Integrin Avb8 Neutralizing Antibody for Diagnosing Cancer, Pulmonary Fibrosis, and Renal Disease

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Technology description

Background

Over a dozen companies have pursued the development of TGF- β modulators for the treatment of cancer, pulmonary fibrosis, and renal disease. However, the near-ubiquitous presence of the three mammalian TGF- β isoforms across tissue types, as well as its complex and diverse effects on downstream signaling pathways, mean there is a high likelihood that chronic global suppression of TGF-β will result in undesirable off-target effects. An agent effecting tissue and disease-specific mitigation of TGF- β activity while sparing much of its contribution to normal cellular function would be of extremely high therapeutic value for a wide range of inflammatory, fibrotic and neoplastic diseases. The integrin family of cell surface receptors are emerging as promising targets for tissue type-selective modulation of TGF- β. Because TGF- β activation in a given tissue type requires association with a specific integrin, it is believed that targeting such interactions will lead to effective therapeutics while avoiding many of the possible systemic effects of indiscriminate TGF- β suppression. In mice, conditional deletion ofavb8 blocks airway inflammation and fibrosis in COPD and asthma models and can completely inhibit experimental autoimmune encephalitis.In human biospecimens, activation of TGF- β byavb8 has been directly implicated in both fibrotic and inflammatory processes of the airway in COPD. Until now, no chemical, small molecule, or high affinity antibody agent was available that selectively blocks the interaction of TGF- β and integrinavb8.

Description

UCSF investigators have developed the first mouse anti-human neutralizing monoclonal antibody that prevents the binding of two TGF- β isoforms to integrinavb8. This is the sole agent of any type that selectively targets these associations, without which TGF-bactivationin vivois severely compromised. UCSF investigators have characterized the target epitope of the antibody.In vivo, this antibody blocks airway inflammation in transgenic mice expressing only human and not mouseavb8. Short-term safety tests show no deleterious effects using high-concentrations of the antibody (7mg/kg). Animal model safety and additional efficacy tests are underway in humanized mice expressing humanavb8.

This antibody offers several distinct advantages over current TGF- β modulators. First, the antibody only inhibits the activation of the TGF-b1 andb3 isoforms, sparing the neutralization of TGF-b2. The TGF-b1 isoform is widely considered to account for the majority of the disease-related biology of TGF-b. Second, the specificity for cells expressing only theavb8 integrin isoform decreases off-target effects

such as autoimmune responses, rapid-onset atherosclerosis, and carcinoma development. Third, the antibody selectively disrupts the binding of TGF- β toavb8 in a way that does not influence general cell adhesion properties mediated by this interaction, further minimizing non-TGF-b-related effects.

Application area

Diagnostic indications include:
COPD
Chronic Asthma
Idiopathic Pulmonary Fibrosis
Renal Fibrosis
Liver Fibrosis
Multiple Sclerosis
Rheumatoid Arthritis and autoimmune disease
Ovarian Cancer
Breast Cancer

Advantages

Tissue specific targeting reduces side effects
Normal cell adhesion unaffected
TGF-b1 andb3 isoform specific inhibition
Existing preclinical disease models
Functional epitope defined
Antibody CDRs conferring enhanced affinity defined

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