The expanding role of immunopharmacology - IUPHAR Review X

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Abbreviated title: IUPHAR Immunopharmacology Section - ImmuPhar

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Abstract

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 made available new classes of clinically relevant drugs. These ~~,~~ comprise~~ing~~ 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 additional human pathologies. Likewise, more effective vaccines utilising novel antigens, adjuvants and routes of administration are valuable tools for the prevention of transmissible infectious diseases and in allergen immunotherapy. Consequently, immunopharmacology is presently considered as one of the expanding fields of pharmacology. It ~~,~~ address~~es~~~~ing~~ the selective regulation of immune responses and aim~~s~~~~ing~~ 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 effectiveness and safety of those currently used 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 aiming to dissect and promote the growing understanding of immune (patho)physiology. Moreover, it ~~as well as to~~ 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.

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Abbreviations

Abl, Abelson kinase; AFPL, *Neisseria meningitidis* B proteoliposome; Akt, serine/threonine kinase Akt; ALK, anaplastic lymphoma kinase; APC, antigen-presenting cell; Bcr, breakpoint cluster region; Btk, Bruton typosine kinase; CD, cluster of differentiation; c-Kit, mast/stem cell growth factor receptor; CpG, unmethylated motifs of bacterial DNA; CTB, cholera toxin subunit B; CTLA, cytotoxic T lymphocyte antigen; D.P.T, diphteria, pertussis and tetanus; DS, delivery system; EGFR, epidermal growth factor receptor; EPH, ephrin kinase; Fab, fragment antigen-binding; FGFR, fibroblast growth factor receptor; GPCR, G protein-coupled receptor; GSK, Glaxo Smith Kline; HAV, hepatitis A virus; HBV, hepatitis B virus; HER, human epidermal growth factor receptor; HGFR, hepatocyte growth factor receptor; HiB, *Haemofilus influenzae* B antigen; HPV, human papilloma virus; HxNx, influenza virus; Ig, immunoglobulin; IFN, interferon; IL, interleukin; IPV, inactivated polio virus; IRAK, interleukin-1 receptor-associated kinase; IS, preferentially activated immune response; IUPHAR, International Union of Basic and Clinical Pharmacology; JAK, Janus kinase; LPS, lipopolysaccharide; 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; NSAIDs, nonsteroidal anti-inflammatory drugs; ODN, oligodeoxynucleotide; PAMP, pathogen-associated molecular pattern; PDGF, platelet derived growth factor; PDGFR, platelet derived growth factor receptor; PI3K, phosphatidylinositol-3-kinase; PK, protein kinase; PKI, protein kinase inhibitor; PRR, pattern recognition receptor; R, receptor; RA, rheumatoid arthritis; Raf, rapidly accelerated fibrosarcoma; RET, receptor for GDNF-family ligands; ROR, retinoic acid receptor-related orphan receptor; SCF, stem cell factor; Src, proto-oncogene tyrosine-protein kinase Src; STAT, signal transducer and activator of transcription; Syk, spleen tyrosine kinase; Th, T helper cell; TK, tyrosine kinase; TLR, toll-like receptor; TNF, tumor necrosis factor; Treg, regulatory T cells; TrkB, tropomyosin receptor kinase B; VEGFR, vascular endothelial growth factor receptor; VLP, virus like particles; WHO, World Health Organization

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 nonsteroidal anti-inflammatory drugs (NSAIDs), 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).

