ELSEVIER

European Journal of Pharmacology 344 (1998) 1–13

ejp

Review

# Pharmacological modulation of cell adhesion molecules

Paul A.J. Henricks *, Frans P. Nijkamp

*Department of Pharmacology and Pathophysiology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, P.O. Box 80.082, 3508 TB Utrecht, Netherlands*

Received 8 December 1997; revised 7 January 1998; accepted 9 January 1998

**Abstract**

Cell adhesion molecules mediate the contact between two cells or between cells and the extracellular matrix. They are essential for morphogenesis, organization of tissues and organs, regulation of immune cell responses and migration of inflammatory cells from the blood vessels into inflamed tissues. Many diseases have been shown to be associated with dysfunction or with overexpression of certain adhesion molecules. Increased cell adhesion molecule function and number are found in clinical disorders in which inflammation and immune cells are involved. Several possible therapeutic agents are described here which have been shown to reduce the expression and/or function of cell adhesion molecules. Anti-adhesion treatment can lead to diminished infiltration and activation of inflammatory immune cells resulting in decreased tissue injury and malfunction. © 1998 Elsevier Science B.V.

*Keywords:* Adhesion; Inflammation; Leukocyte; Anti-adhesion therapy

## 1. Introduction

Adhesion molecules are glycoproteins expressed on cell surfaces, where they mediate the contact between two cells (both homotypic and heterotypic interactions) or between cells and the extracellular matrix (Springer, 1990; Carlos and Harlan, 1994; Gumbiner, 1996). During ontogenesis, cell adhesion molecules provide tissue- and organ-specific information which guarantees the integrity of the entire body. They regulate intercellular interactions, serve as contact molecules during the arrangement of complex tissues and mediate the composition of the intercellular network. Furthermore, cell adhesion molecules play an essential role in the regulation of inflammatory and immune responses. It is now realized that cell adhesion molecules also serve as signaling molecules, thereby influencing several cell functions (Clark and Brugge, 1995; Crockett-Torabi and Fantone, 1995; Hunt et al., 1997)).

The adhesion of cells is influenced by changes in the number of adhesion molecules on the cell surface and/or by alterations in the affinity or avidity of the molecules. Enhanced expression is induced by the movement of adhesion molecules from intracellular stores to cell surface or by the synthesis of new adhesion molecules. For some groups of cell adhesion molecules, function can be modulated by conformational changes or by clustering. A number of different cytokines and other inflammatory mediators affect the number and function of adhesion molecules on cells. Selectivity depends on both the mediator and the cell type involved. Moreover, combinations of different cytokines may produce additive, synergistic or antagonistic effects (Thornhill and Haskard, 1990; Thornhill et al., 1991). These multiple levels of regulation of cell adhesion molecule expression and function, together with leukocyte-specific stimuli, can create a unique sequence of events related to a certain inflammatory or pathophysiological situation (Morland et al., 1992; Moser et al., 1992; Neeley et al., 1993; Austrup et al., 1997).

## 2. Cell adhesion molecules

Most cell adhesion molecules can be classed into a certain family, based on common molecular characteristics (e.g., cadherins, integrins, selectins and immunoglobulin superfamily; see below). In addition to molecules belonging to these families of molecules, other cell adhesion molecules have been identified which are also involved in homing of lymphocytes, interactions between cells and activation of immune cells (e.g., CD44 (Haynes et al., 1989; Kincade et al., 1997), vascular adhesion protein-1

* Corresponding author. Tel.: +31-30-2537358; fax: +31-30-2537420; e-mail: p.a.j.henricks@far.ruu.nl

(Salmi et al., 1993), glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1) (Imai et al., 1993), or CD34 (Baumhueter et al., 1993)).

### 2.1. Cadherins

Cadherins are $Ca^{2+}$-dependent cell adhesion receptors that bind cells to each other by means of hemophilic interactions. Four members of the cadherin family have been characterized at the molecular level: N-(neural), E-(epithelial) P-(placental) cadherins and liver cell adhesion molecule (L-CAM) (Takeichi, 1991). The intercellular part of these molecules interacts via catenins with the cytoskeleton of a cell. Cadherins are crucial in the regulation of morphogenesis and organization of tissues. Heterotypic interactions between E-cadherin on epithelial cells and the $\alpha_E \beta_7$ integrin on T-lymphocytes have also been found (Cepek et al., 1994).

### 2.2. Integrins

Integrins are transmembrane glycoproteins composed of two noncovalently associated heterodimers, designated as the $\alpha$ and $\beta$ subunits. There are at least 16 different $\alpha$ subunits and 8 $\beta$ subunits. The family of the integrins is divided into various subfamilies according to the kind of $\beta$ subunit expressed (Springer, 1990; Kavanaugh, 1997). Integrins mediate cell–cell and cell–matrix interactions and need to be activated for binding to their counter receptors. Engagement of integrins also provides stimulatory or inhibitory signals for the cells expressing these adhesion molecules (Clark and Brugge, 1995; Díaz-González et al., 1996; Giancotti, 1997; Hunt et al., 1997).

Members of the $\beta_1$-integrin, or very late antigen (VLA), subfamily play a role in tissue organization. They appear to bind to the extracellular matrix of many tissues and to basement membranes in the nervous system, muscles, endothelium and epithelium. VLA-4 ($\alpha_4 \beta_1$; CD29/CD49d) functions both as a cellular matrix receptor and as a cellular receptor for another cell adhesion molecule, vascular cell adhesion molecule-1 (VCAM-1) (Postigo et al., 1994). VLA-4 is present on lymphocytes, monocytes, and eosinophils but not on neutrophils.

The subfamily of the $\beta_2$ integrins is more commonly known as leukocyte integrins since they are uniquely expressed on the different types of leukocytes. The $\beta_2$-chain (CD18) can bind to four different $\alpha$-chains resulting in the subfamily members, lymphocyte function-associated antigen-1 (LFA-1; $\alpha_L \beta_2$; CD11a/CD18), complement receptor 3 (Mac-1; $\alpha_M \beta_2$; CD11b/CD18), gp150,95 ($\alpha_X \beta_2$; CD11c/CD18) and $\alpha_d/\beta_2$ (Springer, 1990; Kavanaugh, 1997). $\beta_2$ integrins mediate the contact between leukocytes and different target cells expressing one of the intercellular adhesion molecules (ICAM-1, -2 or -3). During activation of leukocytes, the $\beta_2$ integrins not only show an increased expression on the cell surface but also undergo qualitative transformation, leading to enhanced binding capacity (Loftus and Liddington, 1997). The integrin-mediated contact reactions are always temporary.

Examples of other integrins involved in cell–cell interactions are $\alpha_4 \beta_7$ expressed on leukocytes interacting with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) or VCAM-1 and $\alpha_{IIb}/\beta_3$ (CD41/CD61) and $\alpha_v/\beta_3$ (CD51/CD61) present on platelets involved in platelet aggregation and interaction with endothelial cells (Kavanaugh, 1997).

### 2.3. Selectins

The selectin family is comprised of three proteins: E-(endothelial), P-(platelet), and L-(leukocyte) selectin. E-selectin (CD62E) and P-selectin (CD62P) are expressed by activated endothelial cells while L-selectin (CD62L) is constitutively expressed only on leukocytes (Springer, 1990; Bevilacqua and Nelson, 1993). These structures mediate the initial phase of attachment of leukocytes to vascular endothelial cells. Structural features common to the selectins are the presence of an amino-terminal ($Ca^{2+}$-dependent) carbohydrate-binding (lectin) domain, an epidermal growth factor-like domain, a variable number of consensus repeats of sequences, similar to those appearing in complement-regulatory proteins, a transmembrane domain and a short cytoplasmic carboxyl tail (Bevilacqua and Nelson, 1993).

P-selectin is rapidly mobilized to the cell surface of endothelial cells on activation by histamine, thrombin or cytokines (McEver et al., 1989). Maximal E-selectin expression on the endothelium is found within hours (2 to 6 h) of stimulation by cytokines (Pober et al., 1986; Bevilacqua et al., 1989). P-selectin and E-selectin upregulation is only transient. L-selectin is constitutively expressed on leukocytes but is lost within minutes upon activation of the cells. All selectins can bind to ligands containing sialylated, fucosylated carbohydrate moieties (e.g., sialyl $Lewis^x$) (Varki, 1994, 1997). More specific interactions with higher affinities occur between P-selectin and P-selectin glycoprotein-1 (PGSL-1; CD162) (McEver and Cummings, 1997) or between E-selectin and E-selectin ligand-1 (ESL-1) (Steegmaier et al., 1995).

### 2.4. Immunoglobulin superfamily

The immunoglobulin (Ig)-gene superfamily consists of cell surface proteins that are involved in antigen recognition, complement-binding or cellular adhesion (Springer, 1990; Carlos and Harlan, 1994; Kavanaugh, 1997). These proteins are characterized by a variable number of extracellular Ig-like domains with conserved cysteine sequences that form disulphide bonds to stabilize $\beta$-sheets of the tertiary structure (Williams and Barclay, 1988). Members of this family that are important for cell–cell interactions are intercellular adhesion molecule-1 (ICAM-1; CD54),

ICAM-2 (CD102), ICAM-3 (CD50), VCAM-1 (CD106), LFA-3 (CD58), platelet-endothelial cellular adhesion molecule-1 (PECAM-1; CD31), MAdCAM-1 and CD2 (Springer, 1990; Carlos and Harlan, 1994; Kavanaugh, 1997). These adhesion molecules are important in the interactions between immune cells (e.g., ICAM-1 with LFA-1 or CD2 with LFA-3), in tissue-specific homing of lymphocytes (e.g., MAdCAM-1) and adhesion of leukocytes to endothelial cells, leading to migration of leukocytes into tissues (e.g., ICAM-1 with LFA-1 or Mac-1, VCAM-1 with VLA-4 or PECAM-1 with PECAM-1). VCAM-1 and ICAM-1 expression on endothelial cells is increased after stimulation with tumor necrosis factor-$\alpha$ (TNF-$\alpha$) or interleukin-1$\beta$ (Pober et al., 1986; Thornhill et al., 1991). ICAM-1 expression on endothelial cells can also be upregulated by interferon-$\gamma$ (Pober et al., 1986), whereas interleukin-4 and interleukin-13 are selective for VCAM-1 induction (Thornhill and Haskard, 1990; Thornhill et al., 1991; Bochner et al., 1995; Iademarco et al., 1995). In contrast, ICAM-2 is constitutively expressed on endothelial cells (Staunton et al., 1989; De Fougerolles et al., 1991).

