BIOLOGIC THERAPY FOR TRIPLE-NEGATIVE and TREATMENT-RESISTANT BREAST CANCER

Tech ID: 22373 / UC Case 2010-063-0

INVENTION NOVELTY

These novel, fully human antibodies are demonstrated to eliminate tumor burden in a xenograft mouse model of triple negative breast cancer (TNBC). They competitively block urokinase plasminogen activator receptor (uPAR)-mediated signaling and are effective either as a monotherapy or in radioimmunotherapy.

uPAR expression is highly correlated with aggressive phenotypes of breast cancer and inversely correlated with efficacy of tamoxifen in treatment. Anti-uPAR therapy promises to be effective in treating patients with TNBC, drug-resistant breast cancer and metastatic breast cancer.

TECHNOLOGY DESCRIPTION

UCSF inventors have developed unique fully human Fab and IgG antibody inhibitors of uPAR. These antibodies competitively disrupt the binding of two ligands (uPA and β1 integrin) to uPAR and block uPA and β1-mediated signaling involved in cancer proliferation and invasion. Using Matrigel and Collagen I invasion assays, the investigators have shown that these anti-uPAR antibodies inhibit the invasion of human lung cancer cells in culture. Use of the uPAR/uPA and uPAR/β1 antagonist antibodies together exhibited synergistic effects. In a TNBC xenograft model, in vivo monotherapy with the unconjugated antibody clone 2G10 reduced tumor growth and 2G10 conjugated to a therapeutic radioisotope caused complete tumor regression with no recurrence at 84 days.

These antibodies also have favorable uptake and pharmacokinetic properties which support their use as therapeutics for cancer. Internalization assays using flow cytometry techniques with MDA-MB-231 cells indicated that approximately 50% of 2G10 IgG was endocytosed within one hour. In healthy mice, clones 2G10 and 3C6 were demonstrated to have half-lives of 9.1 days and 5.8 days, respectively.

APPLICATIONS

▶ Biologic therapy for solid cancers, including TNBC
▶ Delivery of therapeutic payloads to uPAR over-expressing cells

ADVANTAGES

▶ Fully human IgGs and antibody fragments
▶ Demonstrated activity against TNBC
▶ Favorable half-life, tumor uptake and pharmacokinetic properties
▶ High affinity and specificity for uPAR

RELATED MATERIALS

Professor Charles Craik studies proteolytic enzymes and their natural inhibitors. His goal is to identify the roles and regulate the activity of proteases associated with infectious diseases, cancer and development. He is a professor in the Departments of Pharmaceutical Chemistry, Cellular & Molecular Pharmacology and Biochemistry & Biophysics at the University of California, San Francisco. He has published over 270 research articles and co-authored two books. He has served on advisory panels for the National Institutes of Health, the National Science Foundation, the National Academy of Sciences and the Department of Energy.

**PATENT STATUS**

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Additional Patent Pending