Chapter 1

General Introduction: Inflammation, pain and analgesic drug effects
GENERAL INTRODUCTION

Pain is a symptom associated overt behavioural, physical and psychological manifestations. In contrast to other therapeutic areas for which the interrelationship between aetiology, symptoms and therapeutic targets are well defined (e.g. insulin secretion and DPP-IV inhibitors in diabetes, GABA-ergic activity and benzodiazepines in sedation), the development of analgesic, anti-inflammatory drugs requires understanding not only of drug-target interaction mechanisms, but also of the time dependencies underlying downstream cascades within complex pathway of nociceptive response in vivo. The consequences of such a complexity are very relevant for the assessment of drug efficacy and safety in early drug development. Nevertheless, the measures of analgesia and anti-inflammatory response currently used in experimental models of pain in animals and humans are often too coarse to distinguish target occupancy and target activation from other determinants of nociception.

A brief overview of the mechanisms involved in pain and chronic inflammation is presented below to provide the reader with sufficient understanding of the elements underlying our claim in this thesis for a mechanism-based approach in the evaluation of non-steroidal anti-inflammatory drugs and in particular of COX inhibitors in early drug development.

PAIN

Pain has been defined by the international association for the study of pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

PAIN PERCEPTION

It is inappropriate to see pain as either a physical or psychological symptom; it is always both, as stated in the IASP definition. Pain sometimes occurs without apparent cause or does not occur despite obvious injury (e.g. in a wounded soldier on the battlefield) (1). It can persist after tissue healing or continue despite appropriate treatments. In contrast, it may wane with other unrelated interventions. An example of this is the placebo response, whereby a 'sham' treatment can produce good analgesia. The converse of this is the nocebo response, where pain can be experimentally induced in the absence of nociceptive stimulus, but rather only the suggestion of one. From the above, it is clear that pain perception and corresponding suffering depend on many other psychological and somatic variables such as: anxiety; past experiences; its meaning to the patient, injury or illness; their beliefs about treatment and medications (fear of dependence, addiction, tolerance, organ damage); and self-management strategies. These factors are equally relevant in acute and chronic pain conditions. Therefore, any attempt to quantify treatment effect in response to a pharmacological intervention requires understanding of the multidimensionality of pain perception, as it involves more than simply nociceptive and inflammatory mechanism. In addition, one should realize that the high variability in the response to pain is not restricted to differences in pharmacokinetics, pharmacodynamics or disease state.
General Introduction: Inflammation, pain, and analgesic drug effects

Ideally, from a drug development perspective, it would be valuable to use mediators of inflammation as surrogates of pain relief and analgesia. As discussed below, such an approach would draw attention to the relative contribution of the pharmacological mechanisms underlying drug-target interaction rather than unrelated pathways downstream in the response cascade.

### PAIN & INFLAMMATION

The definitions of pain perception can be rather subjective and imprecise as stated above. Yet, acute transient pain is associated with negligible tissue damage and is thought to serve as a physiological warning to guard the integrity of the organism (2). This warning purpose of pain is most evident as concerns the skin, which is exposed to external dangers. On the other hand, chronic pain which is associated with tissue damage, inflammation or neuropathologies is regarded as fulfilling no physiological purpose. Moreover, in chronic pain states there is a superimposition of many other processes onto the basic events of nociception, which alters the relationship between stimulus and response, and the modulation of pain. In fact, the type and nature of sensory experience (pain perception) depend on type of injury and accompanying inflammation or neuropathology.

In chronic pain, understanding is beginning to emerge of the complexity of events associated with nociception. Some of these events occur in precise intervals during the development and consolidation of the pain signalling, and can range from changes in the excitability of fine afferent

---

**Figure 1.** Reorganisation in the spinal cord processing following chronic pain. Under normal physiological conditions nociceptive signals generated by C-fibres initiate acute pain and a protective reflex. Activation of low-threshold Ab-fibres by innocuous stimuli does not induce pain. In pathologic pain following various types of injury or nerve damage, C-fibres become hypersensitive and induce hyperalgesia in sensory pathways, resulting in an enhanced and persistent response following sensory nerve stimulation. Under these conditions, low-intensity Ab-fibre stimulation induces pain (allodynia). NA indicates noradrenaline, C - C-fibres, Ab - Ab-fibres, Ad - Ad-fibres. Adapted from (17).
nerves to drastic alterations in their cellular phenotype with the expression of new molecules, including neurotransmitters, enzymes and chemical receptors. In addition, central alterations in the neurochemistry of pain signalling may produce hypersensitivity, which enhances and prolongs relatively low levels of afferent input and allows normally innocuous stimuli to be perceived as painful (figure 1).