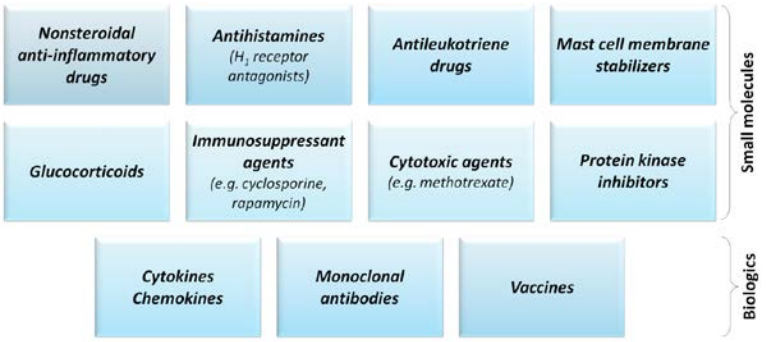

Figure 1
Common clinically relevant drugs used in the treatment of human inflammatory, allergic and other immune system associated disorders.

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 made available new classes of drugs. ~~,~~ For instance, ~~including~~ protein kinase inhibitors (PKIs) and biologics, such as monoclonal antibodies (mAbs) (Figure 1) ~~that~~ are capable of selectively modulating immune cell subsets (Dollery, 2014). At the same time, growing evidence connected 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, immunopharmacology is presently considered as one of the youngest fields of pharmacology. Immunopharmacology addresses the selective up- or down-regulation of immune responses. It ~~and~~ aims to uncover and exploit more effective and safer therapeutic options for unmet clinical needs for a continuing expanding range of pathologies, such as cancer and inflammatory, infectious, immune and metabolic diseases.

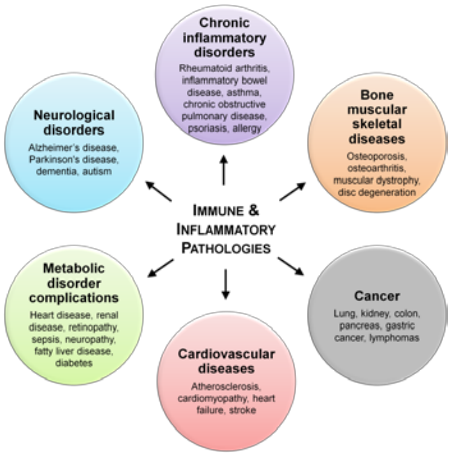

Figure 2
Examples of human pathologies linked to inflammation and to dysfunctions of the immune system.

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 knowledge dissemination in immunopharmacology. The ~~through the~~ activities are organized by the Executive Committee, the International Advisory Board, and the sub-committees on 'molecular targets for immunodulatory drugs' (molecular oriented), 'targets in immune-related diseases' (disease oriented), and 'antibodies as therapeutics'.

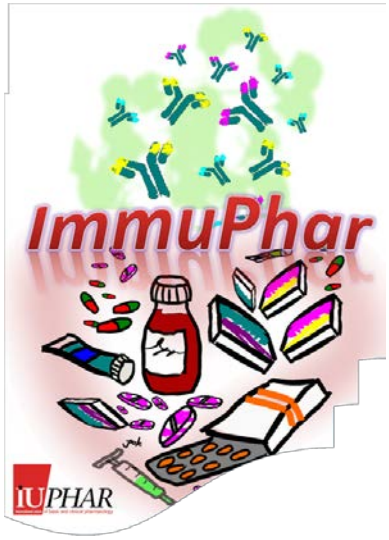

Figure 3
Logo of *ImmuPhar*, the Immunopharmacology Section of the International Union of Basic and Clinical Pharmacology (IUPHAR). *ImmuPhar* aims to promote the international cooperation and knowledge dissemination in the growing field of immunopharmacology.

The objectives of *ImmuPhar* will be achieved by (a) stimulating world-wide research in basic and clinical immunopharmacology, (b) promoting high scientific and ethical standards in research into related medicines and therapeutics, (c) encouraging related scientific meetings, workshops and courses in different parts of the world, (d) improving and harmonising teaching of Immunopharmacology, (e) supporting the utilisation of immunopharmacological agents in health care delivery, particularly in developing countries, (f) evaluating patients experiencing adverse drug reactions by utilising clinical immunopharmacology skills, (g) encouraging collaboration with other agencies and organisations interested in the study, development and rational use of immunopharmacological agents, (h) exchanging and disseminating information on the safety and pharmacovigilance of related medicines and therapeutics, (i) fostering cooperative efforts among educational, research, clinical, industrial and governmental personnel engaged in activities relevant to the translational research in immunopharmacology. Membership to 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, 2015), while 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 innovation 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 these novel options during drug development, without excluding the important advances in the pharmacology of classical therapeutic approaches.

