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INTERNATIONAL UNION OF BASIC AND CLINICAL PHARMACOLOGY REVIEW

The expanding role of immunopharmacology: IUPHAR Review 16

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Drugs targeting the immune system such as corticosteroids, antihistamines and immunosuppressants have been widely exploited in the treatment of inflammatory, allergic and autoimmune disorders during the second half of the 20th century. The recent advances in immunopharmacological research have made available new classes of clinically relevant drugs. These comprise protein kinase inhibitors and biologics, such as monoclonal antibodies, that selectively modulate the immune response not only in cancer and autoimmunity but also in a number of other human pathologies. Likewise, more effective vaccines utilizing novel antigens and adjuvants are valuable tools for the prevention of transmissible infectious diseases and for allergen-specific immunotherapy. Consequently, immunopharmacology is presently considered as one of the expanding fields of pharmacology. Immunopharmacology addresses the selective regulation of immune responses and aims to uncover and exploit beneficial therapeutic options for typical and non-typical immune system-driven unmet clinical needs. While in the near future a number of new agents will be introduced, improving the effectiveness and safety of those currently in use is imperative for all researchers and clinicians working in the fields of immunology, pharmacology and drug discovery. The newly formed *ImmuPhar* (http://iuphar.us/index.php/sections-subcoms/immunopharmacology) is the Immunopharmacology Section of the International Union of Basic and Clinical Pharmacology (IUPHAR, http://iuphar.us/). *ImmuPhar* provides a unique international expert-lead platform that aims to dissect and promote the growing understanding of immune (patho)physiology. Moreover, it challenges the identification and validation of drug targets and lead candidates for the treatment of many forms of debilitating disorders, including, among others, cancer, allergies, autoimmune and metabolic diseases.

Abbreviations

Abl, Abelson kinase; ALK, anaplastic lymphoma kinase; APC, antigen-presenting cell; CD, cluster of differentiation; c-Kit, stem cell factor receptor; CpG, unmethylated motifs of bacterial DNA; CTLA, cytotoxic T-lymphocyte antigen; EPH, ephrin kinase; Fab, *fragment antigen-binding*; HER, human epidermal growth factor receptor; HGFR, hepatocyte growth factor receptor; HiB, *Haemofilus influenzae* B antigen; IRAK, IL-1 receptor-associated kinase; mAbs, monoclonal antibodies; MAMP, microbial-associated molecular pattern; MEK, mitogen activated kinase kinase; MET, mesenchymal epithelial transition factor or hepatocyte growth or scatter factor receptor; MPL, monophosphoryl lipid; mTOR, mammalian target of rapamycin; PAMP, pathogen-associated molecular pattern; PKI, PK inhibitor; PRR, pattern recognition receptor; RA, rheumatoid arthritis; RET, receptor for GDNF-family ligands; ROR, retinoic acid receptor-related orphan receptor; SCF, stem cell factor; Src, proto-oncogene tyrosine-PK Src; Syk, spleen TK; TLR, toll-like receptor; Treg, regulatory T-cells; TrkB, tropomyosin receptor kinase B

Tables of Links

TARGETS

GPCRs[a]	**Catalytic receptors**[c]	**Enzymes**[d]
Chemokine receptors	ALK	Abl
H_1 receptor	CD52	Akt (PKB)
H_2 receptor	CTLA4 (CD152)	Cytochrome P450
H_4 receptor	EGFR	IRAK4
Nuclear hormone receptors[b]	Ephrin receptor family (EPH)	Janus kinase family (JAK)
Retinoic acid receptor-related orphan receptors (ROR)	FGFR1	MEK1
	FLT3	mTOR
	HER2	PI3K
	HGFR	RAF
	IL6R	Src
	KIT (c-Kit)	Syk
	MET	
	NOD-like receptor family (NLR)	
	Pattern recognition receptor family (PRR)	
	PDGFRα	
	PDGFRβ	
	RET	
	Toll-like receptor family (TLR)	
	TrkB	
	VEGFR-1	
	VEGFR-2	
	VEGFR-3	

LIGANDS

Abatacept	Etanercept	Lapatinib	SCF
Adalimumab	Certolizumab pegol	Nilotinib	Secukinumab
Alemtuzumab	Gefitinib	Nintedanib	Sorafenib
Bosutinib	Golimumab	Ocrelizumab	Sunitinib
Brodalumab	Histamine	Ofatumumab	Tocilizumab
Cabozantinib	IFN	Omalizumab	Trametinib
Crizotinib	IL	PDGF	Tumor necrosis factor
Dabrafenib	Imatinib	Rituximab	Vandetanib
Dasatinib	Infliximab	Ruxolitinib	
Erlotinib	Ixekizumab	Sarilumab	

These tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 ([a,b,c,d]Alexander *et al.*, 2013a,b,c,d).