### *2.5. Cell adhesion molecules in inflammation*

Adhesion molecules play a critical role in the communication between different immune cells and in the migration of inflammatory cells from the bloodstream into inflamed tissues (Springer, 1990; Carlos and Harlan, 1994; Konstantopoulos and McIntire, 1996; Luscinskas, 1997). Localized leukocyte accumulation is an essential process for the body's elimination of infectious agents. Leukocyte extravasation is a multi-step process which can be divided into initial attachment (tethering, rolling), firm adhesion and migration through the endothelial layer. This process of extravasation involves the sequential action of distinct adhesion molecules (Butcher, 1991; Konstantopoulos and McIntire, 1996; Luscinskas, 1997). Several pro-inflammatory cytokines and other mediators induce upregulation of adhesion molecule numbers and function on the endothelial cells (Malik and Lo, 1996; see also Section 2.4). Selectin-based interactions mediate the initial interaction between leukocytes and endothelial cells, resulting in slowing down of the velocity of circulating cells. Interactions via other adhesion molecules also takes place during these initial interactions (e.g., VLA-4-VCAM-1 and PECAM-1-PECAM-1). Further activation of leukocytes via selectin and PECAM-1 interactions and via cytokine and chemokine receptors induces upregulation and activation of the integrins on leukocytes. Via these integrins, leukocytes interact with the cellular adhesion molecules on the surface of the endothelial cells (e.g., ICAM-1 and -2 and VCAM-1) resulting in firm adhesion followed by transmigration. Chemokines and their receptors and interactions via $\beta_1$ integrins are important for further migration into the tissues.

Many diseases have been shown to be associated with dysfunction or with overexpression of certain adhesion molecules. Patients with leukocyte adhesion deficiency type 1 (LAD-1) have a lessened or absent expression of $\beta_2$ integrins on their leukocytes and patients with LAD-2 have genetic defects in the fucose metabolism resulting in failure to synthesize selectin ligands (Anderson and Springer, 1987; Etzioni et al., 1992). These types of patients suffer from recurrent infections due to the inability of neutrophils to infiltrate into infected tissues.

Upregulated and/or overexpressed cell adhesion molecules can be found in several diseases where inflammation and immune cells are involved (e.g., arthritis, asthma, ischemia-reperfusion injury, transplant rejection and inflammatory diseases of the cardiovascular system, skin, kidneys, gastrointestinal tract, brain and liver) (Bevilacqua et al., 1994; Menger and Vollmar, 1996). Also, tumor cells use adhesion molecules to grow and spread throughout the body (Huang et al., 1997). Reduction or blockade of the expression or function of a specific cell adhesion molecule is a possible therapeutic way to diminish infiltration and/or activation of inflammatory immune cells in order to reduce inflammation. This approach to therapeutic intervention is, however, complicated by the facts that most types of adhesion molecules are expressed on more than one cell type, that most cells express more than one adhesion molecule on their surface and that several molecules can function as ligand for a single adhesion molecule. Also, blockade of cell adhesion molecules can interfere with functions of immune cells essential for host defence.

## 3. Modulation of cell adhesion molecules

There are several potential sites at which cell adhesion function and expression can be affected. Inhibition of proinflammatory cytokines and other inflammatory mediators that upregulate cell adhesion function and/or number would result in a diminished number of, or less activated, cell adhesion molecules. However, there is enormous redundancy in the biological actions of many of the cytokines, and cytokines are part of a complex network with both stimulatory and inhibitory effects on other cells and mediators. Therefore, it is very difficult to modulate a specific cell adhesion molecule simply by inhibiting a certain cytokine. A second potential mechanism by which upregulation of cell adhesion molecule number can be lessened is inhibition of transcription or translation of DNA or mRNA encoding a certain cell adhesion molecule (e.g., by using antisense oligonucleotides). The third level for inhibition of cell adhesion molecule function is a specific inhibition of the cell adhesion molecule or its counter-structure. This can be achieved by using compounds that will bind to the adhesion molecule or its counter-receptor (e.g., soluble adhesion molecules, mono-

clonal antibodies directed against adhesion molecules or counter-structures and low molecular weight compounds). Furthermore, several anti-inflammatory drugs have been shown to affect cell adhesion function and/or expression apart from their effects on inflammatory mediator synthesis and release.

### 3.1. Antisense oligonucleotides

Antisense oligonucleotides are short pieces of synthetic nucleic acids designed to bind to complementary sequences in DNA or mRNA for blocking the transfer of information leading to the formation of a specific protein. The mechanisms by which interactions of oligonucleotides with nucleic acids induce biological effects are complex and numerous (Crooke and Bennett, 1996; Dean et al., 1996). Phosphorothioate oligonucleotides are more resistant to nucleases compared with phosphodiester oligonucleotides, are taken up by a wide range of cells in vitro and their therapeutic value has been evaluated in animal models and humans (Crooke and Bennett, 1996; Dean et al., 1996). More potent anti-adhesion oligonucleotides with reduced toxicity have been produced with chemical modifications of the original molecules (Baker et al., 1997). Also, carrier molecules can be used to increase the delivery of oligonucleotides into cells to enhance their biological activity (Stewart et al., 1996). It has been demonstrated that phosphorothioate oligonucleotides inhibit the expression of ICAM-1, VCAM-1 or E-selectin on endothelial cells and reduce the adhesion of HL-60 cells to TNF-$\alpha$-activated endothelial cells (Bennett et al., 1994; Condon and Bennett, 1996). ICAM-1 antisense oligonucleotides have been shown to be effective in vivo as inhibitors of upregulation of ICAM-1 expression and of leukocyte emigration in affected tissue in animal models of endotoxin-induced pneumonia (Kumasaka et al., 1996), dextran sulphate sodium-induced colitis (Bennett et al., 1997) and ischemia-induced renal failure (Haller et al., 1996). Moreover, these compounds delay allograft rejection after transplantation (Stepkowski et al., 1994, 1997; Katz et al., 1997). Various oligonucleotides are now being tested for immunosuppressive therapy in several human diseases, for example, ICAM-1 antisense oligonucleotides for the treatment of various inflammatory diseases (Dean et al., 1996).

### 3.2. Soluble adhesion molecules

Circulating forms of cell adhesion molecules have been found and the levels of these molecules can rise during diseases processes (Dana et al., 1991; Rothlein et al., 1991; Seth et al., 1991; Gearing and Newman, 1993). For instance, circulating levels of ICAM-1 and E-selectin, but not VCAM-1, are significantly elevated in the peripheral blood of patients with acute asthma compared to the levels in stable asthmatic patients or normal volunteers (Montefort et al., 1994b). Also, increased levels of soluble ICAM-1 (Takahashi et al., 1994), soluble VCAM-1 (Zangrilli et al., 1995) and soluble E-selectin (Georas et al., 1992) have been detected in the broncho-alveolar lavage fluid from patients with asthma 18 h after antigen challenge. These and other findings indicate that elevated concentrations of soluble cell adhesion molecules can be regarded as markers for the presence of inflammation. Besides, increased levels of soluble adhesion molecules might play a protective role by blocking complementary adhesion receptors and thereby decreasing inflammatory cell recruitment and migration to sites of inflammation. Indeed, it has been shown that soluble adhesion molecules can inhibit the interaction between inflammatory and endothelial cells (Dana et al., 1991; Gearing and Newman, 1993). However, systemic levels of soluble adhesion molecules are often too low to have significant de-adhesive effects (Gearing and Newman, 1993).

### 3.3. Antibodies directed against cell adhesion molecules

The use of antibodies directed against adhesion molecules has revealed associations between a number of diseases and an increased expression of adhesion molecules (Bevilacqua et al., 1994). Also, most studies on anti-adhesion therapy have utilized antibodies as therapeutic agents in experimental animal models. Findings from these studies have led to clinical trials with anti-adhesion therapy in patients suffering from inflammatory diseases, cancer, transplant rejection, ischemia-reperfusion injury, thrombosis, etc. Only a few of these diseases are reviewed here to provide examples of studies utilizing monoclonal antibodies as anti-adhesion therapy.

Results of several studies have indicated that cell adhesion molecules play a role in asthma. Increased expression of E-selectin, ICAM-1 and VCAM-1 has been detected in the endothelium from lung tissue of asthmatic patients after allergen provocation (Georas et al., 1992; Bentley et al., 1993; Montefort et al., 1994a; Gosset et al., 1995; Ohkawara et al., 1995). Additionally, elevated ICAM-1 expression was found in the bronchial epithelium of these patients (Gosset et al., 1995; Ohkawara et al., 1995). In vitro studies also showed that primary cultured human bronchial epithelial cells express ICAM-1, what can be upregulated by incubation with pro-inflammatory cytokines (Look et al., 1992; Bloemen et al., 1993). The functional relevance of adhesion molecules for leukocyte migration into the airways has been demonstrated in several animal models of allergic asthma. Wegner et al. (1990) were the first to show that a monoclonal antibody directed against ICAM-1 not only attenuated eosinophil infiltration, but additionally, suppressed airway hyperresponsiveness in a primate model of asthma. The role of ICAM-1 and other adhesion molecules like VCAM-1, VLA-4, LFA-1 and Mac-1 in the development of airway

hyperresponsiveness has also been shown in other animal models of asthma (Abraham et al., 1994; Milne and Piper, 1994, 1995; Nakajima et al., 1994; Pretolani et al., 1994; Laberge et al., 1995; Nagase et al., 1995; Bloemen et al., 1996; Buckley et al., 1996; Gonzalo et al., 1996; Richards et al., 1996). Results of some of these studies made clear that antibodies directed against adhesion molecules have effects on the development of airway hyperresponsiveness that cannot be explained only by an effect on migration of leukocytes. In addition to their involvement in the recruitment of inflammatory cells, adhesion molecules are important for cell activation (Springer, 1990; Clark and Brugge, 1995; Giancotti, 1997). For example, antibodies directed against LFA-1 and ICAM-1 can prevent the contact between antigen-presenting cells and T-lymphocytes that are needed for costimulatory signals essential for cytokine release and other lymphocyte responses (Wacholtz et al., 1989; Springer, 1990; Van Seventer et al., 1991). Additionally, antibodies directed against $\beta_2$ integrins inhibit degranulation and oxidative metabolism in eosinophils and neutrophils (Horie and Kita, 1994; Nagata et al., 1995). Treatments with monoclonal antibodies directed against cell adhesion molecules may thus affect the development of airway inflammation and hyperresponsiveness in asthma through an impairment of cell activation.

Rheumatoid arthritis is another chronic inflammatory disease in which adhesion molecules play an important role in the invasion of leukocytes into synovial tissues, leading to tissue damage. Increased expression of E-selectin, VCAM-1 and ICAM-1 has been found on the vascular endothelium of synovial tissues (Cronstein and Weissmann, 1993; Paleolog et al., 1996). Treatment of patients suffering from refractory rheumatoid arthritis with monoclonal antibodies directed against ICAM-1 results in a moderate to marked improvement in half the patients (Kavanaugh et al., 1993, 1994). It has also been shown that antibodies directed against ICAM-1 induce a hyporesponsiveness of T-cells from patients with rheumatoid arthritis that was correlated with clinical improvement of these patients (Davis et al., 1995).

