

## **Agtuzumab, a humanized monoclonal antibody blocks AGR2 function through conformational epitopes around its catalytic center**

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**A**GR2 is a member of protein disulfide-isomerase (PDI) family and plays an important role in cancer development including tumorigenesis and metastasis. Unlike the classical PDI protein with a CxxC catalytic center, AGR2 contains a CxxS center that function in Mucin2 formation on the endoplasmic reticulum. However, AGR2 has also been shown to present in blood plasma and is secreted by several cell lines. As a secreted small protein, AGR2 is particularly suitable target for antibody medicine and its functional antibody is under investigation for therapeutic potentials by several major pharmaceutical firms and academic institutions but few showed AGR2 any anti-cancer efficacy. Here we report a humanized monoclonal antibody against AGR2, Agtuzumab, with promising therapeutic potentials. This antibody blocks AGR2 function in cell migration and proliferation assays and reduced tumorigenic and angiogenic potential of xenograft tumors in nude mice. Treatment of AGR2-blocking antibody reduced the expression of VEGF and VEGFR level in xenograft tumor tissues for both human tumor and its mouse stroma cells. Scanning mutagenesis assays revealed discontinuous regions around the CxxS PDI center. on AGR2 protein that are essential for efficient binding of Agtuzumab. Our results for the first time confirmed with a potential therapeutic antibody that AGR2 can be a therapeutic target and its blocking requires the blockage of a conformational epitope. This result also explains why many monoclonal antibodies developed against peptides may not be functional against AGR2 related tumors.

### **Biography**

Dawei Li has completed his Ph.D from Ohio State University and postdoctoral studies from Harvard University School of Medicine. He is a full professor leading the research and development effort of novel biopharmaceuticals at School of Pharmacy of Shanghai Jiao Tong University, a fifth ranking institution in China. He has published more than 25 papers in reputed journals including PNAS, JBC, MCB, Cancer Research and serving as the Chair of Professor Association at SJTU School of Pharmacy.

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