Introduction

For more than 50 years, drugs targeting immune cell pathways and receptors have been extensively exploited in the treatment of inflammatory, allergic and autoimmune disorders, and in preventing rejection following organ transplantation. Among them, many non-steroidal anti-inflammatory drugs, antihistamines, corticosteroids and immunosuppressant agents (Figure 1) have reached blockbuster status and are even included in the list of essential medicines of the World Health Organization (WHO, 2013).

In recent years, several notable changes in our understanding and appreciation of the immune system, greater knowledge of the activity of agents that modify the immune responses and the significant biotechnological advances have made available new classes of drugs. For instance, PK inhibitors (PKIs) and biologics, such as monoclonal antibodies (mAbs) (Figure 1) are capable of selectively modulating immune cell subsets (Dollery, 2014). At the same time, there has been growing evidence connecting the majority of human pathologies to dysfunctions of the innate and adaptive immune systems (Figure 2). Thus, scientists and clinicians working in universities and industry have shown enormous interest in the interrelationship between the disciplines of pharmacology and immunology, including immunotoxicology and immunogenetics (Cohen, 2006). Despite the use of vaccines and immunomodulating agents in clinical practice for many years (Figure 1), immunopharmacology is presently considered as one of the youngest fields of pharmacology. Immunopharmacology addresses the selective up- or down-regulation of immune responses. It aims to uncover and exploit more effective and safer therapeutic options for unmet clinical needs for an expanding range of pathologies, such as cancer and inflammatory, infectious, immune and metabolic diseases (Figure 2).

The importance of this area of pharmacology is evidenced by the recently launched *ImmuPhar* (Figure 3), the Immunopharmacology Section of the International Union of Basic and Clinical Pharmacology (IUPHAR Immunopharmacology Section, 2015). The main objective of *ImmuPhar* is to encourage the international cooperation and dissemination of knowledge in immunopharmacology. The activities are organized by the Executive Committee, the International Advisory Board, and the subcommittees on 'molecular targets for immunomodulatory drugs' (molecular oriented), 'targets in immune-related diseases' (disease oriented) and 'antibodies as therapeutics'.

The objectives of *ImmuPhar* will be achieved by (i) stimulating worldwide research in basic and clinical immunopharmacology; (ii) promoting high scientific and ethical standards in research into related medicines and therapeutics; (iii) encouraging related scientific meetings, workshops and courses in different parts of the world; (iv) improving and harmonizing the teaching of immunopharmacology; (v) supporting the utilization of immunopharmacological agents in health care delivery, particularly in developing countries; (vi) evaluating patients experiencing adverse drug reactions by utilizing clinical immunopharmacology skills; (vii) encouraging collaboration with other agencies and organizations interested in the study, development and rational use of immunopharmacological agents; (viii) exchanging and disseminating information on the safety and pharmacovigilance of related medicines and therapeutics; and (ix) fostering cooperative efforts among educational, research, clinical, industrial and governmental personnel engaged in activities relevant to translational research in immunopharmacology. Membership of the Section is open to pharmacologists, immunopharmacologists, clinical pharmacologists, pathologists, immunologists and clinicians interested in the interrelationships between pharmacology and immunology. *ImmuPhar* works in close collaboration with the IUPHAR Committee on Receptor Nomenclature and Drug Classification (IUPHAR/BPS Guide to PHARMACOLOGY; http://www.guidetopharmacology.org/). Any IUPHAR member societies and their sections are also eligible for affiliation.

This review aims to summarize the new concepts on the role of immunopharmacology in the ongoing innovations in immunomodulatory drug development, from small molecules to vaccines and other biological modifiers. Moreover, due to the increasing number of PKIs and mAbs that enter the clinic, the challenge of both academic and industrial audiences is to consider the complex pharmacological profile of

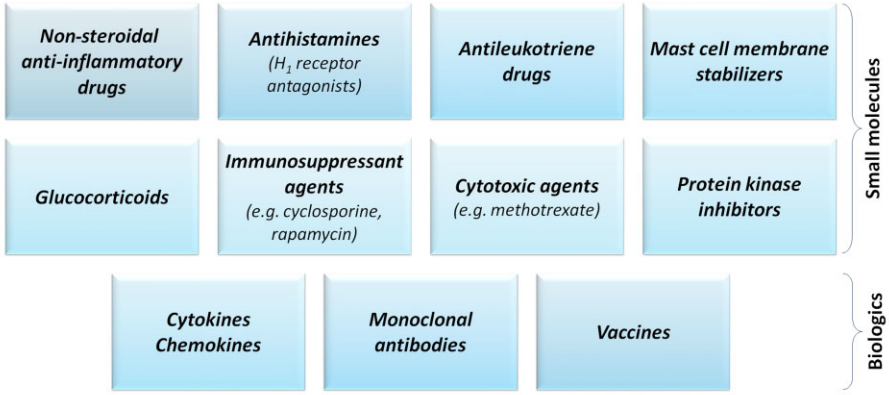

Figure 1

Common clinically relevant drugs used in the treatment of human inflammatory, allergic and other immune system-associated disorders.