Platelet adhesion and aggregation can lead to occlusive thrombus formation and irreversible ischemic damage to, e.g., heart and brain. The integrin, $\alpha_{IIb}\beta_3$, is only present on platelets and plays a major role in platelet adhesion and aggregation as it binds to immobilized fibrinogen (Coller, 1997). Research aimed at the development of anti-thrombotic drugs has therefore focused on this platelet integrin (Lefkovits et al., 1995). Coller and his colleagues were the first to demonstrate that platelet aggregation could be inhibited by a mouse monoclonal antibody directed against $\alpha_{IIb}\beta_3$ (Coller, 1995). The $F_{ab}$ parts of such an antibody have been coupled to the $F_c$ part of a human immunoglobulin to prevent immunogenicity, yielding a compound (ReoPro™) that has been approved for human use for reducing the risk of ischemic complications after percutaneous coronary intervention (Coller, 1995, 1997).

### 3.4. Low molecular weight compounds

To inhibit adhesion instead of using high molecular weight soluble adhesion molecules or antibodies, short peptides and carbohydrates have now been constructed, based on the structural sequences of adhesion molecules and their counter-structures (Lowe and Ward, 1997). Potent and stable mimetics of sialyl Lewis$^x$ have been developed or found which can prevent interactions that are regulated via selectins (Rao et al., 1994; Kogan et al., 1995). Adhesion of neutrophils to cytokine-activated endothelial cells can be inhibited in vitro by synthetic derivatives of sialyl Lewis$^a$ (Nelson et al., 1993). In vivo, sialyl Lewis$^x$ analogues reduce neutrophil accumulation and the extent of tissue damage in animal models of acute lung injury (Mulligan et al., 1993a,b) and myocardial reperfusion (Buerke et al., 1994; Lefer et al., 1994). Also, synthetic peptides based on amino sequences within the lectin domain of selectins, block neutrophil adhesion in in vitro assays (Briggs et al., 1995; Kruszynski et al., 1996; Tam et al., 1996) and neutrophil infiltration into inflammatory sites in vivo (Briggs et al., 1995).

Several $\beta_1$-integrins bind extracellular matrix proteins (e.g., fibronectin) at domains containing a RGD (arginine–glycine–aspartic acid) sequence. Binding of VLA-4 and VLA-5 to fibronectin also takes place at the connecting segment-1 (CS-1) region of fibronectin. Small modified peptides based on the RGD sequence or CS-1 structure block the interaction between VLA-4-bearing cells and extracellular matrix structures or VCAM-1-expressing cells (Cardarelli et al., 1994; Elices et al., 1994; Molossi et al., 1995; Lobb, 1997; Vanderslice et al., 1997). Synthetic peptides based on amino acid sequences in binding regions of ICAM-1 or VCAM-1 can inhibit adherence (Fecondo et al., 1991; Ross et al., 1992; Wang et al., 1995).

### 3.5. Glucocorticoids

Many investigators have found decreased expression and function of adhesion molecules to follow treatment with glucocorticoids. The upregulation of E-selectin and ICAM-1 on human endothelial cells upon stimulation with lipopolysaccharide or cytokines can be inhibited by dexamethasone or cortisol (Cronstein et al., 1992; Brostjan et al., 1997; Wheller and Perretti, 1997). These treatments result in diminished adherence of neutrophils to endothelial cells (Cronstein et al., 1992). In contrast, Burke-Gaffney and Hellewell (1996) found that dexamethasone did not affect the cytokine-induced expression on endothelial cells but inhibited only lipopolysaccharide-induced ICAM-1 expression. Forsyth and Talbot (1992) found no effects of dexamethasone on neutrophil adhesion to lipopolysaccharide-activated endothelial cells and expression of adhesion molecules by these cell types. Dexamethasone treatment, however, inhibited the expression of ICAM-1

on a human bronchial epithelial cell line (Van de Stolpe et al., 1993) and the monocytic cell line U937 (Van de Stolpe et al., 1993; Perretti et al., 1996). The inhibitory effect of glucocorticoids on ICAM-1 and E-selectin expression is probably regulated at the transcription level via reduction of NF-$\kappa$B activity (Van de Stolpe et al., 1994; Van de Stolpe and Van der Saag, 1996; Brostjan et al., 1997).

In vivo treatment of animals with dexamethasone reduces the expression of ICAM-1 on peritoneal macrophages and circulating monocytes (Perretti et al., 1996; Tailor et al., 1997) and of L-selectin and CD18 on neutrophils (Burton et al., 1995). Interestingly, adrenalectomy and treatment of rats with metyrapone both result in increased adhesion and migration of leukocytes, suggesting that secretion of glucocorticoids in vivo normally suppresses leukocyte–endothelial interactions (Farsky et al., 1995). Oral and intravenous methylprednisolone given to humans suffering from multiple sclerosis reduces LFA-1 expression on circulating T-lymphocytes (Pitzalis et al., 1997). In contrast, no effects on CD11b expression on circulating leukocytes were found in rats given dexamethasone (Tailor et al., 1997). Also, the upregulation of CD11b on exudative granulocytes in endotoxin-treated rats is insensitive to dexamethasone pretreatment (O'Leary et al., 1996).

Glucocorticoids given to humans and animals in vivo also influence the synthesis and release of inflammatory mediators and other cytokines (Wilckens and De Rijk, 1997), which affect the upregulation of cell adhesion molecules indirectly. Some of the effects of glucocorticoids in the expression of adhesion molecules might therefore be explained by a reduction in the synthesis and release of inflammatory mediators and cytokines.

### *3.6. Eicosanoids and their inhibitors*

Eicosanoids are important mediators of physiological and pathophysiological processes in the body. Several eicosanoids and their inhibitors of synthesis and action affect the expression and function of adhesion molecules during inflammation. Inhibitors of phospholipase $A_2$ decrease the upregulation of Mac-1 expression on stimulated neutrophils (Jacobson and Schrier, 1993; Amandi-Burgermeister et al., 1997). In contrast, nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin and indomethacin can enhance the surface expression of $\beta_2$-integrins on leukocytes (Yoshida et al., 1993) and ICAM-1 on endothelial cells (Andrews et al., 1994) leading to increased adhesion and emigration of leukocytes, and tissue injury (Asako et al., 1992a,b; Yoshida et al., 1995; Kurose et al., 1996). The formation of leukotriene $B_4$ seems to play a role in the NSAID-induced adhesion of leukocytes to endothelial cells because 5-lipoxygenase inhibitors and leukotriene $B_4$ receptor antagonists inhibit NSAID-induced adhesion (Asako et al., 1992a,b; Yoshida et al., 1993). Leukotriene $B_4$ itself is able to increase Mac-1 expression on neutrophils and to induce a transient state of hyperadhesiveness in endothelial cells, leading to increased binding of neutrophils (Gimbrone et al., 1984; Berger et al., 1985; Palmblad and Lerner, 1992; Palmblad et al., 1994). NSAID-induced adhesion can also be explained by a reduction in the formation of prostaglandins that normally exert an inhibitory effect on leukocyte adhesion (Chopra and Webster, 1988; Riva et al., 1990; Doerr et al., 1992; Bloemen et al., 1997).

Prevention of adhesion by NSAIDs has also been described. Sánchez-Madrid and co-workers have found that different NSAIDs, including indomethacin and aspirin, rapidly decrease the expression of L-selectin on neutrophils and inhibit neutrophil–endothelial cell attachment under nonstatic conditions (Diaz-González et al., 1995; González-Alvaro et al., 1996). Recently, it was found that piroxicam (member of the oxicam family) prevents TNF$\alpha$, granulocyte–macrophage colony-stimulating factor (GM-CSF) and formyl–methionyl–leucyl–phenylalanine (fMLP)-induced L-selectin shedding and CD11b upregulation on neutrophils (Garciá-Vicuña et al., 1997). Furthermore, piroxicam was able to prevent the active conformation of CD11b induced by fMLP and TNF-$\alpha$ (Garciá-Vicuña et al., 1997). One possible mechanism by which NSAIDs decrease the expression of adhesion molecules is via inhibition of the transcription factor nuclear factor-$\kappa$B (NF-$\kappa$B). This transcription factor is critical for the inducible expression of adhesion molecules, and its activation is inhibited by aspirin (Kopp and Ghosh, 1994). However, relatively high concentrations of aspirin are needed to inhibit NF-$\kappa$B, and also experiments with another NSAID (indomethacin) did not show a decreased activity of NF-$\kappa$B (Kopp and Ghosh, 1994). An alternative explanation for inhibition of adhesion by aspirin might be the acetylation of the inducible form of cyclo-oxygenase (COX-2) by this NSAID. The combined action of aspirin-acetylated COX-2 and 5-lipoxygenase enhances the formation of 15 epi-lipoxins (Clària and Serhan, 1995). These compounds, and also lipoxins themselves, inhibit the leukotriene-stimulated interaction of neutrophils with endothelial cells (Clària and Serhan, 1995; Serhan et al., 1995; Papayianni et al., 1996). Others, however, have found that lipoxin $A_4$ induces an increased adhesiveness of endothelial cells to neutrophils (Lerner et al., 1993).

Inhibitors of fatty acid metabolism other than NSAIDs have been shown to influence adhesion molecule function and expression. Tepoxalin, originally identified as a dual inhibitor of cyclo-oxygenase and 5-lipoxygenase activities, suppresses the surface expression of E-selectin and VCAM-1 on endothelial cells and of Mac-1 on granulocytes (Lee et al., 1996). This compound has been shown to inhibit NF-$\kappa$B activation as well (Kazmi et al., 1995). Application of tepoxalin in vivo suppresses the upregulation of Mac-1 on neutrophils and E-selectin expression on endothelial cells and inhibits neutrophil adhesion to vessel walls and migration into inflammatory sites (Zhou et al., 1996; Kirchner et al., 1997). Leukocyte adhesion to en-

dothelial cells can also be inhibited by tenidap (Kyan-Aung et al., 1993). Tenidap is an antirheumatic compound which inhibits mainly the cyclo-oxygenase pathway of eicosanoid formation (Bondeson, 1996). The thromboxane $A_2$ synthetase inhibitor, DP-1904, suppresses ICAM-1 and E-selectin expression on endothelial cells (Ishizuka et al., 1994; Kameda et al., 1995). This effect might be caused by a reduced production of thromboxane $A_2$ or of other mediators which would normally enhance the expression and function of adhesion molecules.

All these data still do not give a clearcut answer to the question of how inhibition of eicosanoid metabolism affects the expression and function of adhesion molecules. Inhibitors of eicosanoid formation are not always very selective and various eicosanoids can have opposite effects. Also, a particular eicosanoid can act on different cell types in multiple ways and can affect the production of other mediators involved regulating adhesion molecule function.

