DEVELOPMENT OF PHOSPHODIESTERASE 4 INHIBITORS FOR ALLERGIC AND NONALLERGIC INFLAMMATORY DISEASES OF THE AIRWAYS

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1 INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are the most common respiratory disorders and together, in the global population, currently afflict >1.5 billion individuals. The prevalence of asthma is rising worldwide, and this has become the most common chronic disease in industrialized nations with 5–10% of the population being affected [1]. For example, in the United States, asthma attacks are a primary cause of hospitalization—497,000 discharges due to asthma were recorded in 2004—and, in the preceding year, were responsible for 4099 deaths [2] (see www.lungusa.org). Asthma is a chronic inflammatory disease characterized by *reversible* airway obstruction, airway remodeling, and nonspecific airway hyperresponsiveness (AHR) [3, 4]. The inflammation in asthma is multifaceted, often allergic and involves both infiltrating leukocytes and structural cells. $CD4^+$ T lymphocytes are believed to play a pivotal pathogenic role; they elicit a Th2-driven inflammatory response and, through orchestrating pulmonary eosinophil recruitment, may contribute to airway remodeling, which is a cardinal feature of this disease [5–7].

COPD is a nonspecific term that embraces several debilitating inflammatory pathologies that often coexist and is characterized by a slowly progressive and largely *irreversible* decrement in lung function [8–10]. Persistent chronic airflow limitation, usually associated with airway collapse, edema, mucus hypersecretion, and fibrosis, is present to a greater or lesser extent and accounts for the wide spectrum of the disease [8–10]. COPD afflicts middle-aged and elderly people [11] and is caused, in approximately 95% of all cases, by chronic cigarette smoking, although other environmental insults such as the burning of biomass fuels are also major risk factors [12, 13]. COPD has a long latency before symptoms become evident, afflicts 9–10% of the population globally over the age of 40 years [14], and *is the only cause of mortality that is increasing worldwide* [15]. Indeed, by 2020 the Global Burden of Disease Study predicts that COPD will be the third leading cause of death, driven by the expanding epidemic of cigarette smoking and changing demographics, with more of the global population living longer [16, 17]. Even in 2007, COPD was underrecognized, underdiagnosed, and underreported [18]. Accordingly, COPD is undertreated [13].

A recent systematic review and meta-analysis of studies performed in 28 countries between 1994 and 2004 provides compelling evidence that the prevalence of COPD is appreciably higher in individuals who smoke or who are ex-smokers when compared to subjects who have never smoked [14]. Accordingly, COPD is largely preventable, and, in the early stages, its progression can be arrested by smoking cessation. Unfortunately, the

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