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

Tech ID: 21233 / UC Case 2010-103-0

FULL 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 of avb8 blocks airway inflammation and fibrosis in COPD and asthma models and can completely inhibit experimental autoimmune encephalitis. In human biospecimens, activation of TGF-β by avb8 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 integrin avb8.

Description

UCSF investigators have developed the first mouse anti-human neutralizing monoclonal antibody that prevents the binding of two TGF-β isoforms to integrin avb8. This is the sole agent of any type that selectively targets these associations, without which TGF-β activation in vivo is 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 mouse avb8. 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 human avb8.

This antibody offers several distinct advantages over current TGF-β modulators. First, the antibody only inhibits the activation of the TGF-β1 and β3 isoforms, sparing the neutralization of TGF-β2. The TGF-β1 isoform is widely considered to account for the majority of the disease-related biology of TGF-β. Second, the specificity for cells expressing only the avb8 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 to avb8 in a way that does not influence general cell adhesion properties mediated by this interaction, further minimizing non-TGF-β-related effects.

ADVANTAGES
Tissue specific targeting reduces side effects
Normal cell adhesion unaffected
TGF-b1 and b3 isoform specific inhibition
Existing preclinical disease models
Functional epitope defined
Antibody CDRs conferring enhanced affinity defined

PATENT STATUS

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LOOKING FOR PARTNERS

To develop and commercialize this technology as a diagnostic test for COPD, Chronic Asthma, Idiopathic Pulmonary Fibrosis, Renal Fibrosis, Liver Fibrosis, Multiple Sclerosis, Rheumatoid Arthritis and Autoimmune Disease, Ovarian Cancer, Breast Cancer

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Bispecific Antibodies for Detection and Treatment of Cancers Associated with EGFR Overexpression
- Collaboration Opportunity: Novel Mouse Models of Human Hepatitis B Virus Infection for Drug Discovery and Vaccine Research