Small molecules - signaling bias ~~– personalized medicine~~

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, and more importantly, lack oral availability and often show inefficient delivery to target tissues *in vivo* (Kopf *et al.*, 2010). By controlling signaling pathways implicated in tissue-specific inflammation, small molecules remain an effective approach to 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. Besides the potent inhibition of growth factor-induced T cell proliferation, the serine/threonine protein kinase (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~~Moreover, the dissection of the physiological relevance of~~ the recently recognized rapid onset and short duration of the non-genomic glucocorticoid actions. These promise to facilitate the development of new improved strategies for the management of inflammatory and autoimmune diseases (Alangari, 2010; Simon *et al.*, 2013).

On the other hand, 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 ~~the treatment of many forms of diseases, such as~~ asthma and~~,~~ allergies~~,~~ ~~dermatitis and arthritis~~ (Schumacher *et al.*, 2014; Chliva *et al.*, 2015~~;~~ ~~Kyriakidis *et al.*, 2015~~). In particular, histamine interacts with four types of G protein-coupled receptors (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 antihistamines targeting the H_1 receptor reflects the ongoing efforts to modulate receptor activity and to translate preclinical drug actions into promising therapies for pathologies with 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 concepts on the extensive biological functions of histamine. Besides its putative role in allergy, ~~and exposed attractive perspectives for~~ the translational potential of this new drug target in acute and chronic inflammation, host defense and neuropathic pain exposes attractive novel perspectives (Tiligada *et al.*, 2009; Zampeli and Tiligada, 2009; Tiligada, 2012; Kyriakidis *et al.*, 2015).

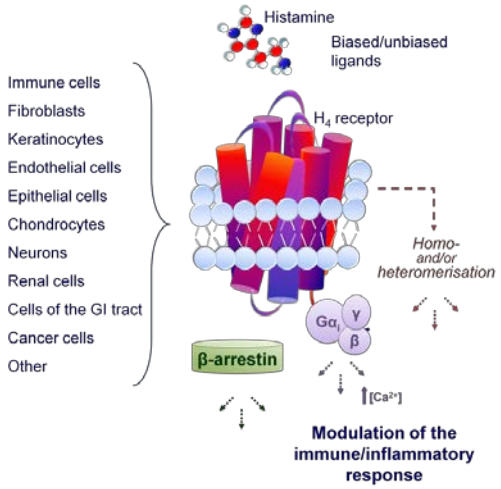

Figure 4
The histamine H_4 receptor is expressed in various cell types and mediates a variety of distinct effects depending on the endogenous complement of receptor expression and signal transduction pathways upon binding of histamine, unbiased or biased ligands.

~~In parallel to t~~The rapid entry of H_4 receptor-targeting compounds into advanced clinical development will ~~in order to~~ benefit patients with poorly treatable chronic diseases. Moreover, the pluridimensional, rather than ~~the~~ 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 signaling 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).