### *3.7. Leumidins*

The term 'leumidins' was introduced by Burch et al. (1991) to describe a series of *N*-(fluorenyl-9-methoxycarbonyl)amino acids found to have a broad spectrum of anti-inflammatory activity. NPC-15199 (*N*-(fluorenyl-9-methoxycarbonyl)-L-leucine) and NPC-15669 (*N*-9H-(2,7-dimethylfluorenyl-9-methoxycarbonyl)-L-leucine) have anti-inflammatory activity in several animal models of inflammation, including oxazolone-induced dermatitis in mice, adjuvant arthritis in rats, reversed passive Arthus reaction in rats, acetic acid-induced colitis in rats and arachidonic acid-induced dermatitis in mice (Burch et al., 1991, 1992a,b; Noronha-Blob et al., 1993a). Further, NPC-15669 diminished pulmonary injury after reperfusion due to cardiovascular bypass (Bator et al., 1993; Friedman et al., 1995) or to preservation of lungs (Uthoff et al., 1995). NPC-15669 also reduced the mortality associated with sepsis in rats (Noronha-Blob et al., 1993b) and with the administration of endotoxin in mice (Noronha-Blob et al., 1991; Burch et al., 1993). In all these animal models, the injury was associated with neutrophil influx, and treatment with leumidins reduced the recruitment of neutrophils into the inflammatory sites. The effects of leumidins on several other neutrophil functions were thus examined in more detail in vitro (Bator et al., 1992; Burch et al., 1992b). It was found that NPC-15669 inhibits the upregulation of Mac-1 on neutrophils upon stimulation with fMLP and that the adhesion of fMLP-stimulated neutrophils to endothelial cells in vitro was inhibited in a concentration-dependent manner (Bator et al., 1992; Burch et al., 1992b). Simplified analogues of leumidins (fluorene-containing carboxylic acids) inhibit neutrophil adherence more selectively and with greater potency than do other leumidins (Hamilton et al., 1995). Further investigations showed that the inhibition of Mac-1 expression was due to the ability of NPC-15669 to inhibit the binding of fMLP to its receptor on neutrophils (Smith et al., 1995; Endemann et al., 1996). However, NPC-15669 also affects the degranulation and adhesion of neutrophils upon stimulation with stimuli other than fMLP (Asako et al., 1992a; Endemann et al., 1996). These findings suggest that leumidins block an event that occurs at a late stage of neutrophil activation and is necessary for adherence but is not involved in the upregulation of Mac-1 expression. NPC-15199 and NPC-15669 were not considered for further clinical development because of lack of adequate oral bio-availability (Burch et al., 1992b). An orally active leumidin (NPC-17923; *N*-(9H-(2,7-dichlorofluorenyl)-9-ethoxycarbonyl)-4-aminobenzoic acid) has been shown to be an effective inhibitor of PAF-induced leukocyte adherence to the endothelium of rat mesenteric post-capillary venules in vivo (McCafferty et al., 1993). Recently, leumidins such as NPC-15669 and NPC-17923 were found to induce the loss of L-selectin from the surface of neutrophils, resulting in blockade of adhesion of neutrophils under conditions of flow (Endemann et al., 1997).

## 4. Concluding remarks

The results of the various studies described above make it clear that the expression and function of cell adhesion molecules are affected by many different compounds. Most of the anti-inflammatory drugs (e.g., corticosteroids, NSAIDs) have the disadvantage that they do not selectively inhibit a particular adhesion molecule and that they influence inflammatory processes at other steps as well. More selective anti-adhesion therapy is available with the use of monoclonal antibodies directed against a particular adhesion molecule or its counter-structure. For their chronic clinical application, however, these types of antibodies must be chimeric or humanized to reduce immunogenicity and other possible adverse effects. At the moment, there has only been one agent, based on a monoclonal antibody directed against the adhesion molecule $\alpha_{IIb}\beta_3$, that has been developed successfully. This compound can be used for inhibition of platelet activation in vivo because the integrin $\alpha_{IIb}\beta_3$, is present only in platelets. The best way to inhibit interactions via adhesion molecules is probably to use low molecular weight peptides or carbohydrates which can inhibit adhesion receptor interactions specifically (e.g., peptides based on the RGD sequence or CS-1 structure or oligosaccharides based on sialyl Lewis$^x$). Chemical modifications can further increase the stability and potency of these compounds with subsequent increased clinical applicability. An alternative approach to

the highly selective inhibition of adhesion molecule function could be to use antisense oligonucleotides.

Complicating factors for selective anti-adhesion therapy are that most types of adhesion molecules are present on more than one cell type and that interactions between two cells can take place through more than one adhesion molecule. Moreover, no matter which anti-adhesion therapy is used, one must remain aware that treatments of this kind can affect essential immune cell functions as well. There is another way in which adhesion molecules can be used for therapeutic intervention. Monoclonal antibodies directed against an adhesion molecule can be conjugated to liposomes (immunoliposomes) and it has been shown that immunoliposomes specifically directed against ICAM-1 or E-selectin will bind only to cells expressing ICAM-1 or E-selectin (Bloemen et al., 1995; Spragg et al., 1997). Adhesion molecule-targeted immunoliposomes can then be used as carriers for drugs to, e.g., sites of inflammation or tumors (Vingerhoeds et al., 1994).

## References


Abraham, W.M., Sielczak, M.W., Ahmed, A., Cortes, A., Lauredo, I.T., Kim, J., Pepinsky, B., Benjamin, C.D., Leone, D.R., Lobb, R.R., Weller, P.F., 1994. $\alpha_4$-Integrins mediate antigen-induced late bronchial responses and prolonged airway hyperresponsiveness in sheep. J. Clin. Invest. 93, 776–787.

Amandi-Burgermeister, E., Tibes, U., Kaiser, B.M., Friebe, W.G., Scheuer, W.V., 1997. Suppression of cytokine synthesis, integrin expression and chronic inflammation by inhibitors of cytosolic phospholipase $A_2$. Eur. J. Pharmacol. 326, 237–250.

Anderson, D.C., Springer, T.A., 1987. Leukocyte adhesion deficiency: an inherited defect in the Mac-1, LFA-1 and p150,95 glycoproteins. Annu. Rev. Med. 38, 175–194.

Andrews, F.J., Malcontenti-Wilson, C., O'Brien, P.E., 1994. Effect of nonsteroidal anti-inflammatory drugs on LFA-1 and ICAM-1 expression in gastric mucosa. Am. J. Physiol. 266, G657–G664.

Asako, H., Kubes, P., Wallace, J., Wolf, R.E., Granger, D.N., 1992a. Modulation of leukocyte adhesion in rat mesenteric venules by aspirin and salicylate. Gastroenterology 103, 146–152.

Asako, H., Kubes, P., Wallance, J., Gaginella, T., Wolf, R.E., Granger, D.N., 1992b. Indomethacin-induced leukocyte adhesion in mesenteric venules: role of lipoxygenase products. Am. J. Physiol. 262, G903–G908.

Austrup, F., Vestweber, D., Borges, E., Löhning, M., Bräuer, R., Herz, U., Renz, H., Hallmann, R., Scheffold, A., Radbruch, A., Hamann, A., 1997. P- and E-selectin mediate recruitment of T-helper-1 but not T-helper-2 cells into inflamed tissues. Nature 385, 81–83.

Baker, B.F., Lot, S.S., Condon, T.P., Cheng-Flournoy, S., Lesnik, E.A., Sasmor, H.M., Bennett, C.F., 1997. 2′-*O*-(2-methoxy)ethyl-modified anti-intercellular adhesion molecule 1 (ICAM-1) oligonucleotides selectively increase the ICAM-1 mRNA level and inhibit formation of the ICAM-1 translation initiation complex in human umbilical vein endothelial cells. J. Biol. Chem. 272, 11994–12000.

Bator, J.M., Weitzberg, M., Burch, R.M., 1992. *N*-[9H-(2,7-dimethylfluorenyl-9-methoxy)carbonyl]-L-leucine, NPC 15669, prevents neutrophil adherence to endothelium and inhibits CD11b/CD18 upregulation. Immunopharmacology 23, 139–149.

Bator, J.M., Gillinov, A.M., Zehr, K.J., Redmond, J.M., Wilson, I.C., Herskowitz, A., Conner, J.R., Burch, R.M., Cameron, D.E., 1993. NPC 15669 blocks neutrophil CD18 increase and lung injury during cardiopulmonary bypass in pigs. Med. Inflammation 2, 135–141.

Baumhueter, S., Singer, M.S., Henzel, W., Hemmerich, S., Renz, M., Rosen, S.D., Lasky, L.A., 1993. Binding of L-selectin to the vascular sialomucin CD34. Science 262, 436–438.

Bennett, C.F., Condon, T.P., Grimm, S., Chan, H., Chiang, M.-Y., 1994. Inhibition of endothelial cell adhesion molecule expression with antisense oligonucleotides. J. Immunol. 152, 3530–3540.

Bennett, C.F., Kornbrust, D., Henry, S., Stecker, K., Howard, R., Cooper, S., Dutson, S., Hall, W., Jacoby, H.I., 1997. An ICAM-1 antisense oligonucleotide prevents and reverses dextran sulfate sodium-induced colitis. J. Pharmacol. Exp. Ther. 280, 988–1000.

Bentley, A.M., Durham, S.R., Robinson, D.S., Menz, G., Storz, C., Cromwell, O., Kay, A.B., Wardlaw, A.J., 1993. Expression of endothelial and leukocyte adhesion molecules intercellular adhesion molecule-1, E-selectin, and vascular cell adhesion molecule-1 in the bronchial mucosa in steady-state and allergen-induced asthma. J. Allergy Clin. Immunol. 92, 857–868.

Berger, M., Birx, D.L., Wetzler, E.M., O'Shea, J.J., Brown, E.J., Cross, A.S., 1985. Calcium requirements for increased complement receptor expression during neutrophil activation. J. Immunol. 135, 1342–1348.

Bevilacqua, M.P., Nelson, R.M., 1993. Selectins. J. Clin. Invest. 91, 379–387.

Bevilacqua, M.P., Stengelin, S., Gimbrone, Jr., M.A., Seed, B., 1989. Endothelial leukocyte adhesion molecule 1: An inducible receptor for neutrophils related to complement regulatory proteins and lectins. Science 243, 1160–1165.

Bevilacqua, M.P., Nelson, R.M., Mannori, G., Cecconi, O., 1994. Endothelial–leukocyte adhesion molecules in human disease. Annu. Rev. Med. 45, 361–378.

Bloemen, P.G.M., Van den Tweel, M.C., Henricks, P.A.J., Engels, F., Wagenaar, S.S., Rutten, A.A.J.J.L., Nijkamp, F.P., 1993. Expression and modulation of adhesion molecules on human bronchial epithelial cells. Am. J. Respir. Cell Mol. Biol. 9, 586–593.