Structural changes, particularly following peripheral nerve injury, include loss of spinal interneurons, inappropriate rearrangements of afferent nerve processes in the spinal cord and proliferation of sympathetic fibres into sensory ganglia, which are not normally innervated to any significant degree. The occurrence of the changes outlined above and their particular features are by no means uniform and depend on the type of tissue injury, the involvement of specific types of afferent fibre and the participation of the immune system. However, chronic pain conditions do not always result from peripheral injuries, but rather from organic or affective disorders of the CNS (2). These latter processes are poorly understood. Furthermore, chronic pain behaviour has added complexities to the understanding of pain signalling, since human reactions can be modified by environmental and sociological settings.

**PERIPHERAL INFLAMMATORY PAIN**

In inflammatory pain, hypersensitivity is the consequence of alterations in the transduction sensitivity of nociceptors, activity-dependent changes in the excitability of spinal neurons and phenotypic changes in the sensory neurons innervating the inflamed tissue (2). Tissue injury results in the release of inflammatory mediators from damaged or infected cells, increasing the transduction of painful stimuli. Among these mediators, a second series of signals is generated or initiated by inflammatory cytokines such as tumour necrosis factor (TNF-α) and interleukins (IL-1β, IL-6). Cytokines act on and between inflammatory cells, inducing some of the features of the inflammatory response. They also mediate some of the systemic effects of inflammation, such as fever or cachexia. In addition, the induction of cytokines can lead to the expression of the inducible form of nitric oxide synthase (iNOS), which in turn provokes the release of excessive amounts of nitric oxide (NO) which may further contribute in the pathogenesis of tissue injury.

The intricate biochemical interactions of short-lived inflammatory mediators after tissue injury, combined with the neural release of substance P and the process of plasma extravasation, result in a positive feedback loop continually refuelling the inflammatory process. The continued synthesis or release of these mediators contributes to the prolonged time course of inflammation, which by far exceeds the initial stimulation. Furthermore, in addition to local cellular events, potassium, prostaglandins, bradykinins, ATP and other mediators from damaged cells trigger the nociceptors to send afferent impulses via the dorsal root ganglion to the spinal cord. These afferent C and Ad nociceptive nerves are activated by a number of potentially harmful stimuli, but their sensitivity to the chemicals generated by tissue damage and inflammation is particularly notable (3).
On the other hand, chemical pain transduction involves interactions with membrane receptors that are coupled to ion channels and second messenger systems, resulting in changes in membrane excitability and cell phenotype. In this environment, many chemical stimuli are available to initiate cascades of signals. Hence, there is enormous potential for signal amplification and modulation, as well as an opportunity for potentiation between neural and non-neural mechanisms. Such interactions are important in producing hyperalgesia but must also be viewed as important mechanisms contributing to tissue regeneration and repair following injury (2).

Centrally, afferent information is transmitted via second-order neurons in the dorsal horn through the spinothalamic tract to the thalamus and to the sensory cortex. These higher centres are responsible for the perception of pain. At different levels of the pain pathway, a complex system of compensatory neuroinhibitory mechanisms is involved in the perception of pain. For detailed information on pain processing, two reviews by M. Millam are recommended (3;4).