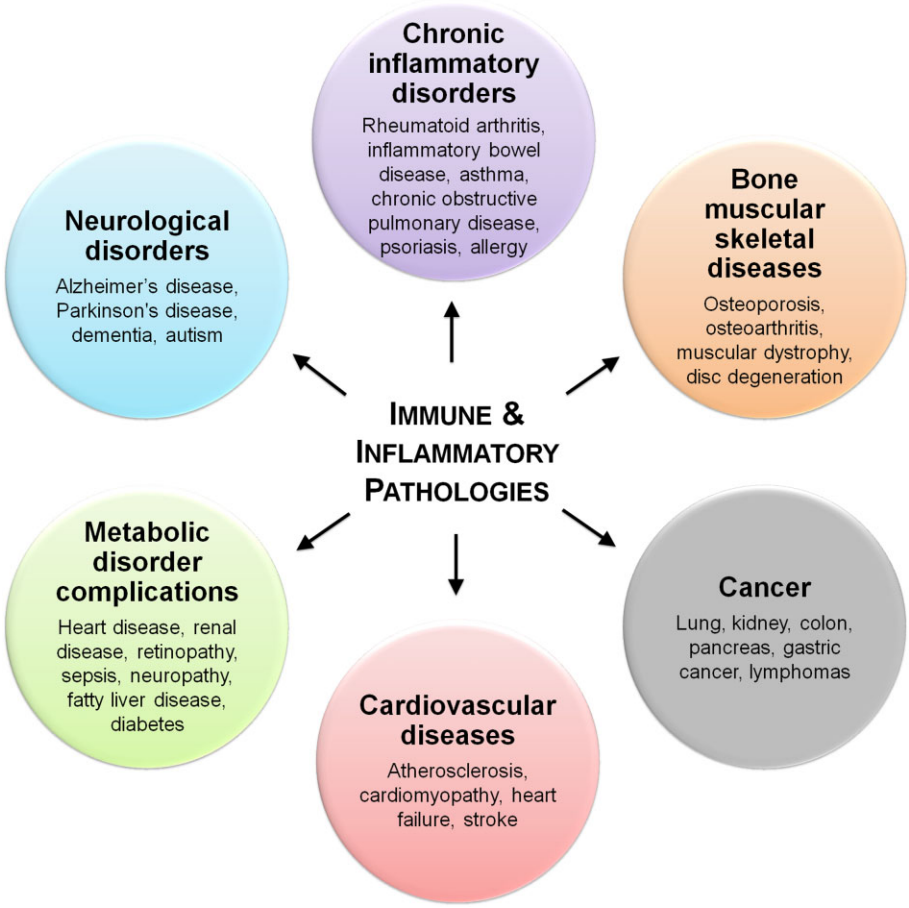

Figure 2
Examples of human pathologies linked to inflammation and to dysfunctions of the immune system.

these novel options during drug development, without excluding the important advances in the pharmacology of classical therapeutic approaches.

Small molecules

Despite the emergence and the clinical success of biologics, several limitations hamper the therapeutic manipulation of the inflammatory networks underlying the multifaceted aetiology of many immune disorders. For instance, agents produced by means of biological processes frequently involving recombinant DNA technology are expensive. More importantly, they lack oral availability and often show inefficient delivery to target tissues *in vivo* (Kopf *et al.*, 2010). By controlling the signalling pathways involved in tissue-specific inflammation, small molecules remain an effective approach for immunomodulatory drug development and repurposing (Thomson *et al.*, 2009; Sundberg *et al.*, 2014). Related emerging data confer new properties to old medications, as is the case with glucocorticoids or the immunosuppressive drug rapamycin. In addition to the potent inhibition of growth factor-induced T-cell proliferation, the serine/threonine PK mammalian target of rapamycin (mTOR) has been reported to play an important role in the regulation of diverse functions of various immune cells (Thomson *et al.*, 2009). Another example is the recently recognized rapid onset and short duration of the non-genomic glucocorticoid actions. These new discoveries should help in facilitating the development of new improved strategies for the management of inflammatory and autoimmune diseases (Alangari, 2010; Simon *et al.*, 2013).

