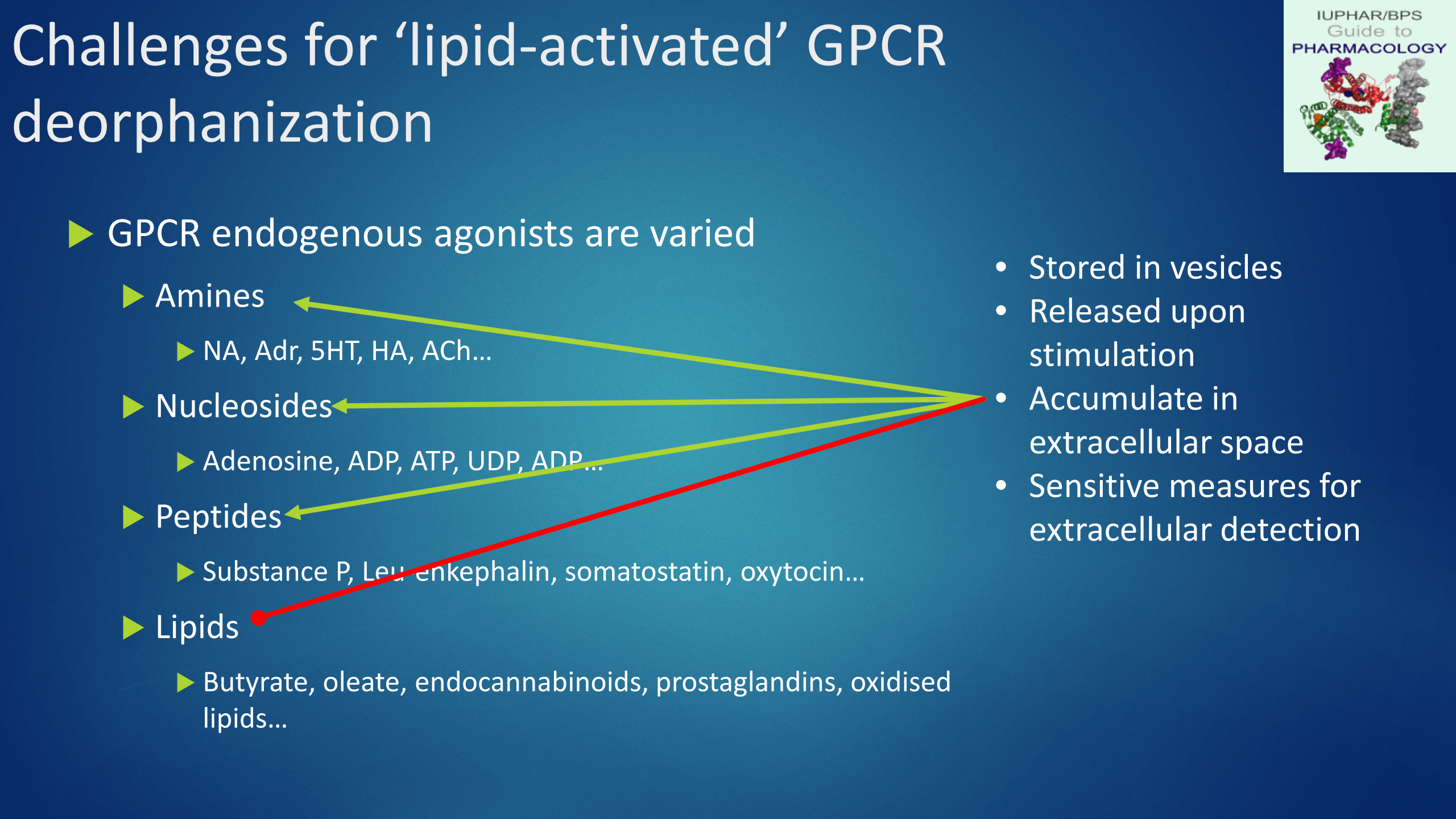
Checklist points 5-7

Agonist effects	What responses does the putative agonist evoke in cells expressing the recombinant receptor? What responses does the putative agonist evoke in native cells/tissues expressing the receptor? Does the putative agonist evoke a response in the absence of the receptor (off-target effects)?
Pharmacology	If synthetic agonists have been described, how closely do they mimic the effects of the putative agonist? Are there antagonists which block the effects of the putative agonist (and/or synthetic agonists)? Does inhibition (pharmacological or genetic) of the enzymes capable of producing or terminating the putative agonist alter the receptor's downstream signalling?
Genetic approaches	Do genetic alterations (natural mutations/SNPs or man-made) which alter receptor sequence or expression levels disrupt cellular/tissue/behavioural responses to the putative agonist? In the case of peptide ligands, do genetic alterations of the coding gene result in changes in receptor expression?

Challenges for ‘lipid-activated’ orphan GPCR

Challenges for ‘lipid-activated’ GPCR deorphanization

- GPCR endogenous agonists are varied
  - Amines
    - NA, Adr, 5HT, HA, ACh…
  - Nucleosides
    - Adenosine, ADP, ATP, UDP, ADP…
  - Peptides
    - Substance P, Leu-enkephalin, somatostatin, oxytocin…
  - Lipids
    - Butyrate, oleate, endocannabinoids, prostaglandins, oxidised lipids…



- Stored in vesicles
- Released upon stimulation
- Accumulate in extracellular space
- Sensitive measures for extracellular detection

Challenges for ‘lipid-activated’ GPCR deorphanization

- Lipid-derived ligands
  - Are often short-lived bio/chemically
  - Often require detergents/binding proteins (albumin) for solubility
  - Can form micelles
- What is the ‘real’ concentration?

Challenges for ‘lipid-activated’ GPCR deorphanization

- Some ‘lipid-activated’ Family A GPCR are constitutively active
  - GPR119 residues in the TM domains (Engelstoft, 2014)
- Lipid-derived ligands can enter/modify cell membranes
  - Lateral diffusion of S1P into its receptor (Hanson, 2012)
- Can act as non-selective surfactants

Retracted report for LPC as a GPR4 agonist
Reported as a GPR132 agonist (Murakami, 2004)

A reflection

- The future is challenging for pinning down lipid-activated orphan GPCR
- The biggest challenge:
  - How can we tell what the bioactive concentration in close proximity to the receptor is?
- Technology may help
  - Mass spectrometry imaging
    - Is the most abundant mediator the most relevant?
- I feel your pain, but …
  - Rarely do we value easy achievements