From the aforementioned it is clear that significant differences may be found in treatment effect if one measures pain signalling, pain processing, pain perception or pain behaviour. These components are further compounded by anatomical, functional and temporal interactions, which progressively develop or intensify during the course of disease. However, as discussed later in this chapter, these factors seem to be overlooked by the approach currently used in the development of nonsteroidal anti-inflammatory drugs. In addition, the results from (pre-)clinical models assume no confounding by major differences in species or experimental setting (e.g., evoked or spontaneous pain). The assessment of drug efficacy and safety is defined primarily by measuring pain perception and pain behaviour, precluding a more mechanistic, integrated evaluation of pharmacology and toxicology.

We plea for a **pathway analysis**, rather than just relying on target characterisation for the evaluation of COX inhibitors, i.e., for an approach which enables discrimination of drug properties beyond selectivity and analgesia for defining the appropriate dosing regimen and therapeutic window. The role of inflammatory mediators, pain signalling and processing is central to this strategy.

**MEDIATORS AND MODULATORS OF INFLAMMATORY PAIN**

Insight into the dynamics of inflammation and inflammatory response is required to endorse the rationale underlying a mechanism-based approach for the development of COX inhibitors and more specifically of selective COX-2 inhibitors. The role of some important mediators involved in pain response during inflammatory disease conditions is discussed briefly in the next paragraphs. Their involvement in homeostatic, regulatory feedback pathways will be relevant for explaining the apparent disconnection between drug exposure, biomarkers, analgesic and anti-inflammatory response during chronic inflammatory conditions.

**Prostanoids.** A variety of prostanoids (PGE$_2$, PGI$_2$ and LTB$_4$) that are produced during inflammation are known to either excite nociceptors or, more usually, to sensitise them to other stimuli and, thus, contribute to peripheral hyperalgesia (2). Phospholipase A$_2$, an enzyme which is present in cell
membranes, is stimulated or activated by tissue injury or microbial products. Activation of phospholipase $A_2$ causes the release of arachidonic acid (AA) from the cell membrane phospholipid. Downstream two reaction pathways are catalysed by the enzymes cyclo-oxygenase (COX) and lipo-oxygenase (LOX) (figure 2) (18). It is important to highlight that these pathways compete with one another. The cyclo-oxygenase pathway results in the formation of prostaglandins and thromboxane. In contrast, the lipo-oxygenase pathway results in the formation of leukotrienes. Since these mediators are lipid soluble, they can easily cross cell membranes and consequently amplifying pain signalling (18).

The cyclo-oxygenase pathway comprises the formation of prostaglandins D, E and F, thromboxanes and prostacyclin. Whilst, thromboxanes cause constriction of vascular smooth muscle an modulate platelet aggregation, prostaglandins have diverse actions depending on cell type. Of particular interest is the role of prostaglandins in secondary hyperalgesia. Prostaglandins are known to sensitisise peripheral nociceptor terminals and produce localised pain hypersensitivity in neighbouring uninjured tissue (secondary hyperalgesia). From a pharmacokinetic-pharmacodynamic perspective, prostaglandins are very potent but are inactivated rapidly in the systemic circulation. On the other hand, leukotrienes are specific inflammatory response from leukocytes and macrophages. They are potent constrictors of the bronchial airways. They are also important in hypersensitivity reactions as they increase vascular permeability and chemotaxis (5;6).

![Figure 2](image-url). General scheme representing the main metabolic pathways leading to arachidonic acid products involved in the inflammatory cascade. Targets of antiinflammatory drugs are also shown. COX = cyclo-oxygenase; 5-LOX = 5-lipo-oxygenase; LTs = leukotrienes; PGs = prostaglandins; PLA$_2$ = phospholipase A2; TxA$_2$ = thromboxane A2. Adapted from (18).
**Bradykinin.** Similar to prostanoids, bradykinin is a potent algogen produced during injury and inflammation. It has been known for a long time that bradykinin plays a significant role in hyperalgesia by activating B2 receptors, which are expressed during prolonged inflammatory conditions. In addition, other inflammatory products, including cytokines such as interleukin (IL)-1β, IL-6 and IL-8 and tumour necrosis factor-α (TNF-α), also induce hyperalgesia by facilitating induction of B1 receptors, by stimulation of prostanoid production and by activation of sympathetic neurons (2;3).

