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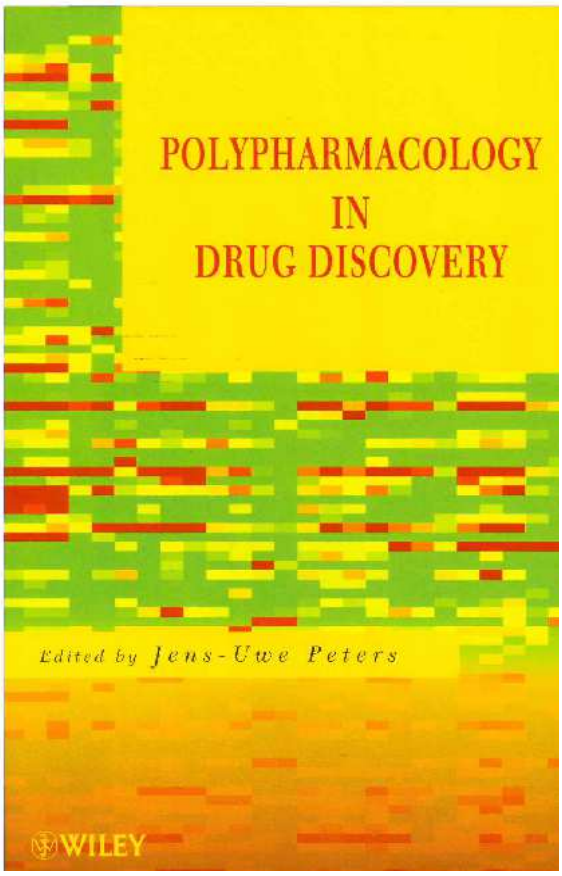

CHAPTER 19

Therapeutic Potential of Small Molecules Modulating the Cyclooxygenase–5-Lipoxygenase Pathway

WOLFGANG ALBRECHT and STEFAN LAUFER

19.1 INTRODUCTION

Prostaglandins (PGs) and leukotrienes (LTs) are biologically active lipids (eicosanoids) that have been implicated in various physiological and pathophysiological processes. As one of the most important aspects, eicosanoids are involved in the regulation of several immunological responses such as cytokine production, cell proliferation, chemotaxis, and antigen presentation [1]. Pharmacological intervention into the metabolic pathway of eicosanoids represents one of the oldest and most successful therapeutic treatments. In terms of the number of prescriptions, traditional nonsteroidal antiinflammatory drugs (tNSAIDs) and gastroprotective NSAIDs, also known as the *coxibs*, are used primarily for treatment of inflammatory pain associated with osteoarthritis or rheumatic diseases, in the most widely used therapeutics. Less popular, but still achieving annual sales of more than a billion US dollars are the leukotriene antagonist montelukast (Singulair) for treatment of asthma or the prostanoid receptor antagonists travoprost and latanoprost for treatment of glaucoma. Despite the verified efficacy of these drugs, however, they are rarely used as monotherapy. Singulair is used mainly as an add-on treatment and administered concomitantly with inhaled steroids. The prostanoid receptor antagonists are already included in fixed-dose combinations with a β-adrenoceptor antagonists. For tNSAIDs and *coxibs*, combination therapies are frequently recommended to reduce the risk of adverse events. The coadministration of protonpump inhibitors or H2-receptor blockers is believed to improve the gastrointestinal safety of tNSAIDs and to reduce

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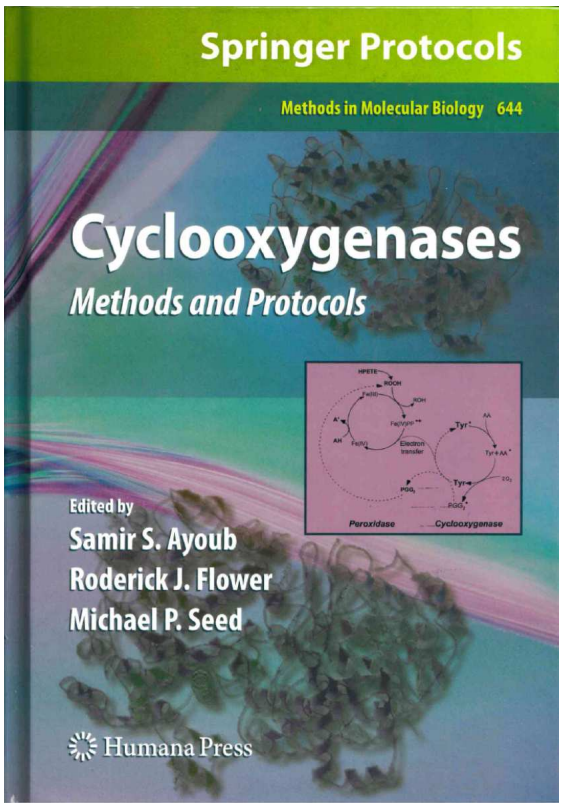