Furthermore, the latest advances in mast cell-derived mediator research, including histamine (Zampeli and Tiligada, 2009; Tiligada, 2012) and prostaglandins (Woodward *et al.*, 2011), are illustrative examples of the existing challenge to identify and validate new targets and to optimize lead candidates for asthma and allergies (Schumacher *et al.*, 2014; Chliva *et al.*, 2015). In particular, histamine interacts with four types of GPCRs, designated as H_1–H_4, and it is a major component of the immune system playing a critical role in inflammation (Parsons and Ganellin, 2006). For more than 70 years, histamine has been one of the most exploited substances in medicine, providing blockbuster drugs acting on H_1 and H_2 receptors for the treatment of allergies and gastric ulcers respectively (Parsons and Ganellin, 2006). Yet, the continuing appreciation of the pharmacodynamic and pharmacokinetic diversity of H_1 antihista-

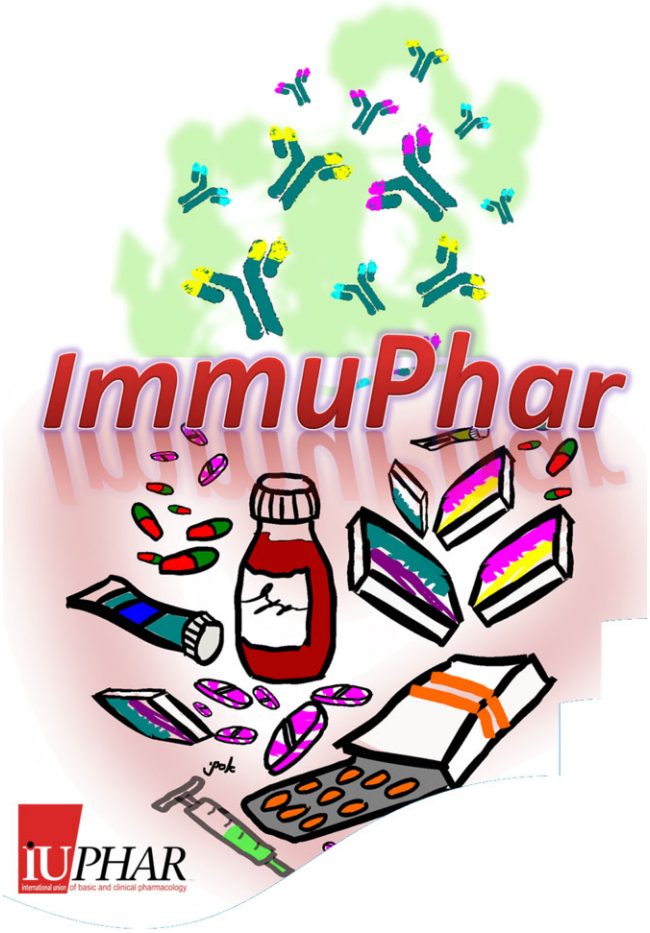

Figure 3

Logo of *ImmuPhar*, the Immunopharmacology Section of the International Union of Basic and Clinical Pharmacology (IUPHAR). *ImmuPhar* aims to promote the international cooperation and knowledge dissemination in the growing field of immunopharmacology.

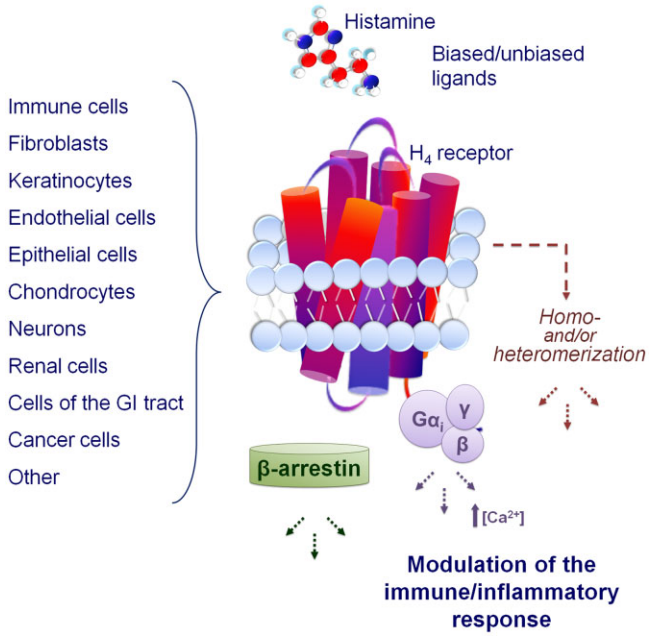

Figure 4

The histamine H_4 receptor is expressed in various cell types and mediates a variety of distinct effects depending on the endogenous complement of receptor expression and signal transduction pathways upon binding of histamine, unbiased or biased ligands.