**Serotonin.** 5-Hydroxytryptamine (5-HT) has an important role in the sensitisation of neurons. 5 HT is released from platelets and mast cells, producing mild and transient pain by direct activation of sensory neurones via 5-HT3, 5-HT1, and 5-HT2 receptors (2;3). A possible basis for sensitisation by 5-HT, as well as by bradykinin and prostanoids, is a reduction of the slow, inhibitory after-potential that follows the action potential in some sensory neurons. Overall serotonin increases the likelihood that a neuron will respond to a relatively weak stimulus with a train of action potentials rather than with a single spike. Such a scenario is particularly relevant in chronic inflammatory pain.

**Histamine.** Histamine, one of the best known inflammatory mediators, can evoke pain sensation at higher concentrations. There is surprisingly little information on how these effects are produced, but activation of histamine HE receptors may increase membrane Ca2+ permeability and the release of tachykinins and CGRP (calcitonin gene-related peptide), resulting in further complex interactions including vascular changes and mast-cell degranulation (2;3).

**Nitric oxide.** Various inflammatory mediators, including substance P and bradykinin, stimulate vascular endothelial cells to release the vasodilator nitric oxide (NO) (2;3). NO is important for intercellular communication in peripheral tissue and within the CNS. NO does not directly alter sensory neuron excitability, but acts indirectly in the anti-nociceptive effects of acetylcholine and morphine, promoting tachyphylaxis to bradykinin. Paradoxically, inhibitors of nitric oxide synthase (NOS), such as LNAME, are also antinociceptive in neuropathic and chemically induced pain.

**Cytokines.** A variety of cytokines are released by phagocytotic and antigen-presenting cells of the immune system during inflammation (2;3). Cytokines stimulate a number of other systems, for example, IL-1, through the production of leukaemia inhibitor factor (LIF), and stimulates the expression of substance P in sympathetic neurons. Their effects seem to be predominant in acute inflammation (7).

**Nerve growth factor.** Inflammation stimulates increased synthesis of NGF in fibroblasts, keratinocytes and Schwann cells. NGF induces prolonged changes in sensory neuron excitability and alterations of cell phenotype that are associated with the development of hyperalgesia (2;3). High concentrations of NGF act on tyrosine-kinase linked receptors to regulate cellular transcription factors and thereby specific gene expression. Importantly, NGF increases the synthesis, transport and neuronal content of substance P and CGRP, thereby making greater amounts available for release.
from central and peripheral terminals of sensory neurones. It also regulates at least two types of ion channel in sensory neurons: the capsaicin receptor ion channel complex and the tetrodotoxin-resistant Na\(^+\) channel. In addition, there is likely to be a subtle interplay between nerves, invasive inflammatory cells and resident cells at sites of tissue damage since NGF stimulates the release of histamine as well as lipid mediators. Furthermore, the synthesis of NGF can be induced by cytokines such as IL-1\(\beta\) and TNF-\(\alpha\). To complete this positive feedback loop, cytokine production is, in turn, upregulated by substance P released from the sensory nerve fibres.

**ROLE OF INFLAMMATION IN CHRONIC PAIN SYNDROMES**

Historically, each disease entity e.g., fibromyalgia, complex regional pain syndrome/reflex sympathetic dystrophy (RSD/CRPS), carpal tunnel syndrome, rheumatoid arthritis and ankylosing spondylitis has been considered distinct from the other entities and therefore classified in terms of symptomatology, structural pathology, genetic markers, presence of auto-antibodies, etc. Consequently, theories have evolved, which assign a different mechanism to nociceptive and neuropathic pain, to acute and chronic pain, and to peripheral and central pain (5;6). Such a conceptual differentiation has resulted in approaches for the evaluation of treatment effect in pain syndromes which focus mainly on structural pathology. In fact, treatment of inflammation in these disease entities has hitherto addressed single biochemical mediator of inflammation in isolation, instead of integrating the dynamic processes underlying all these pain syndromes.

