Discovery of Accolate™
(ICI 204,219), a Peptide Leukotriene Antagonist for Asthma

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Introduction

In 1940 Kellaway and Trethewie reported that perfusate from antigen-stimulated, resected lung of sensitized guinea pigs produced a slowly developing contraction of isolated guinea pig ileum. The name slow-reacting substance of anaphylaxis (SRS-A) was coined to describe the unknown substance(s) mediating this contractile activity. Over the next 30 years a few investigators studied the release of SRS-A from different sources and attempted to purify the highly labile material. Early in the 1970s, scientists from Fisons Ltd. (Augstein et al., 1973) described the discovery of FPL 55712 (Structure 6-A), a relatively potent and competitive antagonist of SRS-A. The compound was identified serendipitously as part of a screening effort at Fisons to identify more potent analogs of their antiasthma drug disodium cromoglycate. While FPL 55712 proved to be relatively nonselective¹ and too metabolically labile to serve as a drug, it became an important pharmacological tool for the evaluation of SRS-A and spurred a resurgence of interest in that substance.

However, the chemical identity of SRS-A remained elusive. A major watershed occurred in the late 1970s when Professor Bengt Samuelsson and co-workers at the Karolinska Institute isolated highly purified SRS-A from ionophore-stimulated leukocytes and identified it as a thioether-linked cysteine-containing derivative of 5-hydroxy-7,9,11,14-eicosatetraenoic acid (Murphy et al., 1979). The definitive, stereochemical proof of the structure of leukotriene C₄ (LTC₄), one of the components of SRS-A, was achieved by total synthesis in the laboratories of Professor Elias Corey at
Harvard (Corey et al., 1980). It was shown that there were other structurally-related components of SRS-A, and that all these compounds were derived from arachidonic acid via the enzymatic action of 5-lipoxygenase. The name leukotriene (LT) was proposed to reflect the leukocyte origins of the molecules and the characteristic conjugated triene component of the chemical structure. The leukotrienes have been categorized into two families: those containing amino acid moieties conjugated at carbon 6 (the peptide leukotrienes), and those characterized by the absence of any amino acids. The parent peptide leukotriene, LTC₄, arises from enzyme-mediated addition of the tripeptide glutathione to 5,6-trans-5,6-oxido-7,9-E-11,14-Z-eicosatetraenoic acid (LTA₄). Sequential, enzyme-induced loss of glutamic acid and glycine generates LTD₄ and LTE₄, respectively. The subscripted numbers refer to the total number of double bonds in the molecules, and the letter suffixes to the biogenetic order of synthesis. The peptide leukotrienes are very potent smooth muscle spasmogens. The nonpeptide leukotriene LTB₄ is primarily an attractant and activator of leukocytes (Structure 6-B).

The seminal discoveries of the biogenesis and structures of SRS-A, combined with knowledge of its pronounced biological activities, prompted many pharmaceutical companies to initiate programs aimed at the discovery of leukotriene receptor antagonists or synthesis inhibitors. ZENECA (then ICI) chose in the early 1980s to explore both means of intervention. A US-based pulmonary group pursued receptor antagonists as potential antiasthmatic agents while a UK-based team targeted 5-lipoxygenase inhibitors for therapeutic utility in arthritis and asthma (see Chapter 7 by Crawley et al. in this volume). Both programs were viewed as exciting, but very challenging, high-risk endeavors, with no guarantee that interference with leukotrienes would lead to successful disease therapy. The circumstantial evidence supporting the involvement of peptide leukotrienes in asthma at that time was: (1) the release of SRS-A from sensitized human lung tissue and its presence in airways secretions following an asthmatic attack; (2) the ability of the peptide leukotrienes to elicit a pronounced contraction of human airway