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Monoclonal antibodies inhibiting fibrin-VLDL receptor-dependent inflammation

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Field
Cardiology

Technology
Antibody Inhibitor

Status
Available for licensing

Patent Status
US Patent Pending,
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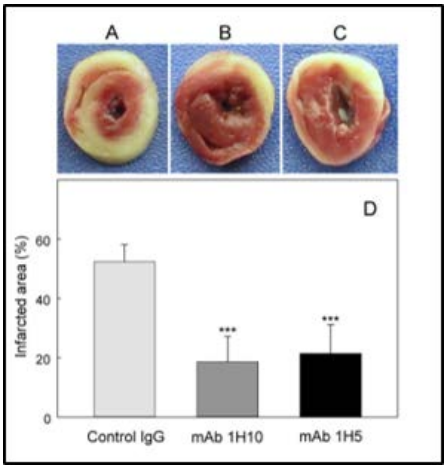
UMB Docket Reference
LM-2016-049

Reference
Thromb Haemost. 2016 Nov 30;116(6):1122-1130. Epub 2016 Sep 1.

Summary

Fibrin is a fibrous, non-globular protein involved in blood clotting and promotes leukocyte transmigration through its interaction with the endothelial cell receptor, the very low density lipoprotein (VLDL) receptor. The VLDL receptor is predominantly expressed in the heart, skeletal muscle, fat, brain and macrophages and involved in neural development, plasticity, angiogenesis, fibrin-dependent inflammation, and wound healing. Increased levels of serum fibrins are associated with the increased risk ischemic heart disease which can lead to a heart attack, arrhythmia, and heart failure.

Anti-VLDLR monoclonal antibodies, 1H5 and lHlO, have been generated that interacted with the VLDLR fragment containing the fibrin binding region $(\beta 15–66)_2$. Studies with the anti-VLDLR antibodies demonstrated the ability to inhibit fibrin interactions with the fibrin-binding region of the VLDL receptor. This in turn significantly reduced the trans endothelial migration of leukocytes in *in vitro* and *in vivo* experiments. Mouse model studies of peritonitis confirmed the reduction of leukocyte infiltration into the peritoneum with the treatment of the 1H5 and lHlO antibodies. Additionally, the cardioprotective effect of both mAbs have been shown in a mouse model of myocardial ischemia-reperfusion injury (see figure). This technology can be developed into novel anti-inflammatory agents for treatment of inflammation-related cardiovascular diseases including myocardial ischemia-reperfusion injury.



Market

Myocardial ischemia is an insufficient flow of blood to the myocardium due to an obstruction or constriction in the coronary arteries leading to inflammation and endothelial dysfuntion. The global myocardial ischemia market is anticipated to reach $50 billion by 2023 largely due to the high prevalence of coronary heart disorders, diabetes, and contributing lifestyle factors such as smoking, obesity, high blood pressure, and a sedantary lifestyle. Current methods of treatment for myocardial ischemia involves improving blood flow to the heart muscle via medications (aspirin, nitroglycerine, calcium channel blockers, angiotensin converting ezyme inhibitors, ranolazine) or a procedure to open blocked arteries (angioplasty, stenting, coronary artery bypass surgery, enhanced external counter pulsation).

In the early 1990s, Fibrex Medical, Inc. developed a peptide called FX06 as an anti-inflammatory drug for the treatment of myocardial ischemia-reperfusion injury. Phase I and II showed relative safety but efficacy studies failed to show significant differences in the sizes of the infarctions. The FX06 peptide targeted the inhibition of the fibrin-VE-cadherin dependent pathway. The 1H5 and lHlO, anti-VLDLR technology specifically inhibits the fibrin-VLDLR-dependent pathway of leukocyte transmigration and was found to be two-fold more efficient than the FX06.

Technology Status

- Initial in vivo and in vitro studies completed

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