Humanized, potent monoclonal antibodies against murine and human integrin avb8 for cancer immunotherapy and prevention of corneal scarring after cataract surgery

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BACKGROUND

Immunotherapy has revolutionized the treatment of many cancers, but even for the most sensitive tumor types most patients do not respond to current immunotherapy regimens. One major block to effective anti-tumor immunity is inhibition of the function of effector T cells by active TGFβ in tumors. For this reason, several major pharmaceutical companies have invested substantial resources in developing inhibitors of TGFβ ligands or TGFβ signaling to enhance anti-tumor immunity. However, because TGFβ isoforms (TGFβ1, 2 and 3) play multiple important homeostatic roles, highly effective inhibition of TGFβ function causes severe toxicity, as seen by the embryonic or perinatal lethality of knockout of each of the 3 mammalian TGFβs. Even the relatively ineffective TGFβ inhibitors that have entered clinical trials have been withdrawn because of unacceptable toxicity (cardiac valve thickening and skin cancer). We have thus spent the past 20 years developing drugs targeting TGFβ activating integrins, which only activate a small fraction of extracellular latent TGFβ in precise contexts relevant to specific diseases, with the goal of increasing precision and greatly reducing the potential for toxicity.

TECHNOLOGY DESCRIPTION

Researchers at UCSF have generated a panel of murine monoclonal antibodies against alpha V beta 8 (AVB8). Among those, two have been shown to bind to cells expressing human AVB8 with high affinity, block LAP adhesion and TGFβ activation in vitro. In the context of cancer immunotherapy, those anti-AVB8 mAbs block immunosuppression by human Treg in vivo. In the context of autoimmunity, human AVB8 levels are increased on CD1c+ DC from inflammatory bowel disease patients to enhance induction of FOXP3 in CD4+ T cells. Anti-AVB8 mAb blocks this induction. In the context of complication post cataract treatment, i.e., posterior capsular opacification, expression of αV integrin and its interacting β-subunits β1, β5, β6, β8 are up-regulated concomitant with α-SMA following surgery, and deletion of αV resulted in no up-regulation of any of the fibrotic markers tested. These beta subunits counteract the wound healing response α-SMA expressing myofibroblasts and lens fibre cells following surgery. Recent studies at UCSF show that AVB8 is the critical player and an anti-AVB8 mAb is effective in reducing posterior capsular opacification in murine models.

Given the demonstrated biological effects of those anti-AVB8 murine mAbs, they are excellent candidates for therapeutic development via full humanization. Researchers have fully humanized these mAbs and, to enable functional study in murine models, aim to impart high affinity cross-species binding to the humanized antibodies.

LOOKING FOR PARTNERS

To develop and commercialize this technology.

STAGE OF DEVELOPMENT

Pre-Clinical
DATA AVAILABILITY
Under CDA

PATENT STATUS
Patent Pending

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