mines reflects the ongoing efforts to translate preclinical drug actions into promising therapies for pathologies with a high economic and societal impact (del Cuvillo *et al.*, 2006; Schumacher *et al.*, 2014). Interestingly, the discovery of the high affinity histamine H_4 receptor in 2000 and its constitutive activity and expression mostly on cells of the immune system (Figure 4) revealed new pathways in the extensive biological functions of histamine. Besides its role in allergy, the translational potential of this new drug target in acute and chronic inflammation, host defence and neuropathic pain provides attractive novel perspectives (Tiligada *et al.*, 2009; Zampeli and Tiligada, 2009; Tiligada, 2012; Kyriakidis *et al.*, 2015).

The rapid entry of H_4 receptor-targeting compounds into advanced clinical development will benefit patients with poorly treatable chronic diseases. Moreover, the pluridimensional rather than linear pharmacological efficacy of H_4 receptor ligands (Figure 4) represents a paradigm of the recently described concept of 'biased agonism' or functional selectivity for GPCRs (Nijmeijer *et al.*, 2013). GPCRs account for more than 65% of the medicines marketed today, highlighting their relevance in human (patho)physiology including immune responses (Rask-Andersen *et al.*, 2011). By realizing the distinct functional outcomes of GPCR-mediated activation of complex signalling networks upon agonist binding, biased ligands represent an opportunity for the discovery of new drugs with specific on-target efficacy and fewer on-target side effects (Kenakin and Christopoulos, 2013). Taken together, the advances in these fields of research suggest that the differential expression and/or the selective modulation of receptor activity can alter pro- and anti-inflammatory signals orchestrating acute and chronic inflammation reflected by the repertoire of immune cells and mediators (Zampeli and Tiligada, 2009; Tiligada, 2012; Nijmeijer *et al.*, 2013; Corbisier *et al.*, 2015).

PK inhibitors

The family of PKs includes two major subfamilies: the serine/threonine kinases and the TKs. PKs are components of signal transduction pathways involved in diverse biological processes. They are now linked either directly or indirectly to more than 400 human diseases ranging from cancer to inflammatory, metabolic and cardiovascular disorders (Steinman *et al.*, 2012; Galluzzi *et al.*, 2014; Fabbro, 2015; Fabbro *et al.*, 2015). There are more than 500 kinases in the human genome and as 30% of the proteome is phosphorylated, the modulators will have a vast pharmacology. Thus, PKs constitute multiple targets for anticancer treatments and

Table 1

Examples of PKIs and cancer therapy

Drug	Molecular target	Tumour
Imatinib	PDGFR, PDGF, SCF, c-Kit, Bcr-Abl	Chronic myeloid leukaemia, gastrointestinal stromal tumours
Gefitinib	EGFR	Metastatic non-small cell lung cancer
Erlotinib	HER2, EGFR	Metastatic non-small cell lung cancer
Sorafenib	VEGFR-2,VEGFR-3, PDGFRβ, c-Kit, Fit-3	Renal cell carcinoma
Sunitinib	PDGFR, VEGFR, c-Kit, Fit-3	Renal cancer, gastrointestinal stromal tumours
Dasatinib	Bcr-Abl, Src, c-Kit, EPH, PDGFRβ	Imatinib-resistant chronic myeloid leukaemia
Nilotinib	PDGFR, c-Kit, Bcr-Abl	Chronic myeloid leukaemia
Lapatinib	HER2, EGFR	Breast cancer
Crizotinib	ALK, HGFR	ALK-positive lung cancer
Ruxolitinib	JAK	Myelofibrosis
Vandetanib	RET, VEGFR2, EGFR	Thyroid cancer
Cabozantinib	RET, MET, VEGFR, c-Kit, TrkB	Thyroid cancer
Bosutinib	Bcr-Abl, Src	Chronic myeloid leukaemia
Dabrafenib	Raf	Melanoma
Trametinib	MEK	Metastatic cutaneous melanoma
Nintedanib	VEGFR, FGFR, PDGFR	Idiopathic pulmonary fibrosis

Abl, Abelson kinase; Bcr, breakpoint cluster region; c-Kit, mast/stem cell growth factor receptor; Raf, rapidly accelerated fibrosarcoma.