Bloemen, P.G.M., Henricks, P.A.J., Van Bloois, L., Van den Tweel, M.C., Bloem, A.C., Nijkamp, F.P., Crommelin, D.J.A., Storm, G., 1995. Adhesion molecules: a new target for immunoliposome-mediated drug delivery. FEBS Lett. 357, 140–144.

Bloemen, P.G.M., Buckley, T.L., Van den Tweel, M.C., Henricks, P.A.J., Redegeld, F.A.M., Koster, A.S., Nijkamp, F.P., 1996. LFA-1, and not Mac-1, is crucial for the development of hyperreactivity in a murine model of nonallergic asthma. Am. J. Respir. Crit. Care Med. 153, 521–529.

Bloemen, P.G.M., Van den Tweel, M.C., Henricks, P.A.J., Engels, F., Kester, M.H.A., Van de Loo, P.G.F., Blomjous, F.J., Nijkamp, F.P., 1997. Increased cAMP levels in stimulated neutrophils inhibit their adhesion to human bronchial epithelial cells. Am. J. Physiol. 272, L580–L587.

Bochner, B.S., Klunk, D.A., Sterbinsky, S.A., Coffman, R.L., Schleimer, R.P., 1995. IL-13 selectively induces vascular cell adhesion molecule-1 expression in human endothelial cells. J. Immunol. 154, 799–803.

Bondeson, J., 1996. Effects of tenidap on intracellular signal transduction and the induction of proinflammatory cytokines: a review. Gen. Pharmacol. 27, 943–956.

Briggs, J.B., Oda, Y., Gilbert, J.H., Schaefer, M.E., Macher, B.A., 1995. Peptides inhibit selectin-mediated cell adhesion in vitro, and neutrophil influx into inflammatory sites in vivo. Glycobiology 5, 583–588.

Brostjan, C., Anrather, J., Csizmadia, V., Natarajan, G., Winkler, H., 1997. Glucocorticoids inhibit E-selectin expression by targeting NF-$\kappa$B and not ATF/*c*-jun. J. Immunol. 158, 3836–3844.

Buckley, T.L., Bloemen, P.G.M., Henricks, P.A.J., Van den Tweel, M.C., Redegeld, F.A.M., Koster, A.S., Nijkamp, F.P., 1996. LFA-1 and ICAM-1 are crucial for the induction of hyperreactivity in the mouse airways. Ann. N.Y. Acad. Sci. 796, 149–161.

Buerke, M., Weyrich, A.S., Zheng, Z., Gaeta, F.C.A., Forrest, M.J., Lefer, A.M., 1994. Sialyl Lewis$^x$-containing oligosaccharide attenu-

ates myocardial reperfusion injury in cats. J. Clin. Invest. 93, 1140–1148.

Burch, R.M., Weitzberg, M., Blok, N., Muhlhauser, R., Martin, D., Farmer, S.G., Bator, J.M., Conner, J.R., Ko, C., Kuhn, W., McMillan, B.A., Raynor, M., Shearer, B.G., Tiffany, C., Wilkins, D.E., 1991. *N*-(fluorenyl-9-methoxycarbonyl) amino acids, a class of antiinflammatory agents with a different mechanism of action. Proc. Natl. Acad. Sci. USA 88, 355–359.

Burch, R.M., Connor, J.R., Bator, J.M., Weitzberg, M., Laemont, K., Noronha-Blob, L., Sullivan, J.P., Steranka, L.R., 1992a. NPC 15669 inhibits the reversed passive arthus reaction in rats by blocking neutrophil recruitment. J. Pharmacol. Exp. Ther. 263, 933–937.

Burch, R.M., Weitzberg, M., Noronha-Blob, L., Lowe, V.C., Bator, J.M., Perumattam, J., Sullivan, J.P., 1992b. Leumidines. Drugs News Perspectives 5, 331–337.

Burch, R.M., Noronha-Blob, L., Bator, J.M., Lowe, V.C., Sullivan, J.P., 1993. Mice treated with a leumidin or antibody to Mac-1 to inhibit leukocyte sequestration survive endotoxin challenge. J. Immunol. 150, 3397–3403.

Burke-Gaffney, A., Hellewell, P.G., 1996. Regulation of ICAM-1 by dexamethasone in a human vascular endothelial cell line EAhy926. Am. J. Physiol. 270, C552–C561.

Burton, J.L., Kehrli, Jr., M.E., Kapil, S., Horst, R.L., 1995. Regulation of L-selectin and CD18 on bovine neutrophils by glucocorticoids: effects of cortisol and dexamethasone. J. Leukocyte Biol. 57, 317–325.

Butcher, E.C., 1991. Leukocyte–endothelial cell recognition: three (or more) steps to specificity and diversity. Cell 67, 1033–1036.

Cardarelli, P.M., Cobb, R.R., Nowlin, D.M., Scholz, W., Gorcsan, F., Moscinski, M., Yasuhara, M., Chiang, S.-L., Lobl, T.J., 1994. Cyclic RGD peptide inhibit $\alpha_4\beta_1$ interaction with connecting segment 1 and vascular cell adhesion molecule. J. Biol. Chem. 269, 18668–18673.

Carlos, T.M., Harlan, J.M., 1994. Leukocyte–endothelial adhesion molecules. Blood 84, 2068–2101.

Cepek, K.L., Shaw, S.K., Parker, C.M., Russell, G.J., Morrow, J.S., Rimm, D.L., Brenner, M.B., 1994. Adhesion between epithelial cells and T lymphocytes mediated by E-cadherin and the $\alpha_E\beta_7$ integrin. Nature 372, 190–193.

Chopra, J., Webster, R.O., 1988. $PGE_1$ inhibits neutrophil adherence and neutrophil-mediated injury to cultured endothelial cells. Am. Rev. Respir. Dis. 138, 915–920.

Clària, J., Serhan, C.N., 1995. Aspirin triggers previously undescribed bioactive eicosanoids by human endothelial cell–leukocyte interactions. Proc. Natl. Acad. Sci. USA 92, 9475–9479.

Clark, E.A., Brugge, J.S., 1995. Integrins and signal transduction pathways: the road taken. Science 268, 233–239.

Coller, B.S., 1995. Blockade of platelet GPIIb/IIIa receptors as an antithrombotic strategy. Circulation 92, 2373–2380.

Coller, B.S., 1997. Platelet GPIIb/IIIa antagonists: the first anti-integrin receptor therapeutics. J. Clin. Invest. 99, 1467–1471.

Condon, T.P., Bennett, C.F., 1996. Altered mRNA splicing and inhibition of human E-selectin expression by an antisense oligonucleotide in human umbilical vein endothelial cells. J. Biol. Chem. 271, 30398–30403.

Crockett-Torabi, E., Fantone, J.C., 1995. The selectins: insight into selectin-induced intracellular signaling in leukocytes. Immunol. Res. 14, 237–251.

Cronstein, B.N., Weissmann, G., 1993. The adhesion molecules of inflammation. Arthritis Rheum. 36, 147–157.

Cronstein, B.N., Kimmel, S.C., Levin, R.I., Martiniuk, F., Weissmann, G., 1992. A mechanism for the antiinflammatory effects of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial–leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. Proc. Natl. Acad. Sci. USA 89, 9991–9995.

Crooke, S.T., Bennett, C.F., 1996. Progress in antisense oligonucleotide therapeutics. Annu. Rev. Pharmacol. Toxicol. 36, 107–129.

Dana, N., Fathallah, D.M., Arnaout, M.A., 1991. Expression of a soluble and functional form of the human $\beta_2$ integrin CD11b/CD18. Proc. Natl. Acad. Sci. USA 88, 3106–3110.

Davis, L.S., Kavanaugh, A.F., Nichols, L.A., Lipsky, P.E., 1995. Induction of persistent T cell hyporesponsiveness in vivo by monoclonal antibody to ICAM-1 in patients with rheumatoid arthritis. J. Immunol. 154, 3525–3537.

Dean, N.M., McKay, R., Miraglia, L., Geiger, T., Müller, M., Fabbro, D., Bennett, C.F., 1996. Antisense oligonucleotides as inhibitors of signal transduction: development from research tools to therapeutic agents. Biochem. Soc. Trans. 24, 623–629.

De Fougerolles, A.R., Stacker, S.A., Schwarting, R., Springer, T.A., 1991. Characterization of ICAM-2 and evidence for a third counter-receptor for LFA-1. J. Exp. Med. 174, 253–267.

Diaz-González, F., González-Alvaro, I., Campanero, M.R., Mollinedo, F., del Pozo, M.A., Muñoz, C., Pivel, J.P., Sánchez-Madrid, F., 1995. Prevention of in vitro neutrophil–endothelial attachment through shedding of L-selectin by nonsteroidal antiinflammatory drugs. J. Clin. Invest. 95, 1756–1765.

Díaz-González, F., Forsyth, J., Steiner, B., Ginsberg, M.H., 1996. Transdominant inhibition of integrin function. Mol. Biol. Cell 7, 1939–1951.

Doerr, T.A., Rosolia, D.L., Peters, S.P., Gee, M.H., Albertine, K.H., 1992. $PGE_1$ inhibited PMN attachment to air emboli in vivo during infusion of ZAP without preventing lung injury. J. Appl. Physiol. 72, 340–351.

Elices, M.J., Tsai, V., Strahl, D., Goel, A.S., Tollefson, V., Arrhenius, T., Wayner, E.A., Gaeta, F.C.A., Fikes, J.D., Firestein, G.S., 1994. Expression and functional significance of alternatively spliced CS1 fibronectin in rheumatoid arthritis microvasculature. J. Clin. Invest. 93, 405–416.

Endemann, G., Feng, Y., Bryant, C.M., Hamilton, G.S., Perumattam, J., Mewshaw, E.M., Liu, D.Y., 1996. Novel anti-inflammatory compounds prevent CD11b/CD18, $\alpha_M\beta_2$(Mac-1)-dependent neutrophil adhesion without blocking activation-induced changes in Mac-1. J. Pharmacol. Exp. Ther. 276, 5–12.

Endemann, G., Abe, Y., Bryant, C.M., Feng, Y., Smith, C.W., Liu, D.Y., 1997. Novel anti-inflammatory compounds induce shedding of L-selectin and block primary capture of neutrophils under flow conditions. J. Immunol. 158, 4879–4885.

Etzioni, A., Frydman, M., Pollack, S., Avidor, I., Phillips, M.L., Paulson, J.C., Gershoni-Baruch, R., 1992. Recurrent severe infections caused by a novel leukocyte adhesion deficiency. New Engl. J. Med. 327, 1789–1792.

Farsky, S.P., Sannomiya, P., Garcia-Leme, J., 1995. Secreted glucocorticoids regulate leukocyte–endothelial interactions in inflammation. A direct vital microscopic study. J. Leukocyte Biol. 57, 379–386.

