Introduction

Dramatic progress in elucidating the molecular basis of inflammation over the past two decades has led to the development new anti-inflammatory and immunomodulatory therapies. In particular, the adhesion molecules involved in leukocyte trafficking from the blood stream to tissue have emerged as important therapeutic targets. Extensive preclinical studies have shown that blockade of leukocyte or endothelial adhesion molecules is efficacious in diverse disease models, prompting many pharmaceutical and biotechnology companies to develop adhesion antagonists. However, because of the close relationship between inflammation and host defense and tissue repair, anti-adhesion therapy may also be a double-edged sword. This chapter reviews the promises and limitations of anti-adhesion therapy, focusing on those drugs that have completed clinical trials.

Approaches to targeting adhesion molecules

There are a number of approaches to anti-adhesion therapy. Blockade of receptor-ligand interactions by a monoclonal antibody (mAb), soluble receptor or peptide, or small-molecule ligand mimic is the most direct, and most drugs that have been tested in clinical trials are of this category. Other potential therapeutics include small-molecule antagonists that interrupt the signaling pathways that regulate integrin receptor affinity or the expression of endothelial adhesion molecules, allosteric inhibitors that prevent the conformational changes necessary for increased integrin receptor affinity, agents that interfere with the biosynthesis of carbohydrate ligands for selectin receptors, and drugs that impair transendothelial migration.
Targeting adhesion molecules in human disease

In reviewing the clinical trials of anti-adhesion therapy, only therapies that have completed Phase II or Phase III studies are considered. Table 1 lists the therapies by mechanism of action and clinical indication.

Asthma

The asthmatic response to allergen is characterized by airway hyper-responsiveness and inflammation with the accumulation of effector cells such as lymphocytes and eosinophils. The trafficking of these immune cells to the lung in asthma involves both selectins (reviewed in [1]) and integrins, particularly $\alpha_4\beta_2$ (LFA-1) and $\alpha_4\beta_1$ (VLA-4) (reviewed in [2]).

Given the efficacy observed in preclinical studies, it is surprising that only a few adhesion agents have completed Phase II testing. A small Phase IIa study was undertaken in asthmatic patients using Bio-1211, an aerosolized small-molecule inhibitor of VLA-4; however, it was determined that that particular compound did not warrant further development [3]. Also, a planned Phase II trial of a small-molecule dual inhibitor of $\alpha_4\beta_1$ and $\alpha_4\beta_7$ was discontinued [4]. Efalizumab, a humanized anti-$\alpha_L$ mAb, was tested in patients with mild asthma. Although the number of activated eosinophils was significantly decreased after 4 and 8 weeks of treatment, the early and late percent fall in forced expiratory volume at 1 s after allergen challenge did not reach statistical significance [5]. Bimosiamose, an E-, P-, and L-selectin antagonist, showed efficacy in a small Phase IIa trial of 12 patients, and it is currently being evaluated in a Phase II trial as an inhaled treatment for mild allergic asthma [6].

Atherosclerosis

Vascular cell adhesion molecule-I (VCAM-1) is an immunoglobulin gene super-family (IgSF) member that is the primary endothelial ligand for $\alpha_4\beta_1$. The interaction of $\alpha_4\beta_1$ on monocytes and lymphocytes with endothelial VCAM-1 is thought to play a pivotal role in atherogenesis [7]. AGI-1067 is an oral antioxidant that inhibits the transcription of VCAM-1 as well as several other cytokine-induced, redox-sensi-

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1 Phase I clinical trials test a new therapy in a small group of people (20–80) to assess safety, establish safe dosage ranges and identify side effects. Phase II clinical trials determine efficacy and further evaluate safety in a larger group of people (several hundred). Phase III studies confirm efficacy in a larger population (several hundred to several thousand) comparing the intervention to standard treatments and continue to monitor adverse effects.