Table 2

Targets that need to be validated for immune and inflammatory diseases

Target, inhibitors	For which diseases?
• **Akt**	• Asthma
• **Multiple chemokine receptors**	• RA
• **IFN α**	• Multiple sclerosis (IL 17+)
• **IL 1**	• Aspects of schizophrenia
• **IL 6**	• Juvenile diabetes
• **IL 17**	• Cardiomyopathy
• **Inflammasome**	• Antiphospholipid syndrome
• **IRAK4**	• Guillain–Barré syndrome
• **JAK/STAT**	• Crohn's disease
• **mTOR**	• Graves' disease
• **PI3K δ /γ**	• Sjogren's syndrome
• **Syk**	• Vitiligo
• **TLR 2/4/7/9**	• Myasthenia gravis
• **TNF α**	• Systemic lupus erythematosus
• **ROR-γ**	• Psoriasis

potentially for the modulation of inflammation and immunity if safety can be assured (Galluzzi *et al.*, 2014; Marfe and Di Stefano, 2014).

PKIs are usually small, cell-permeant molecules, which bind to the ATP-binding region of receptor and non-receptor kinases (Table 1). There are currently 39 marketed drugs acting on kinases and more than 130 in phase II/III ongoing clinical trials since the approval of imatinib in 2001 (Nagar *et al.*, 2002; Fabbro *et al.*, 2015). PKIs have potentiated and sometimes replaced therapy with mAbs or *vice versa*. Whereas kinase inhibitors are validated in certain types of cancer (Table 1), the situation is far from clear in autoimmune and other inflammatory diseases (Table 2). PKIs are designed to have a single or limited number of primary targets. However, most of them might interact with more than one PK and exhibit significant cross-reactivity (Table 1). In fact, among the drugs approved for clinical use, only a few, including lapatinib and imatinib, are highly selective; the majority inhibit more than 10 and up to more than 100 kinases. The non-specificity of the target together with new and still unknown molecular mechanisms may be responsible for unexpected off-target mechanisms and side effects, including drug resistance (Davies *et al.*, 2000; Ubersax and Ferrell, 2007; Loriot *et al.*, 2008; Chen and Fu, 2011).

PKI specificity has been tested *in vitro* with binding affinity and activity inhibition tests have also detected allosteric binding and modulation of TK activity. *In vitro* assays have a number of limitations due, for example, to lack of post-translational target modifications or of other regulatory proteins and non-kinase targets that are often responsible for important off-target effects (see Fabbro *et al.*, 2015). Recent progress in quantitative proteomics has allowed a more impartial interpretation of PKI specificity and provided models for PKI–PK interaction in the biological context. Furthermore, pharmacokinetic characteristics and the possible interaction with drugs modulating their metabolism through cytochrome P450 isoenzymes are as important as the pharmacodynamic parameters for the potential utility of PKIs (van Leeuwen *et al.*, 2014).

The choice of therapeutic target (Table 2) is certainly a critical issue. The broad spectrum of PKI target interactions and the off-target effects are important not only to better understand the actual mechanism of action and the molecular basis of adverse drug reactions, but also to define 'secondary' therapeutic approaches that will permit the use of those drugs in other diseases, in the future. Testing a novel concept in this field is extremely expensive and the idea of pan modulators working in multiple disorders is clearly incorrect. Indeed, Steinman *et al.* (2012) have powerfully argued that different strategies are needed for different diseases. TNF antagonists are active in rheumatoid arthritis (RA), and type 1 interferon modulators inactive, whereas in multiple sclerosis the converse is true and anti-CD20 therapies work in both

Table 3

Representative examples of therapeutic monoclonal antibodies

Molecule	Name	Type	Disease target
TNF	Infliximab	Chimera	RA, Crohn's diseases, Behçet's disease
	Adalimumab	Human	
	Golimumab	Human	
	Etanercept	TNFR-Ig	
	Certolizumab pegol	Fab-pegosyl	
CD20	Rituximab	Chimera	B-cell lymphoma (vasculitis)
	Ocrelizumab	Humanized	
	Ofatumumab	Human	
IL6R	Tocilizumab	Humanized	RA
	Sarilumab	Human	
CTLA4	Abatacept	CTLA4-Ig	RA
IL17	Secukinumab	Human	Psoriasis
	Ixekizumab	Humanized	
	Brodalumab	Human	
CD52	Alemtuzumab	Humanized	Multiple sclerosis
IgE	Omalizumab	Humanized	Severe asthma, chronic urticaria

CTLA, cytotoxic T-lymphocyte-associated protein.

(Steinman *et al.*, 2012). Because of the ability of PKIs to bind TKs in the active or inactive conformation, sometimes they may activate rather than inhibit kinases (Moebitz and Fabbro, 2012). The block in active conformation can explain in part the effect of some drugs that stabilize the phosphorylation state. However, in some cases, following drug binding, the kinase is activated. This paradoxical effect, which may be related to kinase interacting with molecules that affect the conformational state of the kinase, can be part of the drug's action or even constitute a mechanism of resistance (Chen and Fu, 2011; Marfe and Di Stefano, 2014; Fabbro *et al.*, 2015).