As basis for the mechanism-based approach presented in this thesis, we strongly support the hypothesis proposed by Omoiqui, which states that the origin of all pain is inflammation and inflammatory response (5;6). Moreover, nociceptive and neuropathic pain, acute and chronic pain, peripheral and central pain including windup, neuroplasticity and central sensitisation are considered a continuum of inflammation and inflammatory response.

This concept is easily understood if one considers pathways rather than targets in the evaluation of disease and treatment response. In this context, figure 3 and 4 depicts how the interplay between different components of inflammation contributes to differences in acute and chronic progression of disease. Interestingly, this prospect allows for a comprehensive integration of the evolving response of each cell to an injury or noxious stimulus, as well as the molecular signals from neighbouring issue and external environment.

Hence, it can be expected that the assessment of drug effect on mediators of inflammatory response and on disease state will play an important role in the development of new COX inhibitors, in particular for the selection of an appropriate dosing regimen and consequently for the prediction of a compound's (long term) safety profile.

In pursuing this thesis, we assume that the methodology currently available for the analysis of inflammatory mediators does reflect the actual dynamics of inflammation and drug effect *in vivo*. In
that sense, our work will rely on the construct validity rather than on face validity aspects research, which have predominated the evaluation of anti-inflammatory drugs in early and late stages of drug development.

Based on the construct validity (8;9), it is possible to defend the choice of LPS-induced PGE2 formation and TXB2 inhibition in blood as relevant measures of the activity of COX inhibitors in vivo. In fact, evidence exists for the increase of circulating levels of PGE2 in response to local inflammation in animal models of pain (figure 5) as well as in patients with rheumatoid arthritis. The apparent mismatch observed in the target tissue and systemic inflammatory response results from time dependencies in the inflammatory cascade during chronic inflammation.

**Figure 3.** A variety of chemical factors released from blood vessels, damaged tissues, sympathetic neurons and immune cells activate or sensitise primary sensory neurons or alter their cellular phenotype. There is a dynamic interaction between these tissue and the effects of neuropeptides release by sensory nerves. These produce changes in blood flow and blood vessel permeability, stimulate immune cells and activate sympathetic nerves. Adapted from (2).

Based on the construct validity (8;9), it is possible to defend the choice of LPS-induced PGE2 formation and TXB2 inhibition in blood as relevant measures of the activity of COX inhibitors in vivo. In fact, evidence exists for the increase of circulating levels of PGE2 in response to local inflammation in animal models of pain (figure 5) as well as in patients with rheumatoid arthritis. The apparent mismatch observed in the target tissue and systemic inflammatory response results from time dependencies in the inflammatory cascade during chronic inflammation.

**BIOMARKERS: A DIFFERENT APPROACH TO DOSE OPTIMISATION IN INFLAMMATORY PAIN**

Traditionally, the driving force in clinical dose optimisation for pain control has been titration to effect (figure 6) (10). Dose-response relationships, rather than plasma concentration-response relationships, are investigated assuming that dose is a good descriptor of systemic and target exposure. Plasma concentration versus effect relationships are perhaps more subtle in pain control than in some therapeutic areas, and in part because the (deceptively simple) therapeutic target is pain relief, rather than a particular blood pressure or hormonal level. Some 40 years ago, there was a simplistic attempt to define plasma concentrations at which opioids would be effective. In reality, the
variability in the plasma concentration at which analgesia is achieved is tremendous, not least in contexts where patients have had previous exposure to opioids. Moreover, inter-individual variability in pain response itself exceeds variability in pharmacokinetics as e.g. the development of tolerance and the placebo effect must be considered (figure 7).

There is, however, a major difference in terms of rationale for the selection of the dosing regimen for COX inhibitors. COX inhibitors have a relative flat dose-response curve compared to opioids. Despite the difficulties to establish dose-response curves for analgesia within individual trials, systematic reviews have shown that with data from thousands rather than tens of patients the underlying dose-response curve for analgesic effect is revealed (figure 8). In addition, unlike opioids, which have a direct neural component on the pathway of nociception and pain perception, COX inhibitors are primarily linked to inflammatory cascade preceding or triggering nociception. Hence, characterisation of PKPD relationship seems a fundamental step to dose selection and optimisation of the dosing regimen.