~~Besides the efforts to advance the rational design of selective drugs targeting immune cell receptors that exhibit signaling bias (Nijmeijer *et al.*, 2013; Corbisier *et al.*, 2015) and to optimally translate the findings from experimental animals to human pathophysiology (Siebenhaar *et al.*, 2015), attention has also been drawn to the links between genetic, epigenetic and non-genetic factors and their role in disease susceptibility and progression (Almouzni *et al.*, 2014). Furthermore, a personalized approach to immune-driven pathologies, such as asthma requires the reclassification of diseases along causal pathways (Holgate, 2013). The application of the 'omic' technologies to biological samples obtained from deeply phenotyped patients is likely to identify novel pathways shared with many diseases and to effectively repurpose therapeutics, thus offering entirely new avenues and solutions to major problems in immunopharmacology (Holgate, 2013).~~

Protein kinase inhibitors

The family of PKs includes 2 major subfamilies, the serine/threonine kinases and the tyrosine kinases (TKs). PKs are components of signal transduction pathways involved in diverse biological processes. They~~, such as cell growth, metabolism, differentiation and apoptosis, and~~ 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; Fabbro, 2014; Fabbro *et al.*, 2015; Galuzzi *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. ~~Being responsible for important (patho)physiological functions,~~Thus, PKs constitute multiple targets for anticancer treatments and potentially for the modulation of inflammation and immunity if safety can be assured (Marfe and Di Stefano, 2014; Galuzzi *et al.*, 2015).

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 ~~the first PKI,~~ imatinib~~,~~ in 2001 (Nagar *et al.*, 2002; Fabbro *et al.*, 2015). PKIs have potentiated and sometimes replaced the therapy with mAbs. ~~usually directed against the extracellular domains of PK receptors.~~ Whereas kinase inhibitors are validated in certain types of cancer, the situation is far from clear in autoimmune and inflammatory diseases. 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 they can exhibit significant cross-reactivity (Table 1). In fact, among the drugs approved for clinical use, only few, including lapatinib and imatinib are highly selective, ~~while~~ the majority inhibiting 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 ~~that may occur~~ after long-term therapy (Davies *et al.*, 2000; Ubersax and Ferrell, 2007; Loriot *et al.*, 2008; Chen and Fu, 2011).

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Table 1
Examples of protein kinase inhibitors and cancer therapy

Drug	Molecular target	Tumor
Imatinib	PDGFR, PDGF, SCF, c-Kit, Bcr-Abl	Chronic myeloid leukemia, gastrointestinal stromal tumors
Gefitinib	EGFR	Metastatic non-small cell lung cancer
Erlotinib	HER2, EGFR	Metastatic non-small cell lung cancer
Sorafenib	VEGFR-2,VEGFR-3, PDGFR-B, c-Kit, Fit-3	Renal cell carcinoma
Sunitinib	PDGFR, VEGFR, c-Kit, Fit-3	Renal cancer, gastrointestinal stromal tumors
Dasatinib	Bcr-Abl, Src, c-Kit, EPH, PDGFR-B	Imanitib-resistant chronic myeloid leukemia
Nilotinib	PDGFR, c-Kit, Bcr-Abl	Chronic myeloid leukemia
Lapatinib	HER2, EGFR	Brest 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 leukemia
Dabrafenib	Raf	Melanoma
Trametinib	MEK	Metastatic cutaneous melanoma
Nintedanib	VEGFR, FGFR, PDGFR	Idiopathic pulmonary fibrosis

Abl, Abelson kinase; ALK, anaplastic lymphoma kinase; Bcr, breakpoint cluster region; c-Kit, mast/stem cell growth factor receptor; EGFR, epidermal growth factor receptor; EPH, ephrin kinase; FGFR, fibroblast growth factor receptor; HER, human epidermal growth factor receptor; HGFR, hepatocyte growth factor receptor; JAK, Janus kinase; MEK, mitogen activated kinase kinase; MET, mesenchymal epithelial transition factor or hepatocyte growth or scatter factor receptor; PDGF, platelet derived growth factor; PDGFR, platelet derived growth factor receptor; Raf, rapidly accelerated fibrosarcoma; RET, receptor for GDNF-family ligands; SCF, stem cell factor; Src, proto-oncogene tyrosine-protein kinase Src; TrkB, tropomyosin receptor kinase B; VEGFR, vascular endothelial growth factor receptor.