Fecondo, J.V., Kent, S.B.H., Boyd, A.W., 1991. Inhibition of intercellular adhesion molecule 1-dependent biological activities by a synthetic peptide analog. Proc. Natl. Acad. Sci. USA 88, 2879–2882.

Forsyth, K.D., Talbot, V., 1992. Role of glucocorticoids in neutrophil and endothelial adhesion molecule expression and function. Mediators Inflamm. 1, 101–106.

Friedman, M., Wang, S.Y., Sellke, F.W., Cohn, W.E., Weintraub, R.M., Johnson, R.G., 1995. Neutrophil adhesion blockade with NPC 15669 decreases pulmonary injury after total cardiopulmonary bypass. J. Thorac. Cardiovasc. Surg. 111, 460–468.

Garciá-Vicuña, R., Díaz-González, F., del Pozo, M.A., Mollinedo, F., Cabañas, C., González-Amaro, R., Sánchez-Madrid, F., 1997. Prevention of cytokine-induced changes in leukocyte adhesion receptors by nonsteroidal antiinflammatory drugs from the oxicam family. Arthritis Rheum. 40, 143–153.

Gearing, A.J.H., Newman, W., 1993. Circulating adhesion molecules in disease. Immunol. Today 14, 506–512.

Georas, S.N., Liu, M.C., Newman, W., Beall, L.D., Stealey, B.A., Bochner, B.S., 1992. Altered adhesion molecule expression and endothelial activation accompany the recruitment of human granulocytes to the lung after segmental antigen challenge. Am. J. Respir. Cell Mol. Biol. 7, 261–269.

Giancotti, F.G., 1997. Integrin signaling: specificity and control of cell survival and cell cycle progression. Curr. Opin. Cell Biol. 9, 691–700.

Gimbrone, M.A. Jr., Brock, A.F., Schafer, A.I., 1984. Leukotriene $B_4$ stimulates polymorphonuclear leukocyte adhesion to cultured vascular endothelial cells. J. Clin. Invest. 74, 1552–1555.

González-Alvaro, I., Carmona, L., Díaz-González, F., González-Amaro, R., Mollinedo, F., Sánchez-Madrid, F., Laffón, A., García-Vicuña, R., 1996. Aceclofenac, a new nonsteroidal antiinflammatory drug, decrease the expression and function of some adhesion molecules in human neutrophils. J. Rheumatol. 23, 723–729.

Gonzalo, J.-A., Lloyd, C.M., Kremer, L., Finger, E., Martinez-A., C., Siegelman, M.H., Cybulsky, M., Gutierrez-Ramos, J.-C., 1996. Eosinophil recruitment to the lung in a murine model of allergic inflammation. The role of T cells, chemokines and adhesion receptors. J. Clin. Invest. 98, 2332–2345.

Gosset, P., Tillie-Leblond, I., Janin, A., Marquette, C.-H., Copin, M.-C., Wallaert, B., Tonnel, A.-B., 1995. Expression of E-selectin, ICAM-1 and VCAM-1 on bronchial biopsies from allergic and non-allergic asthmatic patients. Int. Arch. Allergy Immunol. 106, 69–77.

Gumbiner, B.M., 1996. Cell adhesion: the molecular basis of tissue architecture and morphogenesis. Cell 84, 345–357.

Haller, H., Dragun, D., Miethke, A., Park, J.K., Weis, A., Lippoldt, A., Groß, V., Luft, F.C., 1996. Kidney Int. 50, 473–480.

Hamilton, G.S., Mewshaw, R.E., Bryant, C.M., Feng, Y., Endemann, G., Madden, K.S., Janczak, J.E., Perumattam, J., Stanton, L.W., Yang, X., Yin, Z., 1995. Fluorenylalkanoic and benzoic acids as novel inhibitors of cell adhesion processes in leukocytes. J. Med. Chem. 38, 1650–1656.

Haynes, B.F., Telen, M.J., Hale, L.P., Denning, S.M., 1989. CD44—a molecule involved in leukocyte adherence and T-cell activation. Immunol. Today 10, 423–428.

Horie, S., Kita, H., 1994. CD11b/CD18 (Mac-1) is required for degranulation of human eosinophils induced by human recombinant granulocyte–macrophage colony-stimulating factor and platelet-activating factor. J. Immunol. 152, 5457–5467.

Huang, Y.-W., Baluna, R., Visetta, E.S., 1997. Adhesion molecules as targets for cancer therapy. Histol. Histopathol. 12, 467–477.

Hunt III, S.W., Kellermann, S.-A., Shimizu, Y., 1997. Integrins, integrin regulators, and the extracellular matrix. The role of signal transduction and leukocyte migration. In: Bochner, B.S. (Ed.), Adhesion Molecules in Allergic Disease. Marcel Dekker, New York, pp. 73–103.

Iademarco, M.F., Barks, J.L., Dean, D.C., 1995. Regulation of vascular cell adhesion molecule-1 expression by IL-4 and TNF-$\alpha$ in cultured endothelial cells. J. Clin. Invest. 95, 264–271.

Imai, Y., Lasky, L.A., Rosen, S.D., 1993. Sulphation requirement for GlyCAM-1, an endothelial ligand for L-selectin. Nature 361, 555–557.

Ishizuka, T., Suzuki, K., Kawakami, M., Kawaguchi, Y., Hidaka, T., Matsuki, Y., Nakamura, H., 1994. DP-1904, a specific inhibitor of thromboxane $A_2$ synthesizing enzyme, suppresses ICAM-1 expression by stimulated vascular endothelial cells. Eur. J. Pharmacol. 262, 113–123.

Jacobson, P.B., Schrier, D.J., 1993. Regulation of CD11b/CD18 expression in human neutrophils by phospholipase $A_2$. J. Immunol. 151, 5639–5652.

Kameda, H., Yoshida, T., Ichikawa, Y., Homma, M., 1995. Thromboxane $A_2$ synthase inhibitor, DP-1904, decreases TNF$\alpha$ secretion from monocytes and inhibits E-selectin and ICAM-1 expression on the endothelial surfaces. Adv. Prostaglandin Thromboxane Leukotriene Res. 23, 423–425.

Katz, S.M., Tian, L., Stepkowski, S.M., Phan, T., Bennett, C.F., Kahan, B.D., 1997. Effect of ICAM-1/LFA-1 blockade on pancreatic islet allograft survival, function, and early cytokine production. Transplant. Proc. 29, 748–749.

Kavanaugh, A., 1997. Overview of cell adhesion molecules and their antagonism. In: Bochner, B.S. (Ed.), Adhesion Molecules in Allergic Disease. Marcel Dekker, New York, pp. 1–24.

Kavanaugh, A., Nichols, L., Davis, L., Rothlein, R., Lipsky, P., 1993. Anti-CD54 (intercellular adhesion molecule-1; ICAM-1) monoclonal antibody therapy in refractory rheumatoid arthritis. Arthritis Rheum. 36, S40.

Kavanaugh, A.F., Davis, L.S., Nichols, L.A., Norris, S.H., Rothlein, R., Scharschmidt, L.A., Lipsky, P.E., 1994. Treatment of refractory rheumatoid arthritis with a monoclonal antibody to intercellular adhesion molecule 1. Arthritis Rheum. 37, 992.

Kazmi, S.M.I., Plante, R.K., Visconti, V., Taylor, G.R., Zhou, L., Lau, C.Y., 1995. Suppression of NFkB activation and NFkB-dependent gene expression by tepoxalin, a dual inhibitor of cyclooxygenase and 5-lipoxygenase. J. Cell. Biochem. 57, 299–310.

Kincade, P.W., Zheng, Z., Katoh, S., Hanson, L., 1997. The importance of cellular environment to function of the CD44 matrix receptor. Curr. Opin. Cell Biol. 9, 635–642.

Kirchner, T., Aparicio, B., Argentieri, D.C., Lau, C.Y., Ritchie, D.M., 1997. Effects of tepoxalin, a dual inhibitor of cyclooxygenase/5-lipoxygenase, on events associated with NSAID-induced gastrointestinal inflammation. Prostaglandins Leukotrienes Essent. Fatty Acids 56, 417–423.

Kogan, T.P., Dupré, B., Keller, K.M., Scott, I.L., Bui, H., Market, R.V., Beck, P.J., Voytus, J.A., Revelle, B.M., Scott, D., 1995. Rational design and synthesis of small molecule, non-oligosaccharide selectin inhibitors: ($\alpha$-D-mannopyranosyloxy)biphenyl-substituted carboxylic acids. J. Med. Chem. 38, 4976–4984.

Konstantopoulos, K., McIntire, L.V., 1996. Effects of fluid dynamic forces on vascular cell adhesion. J. Clin. Invest. 98, 2661–2665.

Kopp, E., Ghosh, S., 1994. Inhibition of NF-$\kappa$B by sodium salicylate and aspirin. Science 265, 956–959.

Kruszynski, M., Nakada, M.T., Tam, S.H., Taylor, A.H., Fieles, W.E., Heavner, G.A., 1996. Determination of the core sequence of an antagonist of selectin-dependent leukocyte adhesion and correlation of its structure with molecular modeling studies. Arch. Biochem. Biophys. 331, 23–30.

Kumasaka, T., Quinlan, W.M., Doyle, N.A., Condon, T.P., Sligh, J., Takei, F., Beaudet, A.L., Bennett, C.F., Doerschuk, C.M., 1996. Role of the intercellular adhesion molecule-1 (ICAM-1) in endotoxin-induced pneumonia evaluated using ICAM-1 antisense oligonucleotides, anti-ICAM-1 monoclonal antibodies, and ICAM-1 mutant mice. J. Clin. Invest. 97, 2362–2369.

Kurose, I., Wolf, R., Miyasaka, M., Anderson, D.C., Granger, D.N., 1996. Microvascular dysfunction induced by nonsteroidal anti-inflammatory drugs: role of leukocytes. Am. J. Physiol. 270, G363–G369.

Kyan-Aung, U., Lee, T.H., Haskard, D.O., 1993. The inhibitory effect of tenidap on leukocyte–endothelial cell adhesion. J. Rheumatol. 20, 1014–1019.

Laberge, S., Rabb, H., Issekutz, T.B., Martin, J.G., 1995. Role of VLA-4 and LFA-1 in allergen-induced airway hyperresponsiveness and lung inflammation in the rat. Am. J. Respir. Crit. Care Med. 151, 822–829.

Lee, D.H.S., Tam, S.S.C., Wang, E., Taylor, G.R., Plante, R.K., Lau, C.Y., 1996. The NF-$\kappa$B inhibitor, tepoxalin, suppresses surface expression of the cell adhesion molecules CD62E, CD11b/CD18 and CD106. Immunol. Lett. 53, 109–113.

Lefer, D.J., Flynn, D.M., Phillips, M.L., Ratcliffe, M., Buda, A.J., 1994. A novel sialyl Lewis$^x$ analog attenuates neutrophil accumulation and myocardial necrosis after ischemia and reperfusion. Circulation 90, 2390–2401.