Different Methods for Testing Potential Cyclooxygenase-1 and Cyclooxygenase-2 Inhibitors

Stefan Laufer and Sabine Luik

Abstract

The need for the development of selective agents, which only inhibit the mainly "harmful" cyclooxygenase-2 (COX-2) while leaving physiological COX-1 mostly unaffected, still remains, especially after the recent issues related to cardiovascular toxicity caused by some COX-2 selective agents. Thus there is still a demand for sensitive and rapid methods to assay for COX-2 selective agents. Among several in vitro testing systems the whole blood assay (WBA) is a well-known method to examine non-steroidal anti-inflammatory drugs (NSAIDs) in view of their potency to inhibit COX activity. This assay has some major advantages over enzyme-based or isolated cell assays. Emergence of artifacts due to cell separation steps is kept to a minimum and substances, even in disproportional high concentrations, can be examined outside the body in a physiological environment resembling most closely the in vivo conditions in living humans, i.e., 37°C, homeostasis, presence of all blood compounds and cell–cell interactions remain intact. While COX-1 human whole blood assays are performed within less than 2 h, for established COX-2 assays one still has to allow for an overnight incubation step before gaining the desired plasma. The aim of the assay described in this chapter is to characterize an optimized human whole blood assay (hWBA). We present a simple, fast and reliable method to examine the capacity of NSAIDs at inhibiting COX-2 activity that can be applied for rapid and routine screening purposes.

Key words: Human whole blood assay, Cyclooxygenase, Nonsteroidal antiinflammatory drugs, Drug screening

1. Introduction

Cyclooxygenase (COX) enzymes exist in two isoforms, COX-1 and COX-2. The first is expressed constitutively in many tissues, i.e., kidney (1), thrombozytes (2), and vascular endothelium (3), and contributes to the healthy state of the human body. COX-2 is the inducible isoenzyme, which is upregulated in response to cytokines, growth factors, and toxins, and displays an indicator of illnesses such as inflammation and cancer and is controversially

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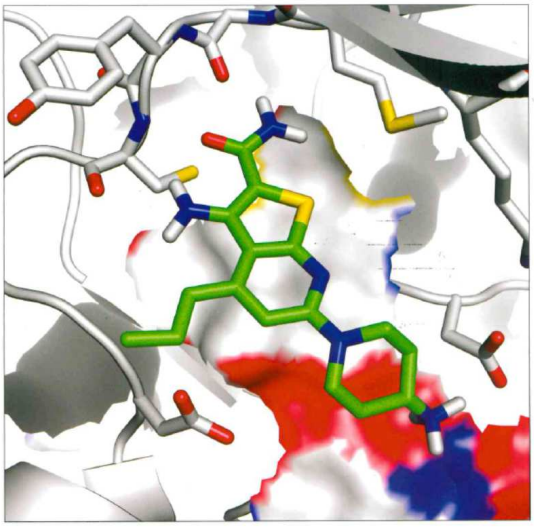

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CHAPTER 5

Dual Inhibition of Phosphodiesterase-4 and p38 MAP Kinase: A Strategy for Treatment of Chronic Inflammatory Diseases

WOLFGANG ALBRECHT[a] AND STEFAN LAUFER*[b]

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5.1 Introduction

The anti-TNFα therapies represent (one of) the most successful pharmacotherapeutic options for treatment of diseases associated with chronic inflammation. Currently, TNFα antagonists (infliximab, adalimumab, etanercept, certolizumab and golimumab) are approved and widely employed for the management of moderately to severely active rheumatoid arthritis (RA), ankylosing spondylitis (AS), Crohn's disease (CD), plaque psoriasis, psoriatic arthritis and juvenile idiopathic arthritis (JIA). More than two million patients worldwide have received treatment with either one of the anti-TNFα biologic agents. Without disregarding the significant improvement for treatment of these severe and

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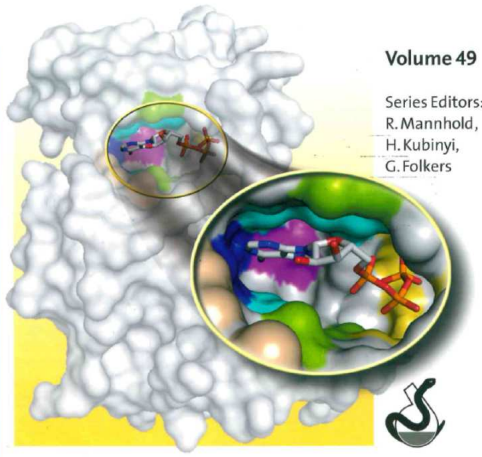