PKI specificity has been tested *in vitro* with binding affinity and activity inhibition tests detecting also~~, if the entire kinase is used,~~ allosteric bindings and ~~allosteric~~ modulation of TK activity. *In vitro* assays have a number of limitations due, for example, to ~~ATP concentration or~~ lack of post-translational target modifications or of ~~,~~ other regulatory proteins and non-kinase targets in the assay that are often responsible for relevant off-target effects (see Fabbro *et al.*, 2015). Recent progresses in quantitative proteomics allow more impartial interpretation on PKI specificity and provide models PKI-PK interaction in the biological context.

Furthermore, pharmacokinetic characteristics ~~such as absorption, (re)distribution, metabolism and elimination, as well as~~and the possible interaction with drugs modulating their metabolism through cytochrome P450 isoenzymes are as important as the pharmacodynamic parameters and the choice of therapeutic target in order to assess the potential utility of PKIs (van Leeuwen *et al.*, 2014).

However, a more critical issue is the choice of therapeutic target (Table 2). 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 ~~both acute and chronic~~ adverse drug reactions, but also to define "secondary" therapeutic approaches that will permit in the future the use of those drugs in other diseases. ~~For example, dasatinib, a breakpoint cluster region-Abelson kinase (Bcr-Abl) inhibitor, after approval for chronic myeloid leukemia, has been shown to strongly inhibit Bruton TK (Btk), important in diffuse large B-cell lymphoma, thus opening to new therapeutic indications~~ (Aalipour and Advani, 2013). Whereas kinase inhibitors are validated in certain types of cancer, the situation is far from clear in autoimmune and inflammatory diseases (Table 2). 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. Tumor necrosis factor (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 (Steinman *et al.*, 2012). ~~Moreover,~~B~~ b~~ecause 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. In some cases, following drug binding, there is a kinase activation. This paradoxical effect which may be related to kinase interaction with molecules affecting the kinase conformational state can be part of drug action or even constitute a mechanism of resistance (Chen and Fu, 2011, Marfe and Di Stefano, 2014; Fabbro *et al.*, 2015).

Table 2

Targets that need to be validated for autoimmune and inflammatory diseases

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

Akt, serine/threonine kinase Akt; IFN, interferon; IL, interleukin; IRAK, interleukin-1 receptor-associated kinase; JAK, Janus kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3-kinase; ROR, retinoic acid receptor-related orphan receptor; STAT, signal transducer and activator of transcription; Syk, spleen tyrosine kinase; TLR, toll-like receptor; TNF, tumor necrosis factor

Although PKIs share the same mechanism of action, competing with ATP to the catalytic site of the enzyme, they differ in specificity of target, pharmacokinetics and side effects. Major acute and chronic side effects, involving different organs, limit the clinical use and cause clinical trial suspension and drug withdrawal (Loriot *et al*., 2008). It is hoped that in the near future new PKIs that target new kinases can reach the preclinical and clinical trials. 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) and will be leading a major initiative on their role in immunopharmacology.

Monoclonal antibody therapies

Advances in basic immunology have contributed to identifications 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, generation of mAbs recognizing various specific targets, such as cell surface molecules and cytokines, accompanied with flow cytometrical methodology, has enabled us to respectively distinguish an increasing number of cellular subsets. This in turn has brought to recent explosive progresses of the immunology research field in identifying new potential drug targets (Thomas, 1989).

mAbs neutralizing and inactivating 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 by using rituximab, an anti-CD20 mAb, for treating 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 ~~tumor necrosis factor (~~TNF~~)~~ are now frequently used for treating ~~rheumatoid arthritis (~~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 interleukin (IL) 6 and its receptor (tocilizumab), cytotoxic T lymphocyte antigen 4 (CTLA-4), and so on. In addition to RA, several immunological disorders are now targeted by mAb therapies, including multiple sclerosis (treated by 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.*, ~~1912~~2012; Tanaka *et al.*, ~~1912~~2012), Some representative examples are illustrated in Table ~~2~~3.