Although PKIs share the same mechanism of action, competing with ATP for the catalytic site of the enzyme, major acute and chronic side effects involving different organs limit their clinical use and have resulted in clinical trials being suspended and drugs being withdrawn (Loriot *et al.*, 2008). Thus, there is a real need for an expert-lead initiative to help drug discovery and development. IUPHAR has developed a database of all the kinases, with their main pharmacology (IUPHAR/BPS Guide to PHARMACOLOGY; http://www.guidetopharmacology.org/), and will be leading a major initiative on their role in immunopharmacology.

Monoclonal antibody therapies

Advances in basic immunology have contributed to the identification of various critical molecules involved in several immune reactions and their respective pathophysiological roles in a variety of immunological diseases. One of the most important key technical advances for promoting immunology research is the establishment of mAbs, led by the Nobel Prize laureates, Milstein and Köhler (Köhler and Milstein, 1975). Interestingly, the generation of mAbs recognizing various specific targets, such as cell surface molecules and cytokines, accompanied by flow cytometrical methodology, has enabled us to respectively distinguish an increasing number of cellular subsets. This in turn has resulted in the recent explosive progress of the immunology research field in identifying new potential drug targets (Thomas, 1989).

mAbs that neutralize and inactivate target molecules/cells have been utilized for a while for treating several human diseases (Beck *et al.*, 2010; Chan and Carter, 2010). For example, the initial trial was done using rituximab, an anti-CD20 mAb, to treat B-cell lymphoma by depleting CD20-expressing B-lineage cells (Reff *et al.*, 1994). In the case of rheumatic diseases, a number of mAbs targeting TNF are now frequently used for treating RA, such as infliximab, adalimumab and golimumab (Breedveld, 2000; Feldmann and Maini, 2001). The development and clinical application of mAbs, so-called 'biological agents', have undoubtedly caused a paradigm shift in the therapeutics of RA. Besides TNF, several targets have been utilized to date, such as IL 6 and its receptor (tocilizumab), cytotoxic T-lymphocyte antigen 4 (CTLA4), and so on. In addition to RA, several immunological disorders are now targeted by mAb therapies. These include multiple sclerosis (treated with alemtuzumab anti-CD52), inflammatory bowel diseases (anti-TNF mAbs), psoriasis (anti-IL17 mAbs) and asthma (omalizumab anti-IgE) (Scalapino and Daikh, 2008; Pelaia *et al.*, 2012; Tanaka *et al.*, 2012). Some representative examples are illustrated in Table 3.

One of the most significant advantages of mAb therapies is the high specificity for their targets, which would minimize

Table 4

Adjuvants licensed for human prophylactic vaccines

	Mechanism of action			
Adjuvants	**DS**	**IS**	**Antigens (in vaccines)**	**Manufacturer**
Aluminium salts	√	Th2	DPT, HBV, IPV, HiB, etc.	Several
Emulsion o/w MF59	√	Th1	H1N1 (Fluad™) H5N1 (Focetria™)	Novartis Vaccines and Diagnostics, Cambridge, MA, USA
Emulsion o/w AS03	√	Humoral (Th?)	H5N1 (Prepandrix™) H1N1 (Arepanrix™)	GSK Biologicals, Rixensart, Belgium
Emulsion o/w AF03	√	Humoral (Th?)	H1N1 (Humenza™)	Sanofi Pasteur, Lyon, France
MPL + Alum (AS04)	√	Th2/Th1	HBV (Fendrix™) HPV (Cervarix™)	GSK Biologicals, Rixensart, Belgium
RC529 + Alum	√	Th1	HBV (Supervax™)	Dynavax, Berkeley, CA, USA
Virosomes	√	Th2/Th1	H5N1 (Inflexal™) HAV (Epaxal™)	Crucell, Leiden, The Netherlands
CTB*	–	IgA?	*Vibrio cholerae* (Dukoral™)	SBL Vaccines, Stockholm, Sweden

*The only mucosal adjuvant licensed in oral cholera vaccine; CTB, cholera toxin subunit B; DPT, diphtheria, pertussis and tetanus; DS, delivery system; GSK, Glaxo Smith Kline; HAV, hepatitis A virus; HBV, hepatitis B virus; HPV, human papilloma virus; HxNx, influenza virus; IPV, inactivated polio virus; IS, preferentially activated immune response.