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9 Medicinal Chemistry Approaches for the Inhibition of the p38 MAPK Pathway

Stefan Laufer L, Simona Margutti, Dowinik Hauser

9.1 Introduction

The MAP kinases are a family of enzymes that participate in many cellular activities and are divided into three subfamilies: (1) The extracellular signal-related kinases (ERKs) that are widely expressed and that typically regulate cellular proliferation and differentiation. (2) The c-Jun-N-terminal kinases (JNKs) play a major role in extracellular matrix regulation through the production of metalloproteinases [1]. (3) p38 MAP kinase has four isoforms (α, β, γ, and δ) and plays an especially important role in the production of cytokines such as interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), and IL-6 [2]. p38 MAP kinase, its central role in numerous proinflammatory cellular responses and the approaches of its inhibition by "small-molecule" chemical entities is the subject of this chapter.

The p38 mitogen-activated protein kinase (p38 MAPK) is known under several other names such as cytokine suppressive anti-inflammatory drug binding protein (CSPB) [3], stress-activated protein kinase 2 (SAPK2), and mHOG1 protein which is a yeast analogue encoded by the budding yeast HOG1 gene that is activated in response to hyperosmolarity.

9.2 p38 MAP Kinase Basics

The p38 MAP kinases are widely expressed in many cell types, including immune, inflammatory, and endothelial cells. Originally described as a 38 kDa polypeptide that underwent Tyr phosphorylation in response to endotoxin treatment and osmotic shock [4], p38 (the α-isoform) was purified by anti-phosphotyrosine immunoaffinity chromatography; p38α is 50% identical to ERK2 and bears significant identity to the yeast kinase Hog1p involved in the response to hyperosmolarity [5, 6].

The p38α-isoform has been associated most closely to inflammatory responses. A variety of factors, including stress, endotoxin, cytokines such as TNF-α and

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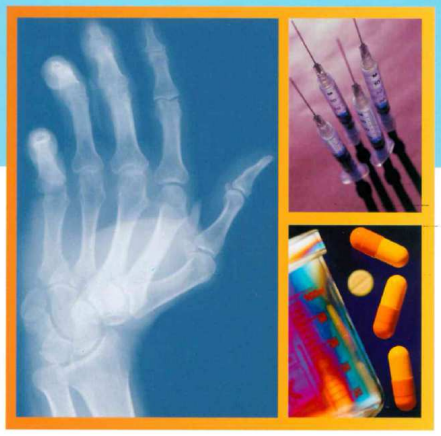
Rheumatische Erkrankungen und Entzündung

Von den molekularen Grundlagen zur medikamentösen Therapie

Stefan Laufer
Steffen Gay
Kay Brune



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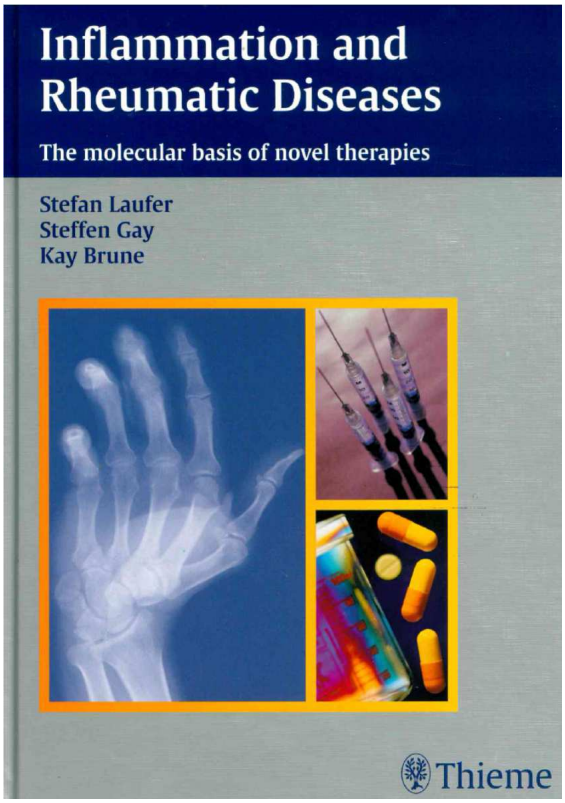
2 Biochemie und Mediatoren der Entzündung