As one can easily deduce, in contrast to the possibility of titration to the effect with increasing exposure to opioids, the efficacy of COX inhibitors is limited to the degree of blockade of COX, irrespective of how counter-regulatory mechanisms affect pain perception. By studying the titration to effect of NSAIDs, the PKPD relationships are confined to discrete dose levels, rather than exploring the concentration-effect curve. Furthermore, in these titration studies, the assumption is made that
drug-receptor interaction does not change over time in chronic inflammation. Yet, numerous publications suggest that the drug-receptor interaction could be dependent upon disease status or chronic administration (11;12).

**Figure 5.** Time dependencies in inflammatory response during chronic inflammation. (left panel) knee joint swelling; and (right panel) PGE$_2$ expressed as percentage change compared with pre-injection values in response to intra-articular injection of FCA. There was a significant swelling and increase in PGE$_2$ production in vehicle, L-NIL (43 mg/kg) and SC-236 (5.6 mg/kg) treated groups. A non-inflamed, untreated group is included for comparison. Values represent means ± SEM.

**Figure 6.** Titrating opioids against effect. Schematic representation of the current approach to dose selection for effective analgesia. Adapted from (10).

**SELECTIVITY AS DEVELOPABILITY CRITERION FOR NOVEL COX INHIBITORS**
The current assumption that selectivity of action is a key determinant of efficacy and safety must be revisited. Integrated criteria, which account for more than just affinity for the receptor, are required in the development of COX inhibitors and other analgesic drugs. As highlighted in previous paragraphs, the characterisation of receptor activation and subsequent downstream effects on the
inflammatory response are necessary to establish dosing requirements for efficacy and safety and unravel the underlying risk: benefit ratio.

At present, it is generally accepted that COX inhibitors can be classified on their mode of inhibition of COX in three classes: Class 1 inhibitors are simple competitive inhibitors, Class 2 COX inhibitors

Figure 7. Effect of prior exposure on the pharmacodynamics of opioids. Graph depicts the dose required to achieve the same level of pain relief (i.e., equi-analgesic dose) when re-challenged after 1 week chronic dosing. Adapted from (10).

Figure 8. Dose response for oral ibuprofen, diclofenac and paracetamol for number-needed to treat (NNT-95% CI) to achieve at least 50% pain relief compared with placebo. Adapted from (10).
are time-dependent inhibitors and Class 3 COX inhibitors are irreversible inhibitors (13). In contrast to classical non-selective COX inhibitors, which are Class 1, 2 or 3 for both COX enzymes, all diaryl-heterocyclic COX-2 selective inhibitors like celecoxib and rofecoxib are Class 2 for COX-2 and Class 1 for COX-1. Thus, selective COX-2 inhibitors are Class 1 inhibitors for COX-1, binding to COX-1 for a short period, but are Class 2 inhibitors for COX-2, and therefore display time-dependent binding to COX-2. On the other hand, it has been demonstrated that drugs like nimesulide and meloxicam, which have time-dependent binding to COX-2, also display time-dependent binding to COX-1. However, these classical COX inhibitors bind differently to the enzyme than the newly developed coxibs. Class 3 inhibitors irreversibly inhibit COX. Aspirin is the only example of a marketed class 3 inhibitor (14). The pharmacodynamics of aspirin depends on the synthesis and degradation of the COX-enzyme. By investigating the dose or concentration-pain relief relationship, the mechanisms by which COX inhibitors bind to their target (COX-1 and/or COX-2) are overlooked. And so are the consequences of subsequent downstream inflammatory response, which may ultimately determine efficacy and safety of these compounds.

CARDIOVASCULAR ADVERSE EVENTS AND THERAPEUTIC WINDOW

The search for selective COX-2 inhibitors has been motivated by the need to improve the efficacy and safety of the NSAIDs which were available for the treatment of chronic inflammatory conditions. In particular, it has been claimed that enhanced selectivity was sufficient to reduce and eventually suppress the severe gastro-intestinal effects (i.e., ulcer bleed and perforation) observed after administration of non-selective COX inhibitors. Whilst little doubt existed about the pharmacological nature of these effects and even a dose-response curves have been identified for the effect of such compounds, allowing inferences about the risk associated with a specific a dosing regimen and treatment duration (figure 9), a completely different scenario evolved when cardiovascular adverse events were observed with selective COX-2 (figure 10).