Lefkovits, J., Plow, E.F., Topol, E.J., 1995. Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. New Engl. J. Med. 332, 1553–1559.

Lerner, R., Helmburger, M., Palmblad, J., 1993. Lipoxin $A_4$ induces hyperadhesiveness in human endothelial cells for neutrophils. Blood 82, 948–953.

Lobb, R.R., 1997. Adhesion molecule antagonists in animal models of asthma. In: Bochner, B.S. (Ed.), Adhesion Molecules in Allergic Asthma. Marcel Dekker, New York, pp. 393–405.

Loftus, J.C., Liddington, R.C., 1997. New insights into integrin–ligand interaction. J. Clin. Invest. 99, 2302–2306.

Look, D.C., Rapp, S.R., Keller, B.T., Holtzman, M.J., 1992. Selective induction of intercellular adhesion molecule-1 by interferon-$\gamma$ in human airway epithelial cells. Am. J. Physiol. 263, L79–L87.

Lowe, J.B., Ward, P.A., 1997. Therapeutic inhibition of carbohydrate–protein interactions in vivo. J. Clin. Invest. 99, 822–826.

Luscinskas, F.W., 1997. The endothelium in leukocyte recruitment. In: Bochner, B.S. (Ed.), Adhesion Molecules in Allergic Disease. Marcel Dekker, New York, pp. 25–41.

Malik, A.B., Lo, S.K., 1996. Vascular endothelial adhesion molecules and tissue inflammation. Pharmacol. Rev. 48, 213–229.

McCafferty, D.-M., Kubes, P., Wallace, J.L., 1993. Inhibition of platelet-activating factor-induced leukocyte adhesion in vivo by a leumidin. Eur. J. Pharmacol. 232, 169–172.

McEver, R.P., Cummings, R.D., 1997. Role of PSGL-1 binding to selectins in leukocyte recruitment. J. Clin. Invest. 100, 485–492.

McEver, R.P., Beckstead, J.H., Moore, K.L., Marshall-Carlson, L., Bainton, D.F., 1989. GMP-140, a platelet $\alpha$-granule membrane protein, is also synthesized by vascular endothelial cells and is located in Weibel-Palade bodies. J. Clin. Invest. 84, 92–99.

Menger, M.D., Vollmar, B., 1996. Adhesion molecules as determinants of disease: from molecular biology to surgical research. Br. J. Surg. 83, 588–601.

Milne, A.A.Y., Piper, P.J., 1994. The effects of two anti-CD18 antibodies on antigen-induced airway hyperresponsiveness and leukocyte accumulation in the guinea pig. Am. J. Respir. Cell Mol. Biol. 11, 337–343.

Milne, A.A.Y., Piper, P.J., 1995. Role of VLA-4 integrin in leucocyte recruitment and bronchial hyperresponsiveness in the guinea-pig. Eur. J. Pharmacol. 282, 243–249.

Molossi, S., Elices, M., Arrhenius, T., Diaz, R., Coulber, C., Rabinovitch, M., 1995. Blockade of very late antigen-4 integrin binding to fibronectin with connecting segment-1 peptide reduces accelerated coronary arteriopathy in rabbit cardiac allografts. J. Clin. Invest. 95, 2601–2610.

Montefort, S., Gratziou, C., Goulding, D., Polosa, R., Haskard, D.O., Howarth, P.H., Holgate, S.T., Carroll, M.P., 1994a. Bronchial biopsy evidence for leukocyte infiltration and upregulation of leukocyte–endothelial cell adhesion molecules 6 hours after local allergen challenge of sensitized asthmatic airways. J. Clin. Invest. 93, 1411–1421.

Montefort, S., Lai, C.K.W., Kapahi, P., Leung, J., Lai, K.N., Chan, H.S., Haskard, D.O., Howarth, P.H., Holgate, S.T., 1994b. Circulating adhesion molecules in asthma. Am. J. Respir. Crit. Care Med. 149, 1149–1152.

Morland, C.M., Wilson, S.J., Holgate, S.T., Roche, W.R., 1992. Selective eosinophil leukocyte recruitment by transendothelial migration and not by leukocyte–endothelial cell adhesion. Am. J. Respir. Cell Mol. Biol. 6, 557–566.

Moser, R., Fehr, J., Bruijnzeel, P.L.B., 1992. IL-4 controls the selective endothelium-driven transmigration of eosinophils from allergic individuals. J. Immunol. 149, 1432–1438.

Mulligan, M.S., Lowe, J.B., Larsen, R.D., Paulson, J., Zheng, Z., DeFrees, S., Maemura, K., Fukuda, M., Ward, P.A., 1993a. Protective effects of sialylated oligosaccharides in immune complex-induced acute lung injury. J. Exp. Med. 178, 623–631.

Mulligan, M.S., Paulson, J.C., De Frees, S., Zheng, Z.-L., Lowe, J.B., Ward, P.A., 1993b. Protective effects of oligosaccharides in P-selectin-dependent lung injury. Nature 364, 149–151.

Nagase, T., Fukuchi, Y., Matsuse, T., Sudo, E., Matsui, H., Orimo, H., 1995. Antagonism of ICAM-1 attenuates airway and tissue responses to antigen in sensitized rats. Am. J. Respir. Crit. Care Med. 151, 1244–1249.

Nagata, M., Sedgwick, J.B., Bates, M.E., Kita, H., Busse, W.W., 1995. Eosinophil adhesion to vascular cell adhesion molecule-1 activates superoxide anion generation. J. Immunol. 155, 2194–2202.

Nakajima, H., Sano, H., Nishimura, T., Yoshida, S., Iwamoto, I., 1994. Role of vascular cell adhesion molecule 1/very late activation antigen 4 and intercellular adhesion molecule 1/lymphocyte function-associated antigen 1 interactions in antigen-induced eosinophil and T cell recruitment into the tissue. J. Exp. Med. 179, 1145–1154.

Neeley, S.P., Hammann, K.J., White, S.R., Baranowski, S.L., Burch, R.A., Leff, A.R., 1993. Selective regulation of expression of surface adhesion molecules Mac-1, L-selectin, and VLA-4 on human eosinophils and neutrophils. Am. J. Respir. Cell Mol. Biol. 8, 633–639.

Nelson, R.M., Dolich, S., Aruffo, A., Ceconi, O., Bevilacqua, M.P., 1993. Higher-affinity oligosaccharide ligands for E-selectin. J. Clin. Invest. 91, 1157–1166.

Noronha-Blob, L., Lowe, V.C., Weitzberg, M., Burch, R.M., 1991. NPC 15669 enhances survival and reverses leukopenia in endotoxin-treated mice. Eur. J. Pharmacol. 199, 387–388.

Noronha-Blob, L., Lowe, V.C., Muhlhauser, R.O., Burch, R.M., 1993a. NPC 15669, an inhibitor of neutrophil recruitment, is efficious in acetic acid-induced colitis in rats. Gastroenterology 104, 1021–1029.

Noronha-Blob, L., Lowe, V.C., Otterbein, L., Steranka, L., Burch, R.M., 1993b. NPC 15669 reduces mortality associated with sepsis in rats. J. Pharmacol. Exp. Ther. 267, 664–669.

Ohkawara, Y., Yamauchi, K., Maruyama, N., Hoshi, H., Ohno, I., Honma, M., Tanno, Y., Tamura, G., Shirato, K., Ohtani, H., 1995. In situ expression of the cell adhesion molecules in bronchial tissues from asthmatics with air flow limitation: in vivo evidence of VCAM-1/VLA-4 interaction in selective eosinophil infiltration. Am. J. Respir. Cell Mol. Biol. 12, 4–12.

O'Leary, E.C., Marder, P., Zuckerman, S.H., 1996. Glucocorticoid effects in an endotoxin-induced rat pulmonary inflammation model: differential effects on neutrophil influx, integrin expression, and inflammatory mediators. Am. J. Respir. Cell Mol. Biol. 15, 97–106.

Paleolog, E.M., Hunt, M., Elliott, M.J., Feldmann, M., Maini, R.N., Woody, J.N., 1996. Deactivation of vascular endothelium by monoclonal anti-tumor necrosis factor $\alpha$ antibody in rheumatoid arthritis. Arthritis Rheum. 39, 1082–1091.

Palmblad, J.E.W., Lerner, R., 1992. Leukotriene B4-induced hyperadhesiveness of endothelial cells for neutrophils: relation to CD54. Clin. Exp. Immunol. 90, 300–304.

Palmblad, J., Lerner, R., Larsson, S.H., 1994. Signal transduction mechanisms for leukotriene $B_4$ induced hyperadhesiveness of endothelial cell for neutrophils. J. Immunol. 152, 262–269.

Papayianni, A., Serhan, C.N., Brady, H.R., 1996. Lipoxin $A_4$ and $B_4$ inhibit leukotriene-stimulated interactions of human neutrophils and endothelial cells. J. Immunol. 156, 2264–2272.

Perretti, M., Wheller, S.K., Harris, J.G., Flower, R.J., 1996. Modulation of ICAM-1 levels on U-937 cells and mouse macrophages by interleukin-1$\beta$ and dexamethasone. Biochem. Biophys. Res. Commun. 223, 112–117.

Pitzalis, C., Sharrack, B., Gray, I.A., Lee, A., Hughes, R.A.C., 1997. Comparison of the effects of oral versus intravenous methylprednisolone regimens on peripheral blood T lymphocyte adhesion molecule expression, T cell subsets distribution and TNF alpha concentrations in multiple sclerosis. J. Neuroimmunol. 74, 62–68.

Pober, J.S., Gimbrone, M.A. Jr., Lapierre, L.A., Mendrick, D.L., Fiers, W., Rothlein, R., Springer, T.A., 1986. Overlapping patterns of activation of human endothelial cells by interleukin 1, tumor necrosis factor, and immune interferon. J. Immunol. 137, 1893–1896.

Postigo, A.A., Teixidó, J., Sánchez-Madrid, F., 1994. The $\alpha_4\beta_1$/VCAM-1 adhesion pathway in physiology and disease. Res. Immunol. 145, 723–735.

Pretolani, M., Ruffié, C., Lapa e Silva, J.-R., Joseph, D., Lobb, R.R., Vargaftig, B.B., 1994. Antibody to very late activation antigen 4 prevents antigen-induced bronchial hyperreactivity and cellular infiltration in the guinea pig airways. J. Exp. Med. 180, 795–805.

Rao, B.N.N., Anderson, M.B., Musser, J.H., Gilbert, J.H., Schaeffer,

M.E., Foxall, C., Brandley, B.K., 1994. Sialyl Lewis X mimics derived from a pharmacophore search are selectin inhibitors with anti-inflammatory activity. J. Biol. Chem. 269, 19663–19666.