off-target adverse effects. It is really surprising that depletion or inactivation of a single molecule by a mAb alters the cytokine cascade and blocks inflammatory responses in certain conditions. However, one should not disregard the challenges that therapeutic mAb therapy is raising, such as their immunogenicity, delivery only through injection and the usually extremely long half-life. Nevertheless, recent bioengineering technology has enabled us to develop less immunogenic mAbs, such as 'chimera' (having murine variable regions), 'humanized' (with murine complementary determining regions) or complete 'human' therapeutic mAbs. In addition to conventional mAbs, the pegylated Fab portion of IgG, for example, against TNF (certolizumab pegol) and a fusion protein of IgG Fc region with several targets, such as the extracellular domain of CTLA4 (abatacept) or TNF receptor (etanercept), also have the potential to be used clinically. These and possibly other developments will facilitate the creation of mAbs with fewer side-effects and perhaps even patient-specific drugs (Breedveld, 2000; Beck *et al.*, 2010).

Vaccines and adjuvants

Vaccines have had an enormous impact on human health and are probably the most important tool for preventing transmissible infectious diseases. There have been many new developments in the search for vaccines. These include novel techniques for the attenuation or inactivation of microorganisms, new ways of delivering antigens, such as the use of viruses or liposomes, emulsions and low size particles and, more recently, novel adjuvants with known mechanisms of action (Leroux-Roels, 2010; Gebril *et al.*, 2012).

The discovery of pattern recognition receptors (PRRs) and their role in innate immunity to identify pathogen or microbial-associated molecular patterns (PAMPs or MAMPs, respectively) have literally boosted interest in the field of vaccinology (Song and Lee, 2012). In fact, an expert subcommittee recently published new propositions for PRR nomenclature (Bryant *et al.*, 2015). PAMPs, including LPS and unmethylated motifs of bacterial DNA (CpG), can activate toll-like receptors (TLRs) on the surface or in the cytosolic compartments of antigen-presenting cells (APCs) (Song and Lee, 2012). Aluminium salts are the most commonly used adjuvants in clinical practice and activate another class of PRRs, namely the nucleotide-binding oligomerization domain (NOD)-like receptors (NLR), thus leading to the activation of APCs (Eisenbarth *et al.*, 2008). APC activation increases cytokine expression, antigen presentation and other events that cause maturation of APCs. Mature APCs modulate the activation of T- and B-cells and the commitment of CD4+ T-cells to the various subsets of Th and to regulatory (Treg) cells (Zhu *et al.*, 2010). It is now clear that activation of different PRRs may favour preferentially specific Th subsets and various aspects of the immune response, hence favouring better protective responses against microorganisms (Medzhitov, 2007). The adjuvant component of vaccines also appears to contribute to the local and systemic side effects of vaccination (Eisenbarth *et al.*, 2008). A list of adjuvants available for human use is shown in Table 4.

In the context of allergy, there are now vaccines developed from a number of allergens that are used for allergen-specific immunotherapy (Akkoc *et al.*, 2011). Recently, a detoxified derivative of LPS from *Salmonella minnesota*, referred to as monophosphoryl lipid A (MPL), has been used in adjuvanted pollen allergy vaccines (Patel and Salapatek, 2006). MPL is an adjuvant that induces a Th1-skewed immune response through binding to the TLR4 on APCs. The subsequent stimulation of cytokine secretion, such as IL-12,

favours the reduction of IgE and the induction of protective IgG antibodies in allergic individuals (Mothes *et al.*, 2003). Pollinex Quattro is a vaccine for the treatment of pollen allergies that is enhanced with MPL (Rosewich *et al.*, 2013). Therefore, the search for novel adjuvants with a known molecular mechanism of action, greater efficacy and safety profile is an area of particular interest to immunopharmacologists.

Summary and conclusions

In addition to the classical therapeutic approaches, the novel immunopharmacological concepts and tools and their relevance to human disease offer new options for unmet medical needs including, among others, cancer, inflammatory, autoimmune, metabolic and infectious diseases. The recent developments in immunology and pharmacology emphasize the necessity not only to exploit new classes of drugs, such as cytokines, PKIs and mAbs, but also to improve those that are already in use. The optimal translation of experimental data (Siebenhaar *et al.*, 2015), the characterization of the links between genetic, epigenetic and non-genetic factors (Almouzni *et al.*, 2014), and the application of the 'omic' technologies are likely to identify novel disease pathways and to repurpose a number of therapeutics (Holgate, 2013). While in the near future a number of new agents will be introduced, the common challenge for all researchers and clinicians working in the fields of immunology, pharmacology and drug development is to improve the efficacy and safety of the diverse classes of drugs discussed herein. The newly formed *ImmuPhar* is the Immunopharmacology Section of the IUPHAR that provides a unique international expert-lead platform to dissect and promote the growing knowledge and understanding of immune (patho)physiology and its exploitable modification by a variety of medicines.

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Conflict of interest

None.

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