Stefan Laufer



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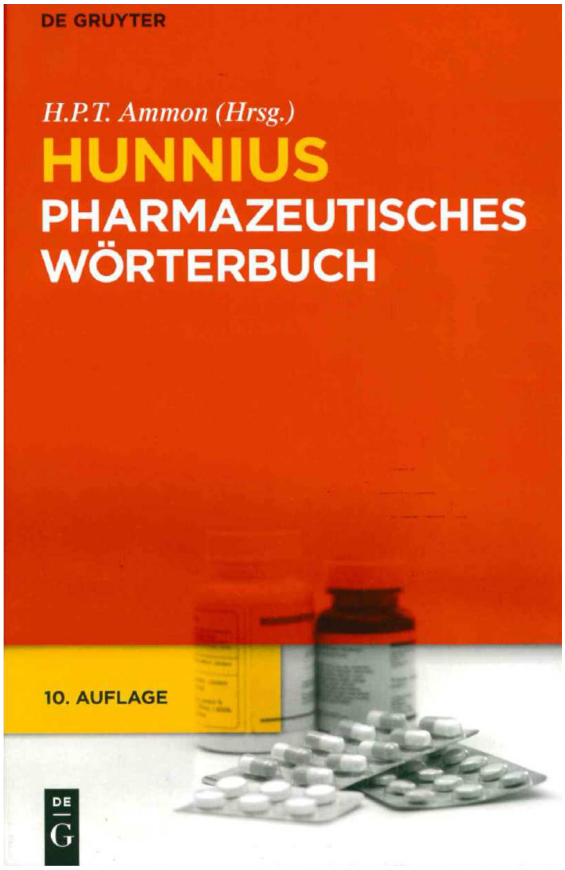
Fiorella Calanni, Stefan Laufer



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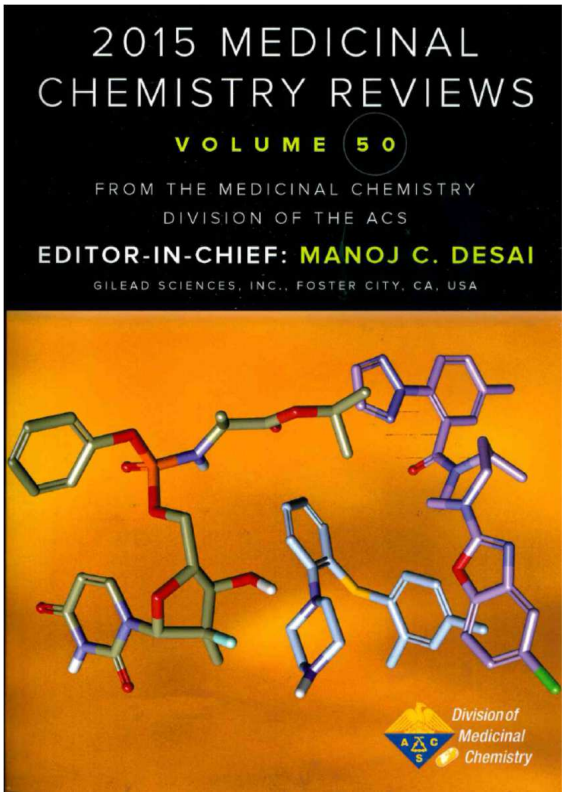

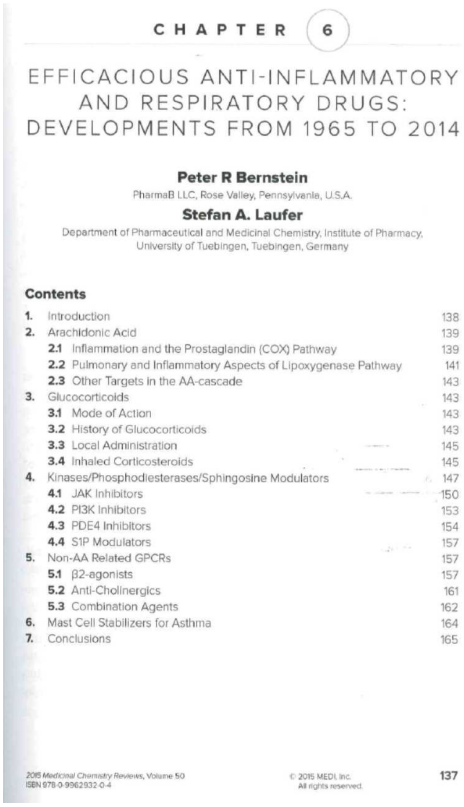

CHAPTER 6

EFFICACIOUS ANTI-INFLAMMATORY AND RESPIRATORY DRUGS: DEVELOPMENTS FROM 1965 TO 2014

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