Richards, I.M., Kolbasa, K.P., Hatfield, C.A., Winterrowd, G.E., Vonderfecht, S.L., Fidler, S.F., Griffin, R.L., Brashler, J.R., Krzesicki, R.F., Sly, L.M., Ready, K.A., Staite, N.D., Chin, J.E., 1996. Role of very late activation antigen-4 in the antigen-induced accumulation of eosinophils and lymphocytes in the lungs and airway lumen of sensitized Brown Norway rats. Am. J. Respir. Cell Mol. Biol. 15, 172–183.

Riva, C.M., Morganroth, M.L., Ljungman, A.G., Schoeneich, S.O., Marks, R.M., Todd, R.F. III, Ward, P.A., Boxer, L.A., 1990. Iloprost inhibits neutrophil-induced lung injury and neutrophil adherence to endothelial monolayers. Am. J. Respir. Cell Mol. Biol. 3, 301–309.

Ross, L., Hassman, F., Molony, L., 1992. Inhibition of Molt-4-endothelial adherence by synthetic peptides from the sequence of ICAM-1. J. Biol. Chem. 267, 8537–8543.

Rothlein, R., Mainolfi, E.A., Czajkowski, M., Marlin, S.D., 1991. A form of circulating ICAM-1 in human serum. J. Immunol. 147, 3788–3793.

Salmi, M., Kalimo, K., Jalkanen, S., 1993. Induction and function of vascular adhesion protein-1 at sites of inflammation. J. Exp. Med. 178, 2255–2260.

Serhan, C.N., Maddox, J.F., Petasis, N.A., Akritopoulou-Zanze, I., Papayianni, A., Brady, H.R., Colgan, S.P., Madara, J.L., 1995. Design of lipoxin $A_4$ stable analogs that block transmigration and adhesion of human neutrophils. Biochemistry 34, 14609–14615.

Seth, R., Raymond, F.D., Makgoba, M.W., 1991. Circulating ICAM-1 isoforms: diagnostic prospects for inflammatory and immune disorders. Lancet 338, 83–84.

Smith, R.J., Justen, J.M., Bleasdale, J.E., Sly, L.M., 1995. NPC 15669-modulated human polymorphonuclear neutrophil functional responsiveness: effects on receptor-coupled signal transduction. Br. J. Pharmacol. 114, 1694–1702.

Spragg, D.D., Alford, D.R., Greferath, R., Larsen, C.E., Lee, K.-D., Gurtner, G.C., Cybulsky, M.I., Tosi, P.F., Nicolau, C., Gimbrone, M.A. Jr., 1997. Immunotargeting of liposomes to activated vascular endothelial cells: a strategy for site-selective delivery in the cardiovascular system. Proc. Natl. Acad. Sci. USA 94, 8795–8800.

Springer, T.A., 1990. Adhesion receptors of the immune system. Nature 346, 425–434.

Staunton, D.E., Dustin, M.L., Springer, T.A., 1989. Functional cloning of ICAM-2, a cell adhesion ligand for LFA-1 homologous to ICAM-1. Nature 339, 61–64.

Steegmaier, M., Levinovitz, A., Isenmann, S., Borgers, E., Lenter, M., Kocher, H.P., Kleuser, B., Vestweber, D., 1995. The E-selectin-ligand ESL-1 is a variant of a receptor for fibroblast growth factor. Nature 373, 615–620.

Stepkowski, S.M., Tu, Y., Condon, T.P., Bennett, C.F., 1994. Blocking of heart allograft rejection by intercellular adhesion molecule-1 antisense oligonucleotides alone or in combination with other suppressive modalities. J. Immunol. 153, 5336–5346.

Stepkowski, S.M., Wang, M.E., Amante, A., Kalinin, D., Qu, X., Blasdel, T., Condon, T., Kahan, B.D., Bennett, F.C., 1997. Antisense ICAM-1 oligonucleotides block allograft rejection in rats. Transplant. Proc. 29, 1285.

Stewart, A.J., Pichon, C., Meunier, L., Midoux, P., Monsigny, M., Roche, A.C., 1996. Enhanced biological activity of antisense oligonucleotides complexed with glycosylated poly-L-lysine. Mol. Pharmacol. 50, 1487–1494.

Tailor, A., Das, A.M., Getting, S.J., Flower, R.J., Perretti, M., 1997. Subacute treatment of rats with dexamethasone reduces ICAM-1 levels on circulating monocytes. Biochem. Biophys. Res. Commun. 231, 675–678.

Takahashi, N., Liu, M.C., Proud, D., Yu, X.-Y., Hasegawa, S., Spannhake, E.W., 1994. Soluble intracellular adhesion molecule 1 in bronchoalveolar lavage fluid of allergic subjects following segmental antigen challenge. Am. J. Respir. Crit. Care Med. 150, 704–709.

Takeichi, M., 1991. Cadherin cell adhesion receptors as a morphogenetic regulator. Science 251, 1451–1455.

Tam, S.H., Nakada, M.T., Kruszynski, M., Fieles, W.E., Taylor, A.H., Mervic, M., Heavner, G.A., 1996. Structure-function studies on synthetic peptides derived from the 109-118 lectin domain of selectins. Biochem. Biophys. Res. Commun. 227, 712–717.

Thornhill, M.H., Haskard, D.O., 1990. IL-4 regulates endothelial cell activation by IL-1, tumor necrosis factor, or IFN-$\gamma$. J. Immunol. 145, 865–872.

Thornhill, M.H., Wellicome, S.M., Mahiouz, D.L., Lanchbury, J.S.S., Kyan-Aung, U., Haskard, D.O., 1991. Tumor necrosis factor combines with IL-4 or INF-$\gamma$ to selectively enhance endothelial cell adhesiveness for T cells. The contribution of vascular cell adhesion molecule-1-dependent and -independent binding mechanisms. J. Immunol. 146, 592–598.

Uthoff, K., Zehr, K.J., Lee, P.C., Low, R.A., Baumgartner, W.A., Cameron, D.E., Stuart, R.S., 1995. Neutrophil modulation results in improved pulmonary function after 12 and 24 hours of preservation. Ann. Thorac. Surg. 59, 7–13.

Vanderslice, P., Ren, K., Revelle, J.K., Kim, D.C., Scott, D., Bjercke, R.J., Yeh, E.T.H., Beck, P.J., Kogan, T.P., 1997. A cyclic hexapeptide is a potent antagonist of $\alpha_4$ integrins. J. Immunol. 158, 1710–1718.

Van de Stolpe, A., Van der Saag, P.T., 1996. Intercellular adhesion molecule-1. J. Mol. Med. 74, 13–33.

Van de Stolpe, A., Caldenhoven, E., Raaijmakers, J.A.M., Van der Saag, P.T., Koenderman, L., 1993. Glucocorticoid-mediated repression of intracellular adhesion molecule-1 expression in human monocytic and bronchial epithelial cell lines. Am. J. Respir. Cell Mol. Biol. 8, 340–347.

Van de Stolpe, A., Caldenhoven, E., Stade, B.G., Koenderman, L., Raaijmakers, J.A.M., Johnson, J.P., Van der Saag, P.T., 1994. 12-*O*-tetradecanoylphorbol-13-acetate and tumor necrosis factor $\alpha$-mediated induction of intercellular adhesion molecule-1 is inhibited by dexamethasone. Functional analysis of the human intercellular adhesion molecule-1 promoter. J. Biol. Chem. 269, 6185–6192.

Van Seventer, G.A., Newman, W., Shimizu, Y., Nutman, T.B., Tanaka, Y., Horgan, K.J., Gopal, T.V., Ennis, E., O'Sullivan, D., Grey, H., Shaw, S., 1991. Analysis of T cell stimulation by superantigen plus major histocompatibility complex class II molecules or by CD3 monoclonal antibody: costimulation by purified adhesion ligands VCAM-1, ICAM-1, but not ELAM-1. J. Exp. Med. 174, 901–913.

Varki, A., 1994. Selectin ligands. Proc. Natl. Acad. Sci. USA 91, 7390–7397.

Varki, A., 1997. Selectin ligands: will the real ones please stand up?. J. Clin. Invest. 99, 158–162.

Vingerhoeds, M.H., Storm, G., Crommelin, D.J.A., 1994. Immunoliposomes in vivo. Immunomethods 4, 259–272.

Wacholtz, M.C., Patel, S.S., Lipsky, P.E., 1989. Leukocyte function-associated antigen 1 is an activation molecule for human T cells. J. Exp. Med. 170, 431–448.

Wang, J.-H., Pepinsky, R.B., Stehle, T., Liu, J.-H., Karpusas, M., Browning, B., Osborn, L., 1995. The crystal structure of an N-terminal two-domain fragment of vascular cell adhesion molecule 1 (VCAM-1): a cyclic peptide based on the domain 1 C-D loop can inhibit VCAM-1-$\alpha_4$ integrin interaction. Proc. Natl. Acad. Sci. USA 92, 5714–5718.

Wegner, C.D., Gundell, R.H., Reilly, P., Hayness, N., Letts, L.G., Rothlein, R., 1990. Intercellular adhesion molecule-1 (ICAM-1) in the pathogenesis of asthma. Science 247, 456–459.

Wheller, S.K., Perretti, M., 1997. Dexamethasone inhibits cytokine-induced intercellular adhesion molecule-1 up-regulation on endothelial cell lines. Eur. J. Pharmacol. 331, 65–71.

Wilckens, T., De Rijk, R., 1997. Glucocorticoids and immune function: unknown dimensions and new frontiers. Immunol. Today 18, 418–424.

Williams, A.F., Barclay, A.N., 1988. The immunoglobulin superfamily. Annu. Rev. Immunol. 6, 381–405.

Yoshida, N., Takemura, T., Granger, D.N., Anderson, D.C., Wolf, R.E.,

McIntire, L.V., Kvietys, P.R., 1993. Molecular determinants of aspirin-induced neutrophil adherence to endothelial cells. Gastroenterology 105, 715–724.

Yoshida, N., Cepinskas, G., Granger, D.N., Anderson, D.C., Wolf, R.E., Kvietys, P.R., 1995. Aspirin-induced, neutrophil-mediated injury to vascular endothelium. Inflammation 19, 297–312.

Zangrilli, J.G., Shaver, J.R., Cirelli, R.A., Cho, S.K., Garlisi, C.G., Falcone, A., Cuss, F.M., Fish, J.E., Peters, S.P., 1995. sVCAM-1 levels after segmental antigen challenge correlate with eosinophil influx, IL-4 and IL-5 production, and the late phase response. Am. J. Respir. Crit. Care Med. 151, 1346–1353.

Zhou, L., Pope, B.L., Chourmouzis, E., Fung-Leung, W.-P., Lau, C.Y., 1996. Tepoxalin blocks neutrophil migration into cutaneous inflammatory sites by inhibiting Mac-1 and E-selectin expression. Eur. J. Immunol. 26, 120–129.