One of the most remarkable advantages of mAb therapies is its high specificity for their targets, which would minimize off-target adverse effects. It is really surprising that depletion or inactivation of a single molecule by mAb alters cytokine cascade and blocks inflammatory responses in certain conditions. However, one should not disregard the challenges that therapeutic mAb therapy are raising, such as their immunogenicity, delivery only through

injection, the usually extremely long half-life etc. Nevertheless, recent bioengineering technology 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, pegylated Fab portion of IgG, e.g. against TNF (certolizumab pegol) and a fusion protein of immunoglobulin (Ig) G Fc region with several targets, such as the extracellular domain of CTLA-4 (abatacept) or TNF receptor (etanercept), could also be used clinically. These and possibly other developments will facilitate the creation of less side-effects-prone mAbs and perhaps even patient-specific drugs (Breedveld, 2000; Beck *et al.*, 2010~~; Breedveld, 2000~~).

Table ~~2~~3
Representative examples of therapeutic monoclonal antibodies

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

CD, cluster of differentiation; CTLA, cytotoxic T-lymphocyte-associated protein; Fab, fragment antigen-binding; Ig, immunoglobulin; IL, interleukin; R, receptor; TNF, tumor necrosis factor.

Vaccines and adjuvants

Vaccines have had an enormous impact on human health and are likely the most important tool to prevent transmissible infectious diseases. There has been much development in the search for novel attenuated or inactivated microorganisms, various delivery viruses or particles; novel antigens, peptides or DNA; novel routes of administration (e.g. subcutaneous *versus* mucosal routes) and, more recently, novel adjuvants with known mechanisms of action. The discovery of pattern recognition receptors (PRRs) of innate immunity and their respective ligands, pathogen or microbial-associated molecular patterns (PAMPs or MAMPs) have literally boosted interest in the field (Song and Lee, 2012). Activation of PRRs, such as toll-like receptors (TLRs), stimulates immune responses when PAMPs are given with the

antigen in a proper delivery vehicle. Such receptors and delivery systems have thus received much attention for the development of novel adjuvants (Reed *et al.*, 2009) (Table ~~34~~). The search for novel, local and long-acting selective agonists of TLRs is an area of particular interest to immunopharmacologists. In addition, there is much interest in understanding their exact mechanisms of action and potential local and systemic side effects. Custom-made adjuvants may enhance vaccine efficacy with significantly less side-effects. Another aspect of immunization that is of interest to immunopharmacology relates to the use of immunotherapy in the context of allergic diseases, largely concerning optimization of antigen dose, delivery route and mechanism of action.

Table ~~34~~

Adjuvants licensed for human prophylactic vaccines (Reed *et al.*, 2009; Leroux-Roels, 2010)

Adjuvants	Mechanism of action		Antigens (in vaccines)	Manufacturer
	DS	IS		
Alumminium salts	✓	Th2	D.P.T, HBV, IPV, HiB, etc	Several
Emulsion o/w MF59	✓	Th1	H1N1 (Fluad™) H5N1 (Focetria™)	Novartis
Emulsion o/w AS03	✓	Humoral (Th?)	H5N1 (Prepandrix™), H1N1 (Arepanrix™)	GSK
Emulsion o/w AF03	✓	Humoral (Th?)	H1N1 (Humenza™)	Sanofi Pasteur
MPL+Alum (AS04)	✓	Th2/Th1	HBV (Fendrix™) HPV (Cervarix™)	GSK
RC529+Alum	✓	Th1	HBV (Supervax™)	Dynavax
Virosomes	✓	Th2/Th1	H5N1 (Inflexal™) HAV (Epaxal™)	Crucell
CTB*	-	IgA?	*V. cholerae* (Dukoral™)	SBL

*, the only mucosal adjuvant licensed in oral cholera vaccine; CTB, cholera toxin subunit B; D.P.T, diphteria, pertussis and tetanus; DS, delivery system; GSK, Glaxo Smith Kline; HAV, hepatitis A virus; HBV, hepatitis B virus; HiB, *Haemofilus influenzae* B; HPV, human papilloma virus; HxNx, influenza virus; Ig, immunoglobulin; IPV, inactivated polio virus; IS, preferentially activated immune response; MPL, monophosphoryl lipid A; Th, T helper cell; VLP, virus like particles.