On September 30 2004, Vioxx was voluntarily withdrawn from the market because of an increase risk of major cardiovascular events. This was due to the premature cessation of the APPROVe (Adenomatous Polyp Prevention on Vioxx) trial, because of a significant increase in the incidence of serious thromboembolic adverse events in the group receiving rofecoxib as compared with the placebo group (15). More recently, etoricoxib and lumiracoxib submissions were trounced by the FDA.

The media coverage and the expert opinion evoked by these findings are far from logical, as standpoints have been taken that argue for a class effect and hence underline the need for a ban. In very few occasions emphasis was given to the importance of a quantitative, integrated evaluation of the pathways and physiological cascades associated with COX-2 inhibition. Most sadly, discussion have stranded in speculations. Instead of approaching this serious problem from a pharmacological perspective, subsequent initiatives have focused on the same coarse measures of risk, relating frequency and incidence of events to treatment, rather than exploring the concentration-exposure-response relationship of rofecoxib accordingly.
Currently, changes in the drug approval process are being discussed as the consequence of the coxib experience. Proposals include an intensification of post marketing drug safety programs, including more sophisticated pharmacovigilance and pharmacoepidemiological strategies and staged approval strategies with initial limitation to populations like those that were exposed during pre-approval trials. Such strategies, however, still rely strongly on the pre-specification of potential problems based on biological, pharmacological or clinical evidence. They will not solve the key issue underlying drug safety: the need to accurately assess the risk: benefit ratio of a treatment.

The risk of any drug is never zero. There are no drugs without side effects, even though such effects may not be clearly evident at the therapeutic dose range. The withdrawal of rofecoxib clearly shows how rudimentary are the tools currently used to assess risk:benefit ratio associated with a pathway for which considerable knowledge exists about its role in physiological and pathophysiological conditions. The call for caution and additional risk assessment does not really provide advancement of sciences or benefits for patients. We envisage the need to define therapeutic benefit by utility functions, an approach which weighs in a systematic manner the pros- and cons of a specific treatment, allowing for conclusions about risk, which cannot be achieved by standard evidence-based, prospective, controlled or observational clinical trials. A model-based approach is required! It is clear that by just running clinical trials, one will not prove the absence of risk, particularly if the events of interest have low incidence in the population.

The use of a model-based approach to identify a dosing regimen, which is clearly supported by the relationship between drug exposure and the underlying inflammatory response may have considerable impact on the incidence of the side effects associated with COX-2 inhibition. Even though important components of this complex biosynthetic-response pathway still remain to be studied, we believe that the open questions pertaining to functional interactions and distinctions of the two isoforms could be evaluated in a quantitative manner by modelling and simulation scenarios.
Such scenarios may be particularly important to clarify the impact of treatment when expression of the isozymes occurs in the same cells, as well as to explore the consequences of redundancies or differences in the molecular pathways downstream of the COXs.

**Figure 10.** Implications of the relative degrees of selectivity. Increasing degrees of selectivity for COX-2 are associated with augmented cardiovascular risk while increasing degrees of selectivity for COX-1 are associated with augmented GI risk. The relative size of the circles indicates approximately the variation in sample sizes among the trials. Adapted from (16).

The delicate balance between efficacy and safety for COX inhibitors as first choice drugs in the treatment of chronic inflammatory pain must be investigated in view of the underlying pathways, rather than by judgment of isolated drug properties such as selectivity and potency. Mechanism-based modelling of drug effect on biomarkers of inflammatory response and clinical trial simulations will be essential for the evaluation of the appropriate dose range and dosing regimen of selective COX-2 inhibitors in the future. Both the scientific community and regulatory authorities must recognise the importance of assessing drug effects on biomarkers for optimisation of the therapeutic use of these compounds and accurate interpretation of the findings in early drug development (16).
REFERENCES