Several immune stimulator components from bacteria and viruses have been identified, including lipopolysaccharide (LPS) and unmethylated motifs of bacterial DNA (CpG), which can activate TLRs on the surface or in the cytosolic compartments of antigen-presenting cells (APCs) (Song and Lee, 2012). APC activation increases cytokine expression, antigen presentation, and other events causing the maturation of APCs. Activated APCs modulate the activation of T and B cells, as well as the commitment of CD4+ T cells in T helper cells Th1, Th2, Th17 and in regulatory T (Treg) cells (Zhu *et al.*, 2010). Activation of TLR9 by CpG oligodeoxynucleotides (ODNs) inhibits a Th2 response and favors a Th1 pattern. The Th1 pattern is characterized by induction of interferons and other cytokines which favors the elimination of bacteria and viruses, whereas Th2 pattern is elicited to eliminate parasitic infections and is also related with allergy reactions (Medzhitov, 2007).

Delivery systems are vehicles carrying antigens and also immune stimulators to APCs. Aluminum salts have been widely used in human vaccines and are an example of a depot adjuvant. A depot effect promotes the presentation of antigens to APCs, although Th2 responses have been reported to be associated with stimulation of inflammasome signaling (Eisenbarth *et al.*, 2008). For this reason, alum adjuvants have been used less in novel vaccine strategies. However, the combination of aluminum salts with potent immune stimulators, such as LPS, monophosphoryl lipid (MPL), or *Neisseria meningitidis* B proteoliposome (AFPL) 1 may switch the Th2 response to a Th1 pattern (Moschos *et al.*, 2006; Perez *et al.*, 2007). Non depot adjuvant, like liposomes, emulsions and low size particles have been evaluated and are under development in new vaccine candidates (Leroux-Roels, 2010).

Current prophylactic vaccines are administered parenterally and several disadvantages have been associated with this practice, such as the risk of injury and cross-infection through contaminated needles (Shah *et al.*, 2005), the lack of potential for self-administration and the induction of mainly systemic immune response (Giudice and Campbell, 2006). Several researchers are working together to find proper delivery systems and immune-adjuvants to develop mucosal vaccines (Gebril *et al.*, 2012).

Regarding allergy, there are traditional vaccines developed from pollen, house dust mites, pets, molds, food, and insects, as well as improved allergen ones that use PAMPs and different delivery systems (Akkoc *et al.*, 2011). An example is the use of detoxified LPS from *Salmonella minnesota*, known as MPL A, which has been evaluated with pollen allergens. MPL is thought to be a Th1-inducing adjuvant. Engagement of MPL with TLR4 in APCs stimulates the secretion of cytokines such as IL12, which is closely related to the reduced induction of IgE and switching to IgG1 and IgG4 in humans (Mothes *et al.*, 2003). Pollinex Quatro™, licensed in Europe and Canada, contains MPL and is used for the treatment of allergy to grass, tree, or ragweed pollen (Patel *et al.*, 2006).

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 cancer, inflammatory, autoimmune, metabolic and infectious diseases among others. The recent developments in immunology and pharmacology emphasize the necessity not only to exploit new classes of drugs, such as cytokines, PKIs and mAbs~~, targeting the modulation of decisive immune responses for a range of human pathologies~~, 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 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.

Formatiert: Abstand zwischen asiatischem und westlichem Text anpassen, Abstand zwischen asiatischem Text und Zahlen anpassen

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Conflicts of interest

None.

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