BETA CELL MARKER ANTIBODY

The present invention relates to an antibody directed to a beta cell marker protein, in particular to an antibody directed to the protein TMEM27.

Loss of functional beta-cell mass underlies the pathogenesis of both type 1 and type 2 diabetes. Noninvasive imaging of beta-cell mass in vivo would therefore provide a valuable diagnostic and research tool for quantifying progression to diabetes and response to therapeutic intervention. In addition, non-invasive and targeted beta-cell siRNA delivery in vivo would be very valuable for both research and therapy.

The transmembrane protein Tmem27 (Collectrin) is expressed in pancreatic β-cells where it regulates pancreatic β - cell mass, and insulin secretion. Tmem27 is inactivated at the plasma membrane by proteolytic cleavage and shedding.

Therefore, there is a need for a diagnostic and/or research tool for quantifying beta-cell mass and there is a need for a tool for targeted drug delivery to beta-cells.

It is an object of the embodiments disclosed hereinpresent invention to provide an antibody directed to an epitope of a Tmem27 polypeptide. In a first aspect, there is provided an antibody directed to an epitope of a Tmem27 polypeptide, wherein the antibody comprises CDR1 to CDR3 of a V_H domain of an antibody obtainable from hybridoma cell line TMEM27-8/9 (DSM ACC2995) and CDR1 to CDR3 of a V_L domain of an antibody obtainable from hybridoma cell line TMEM27-8/9 (DSM ACC2995).

In a preferred embodiment the antibody is directed to human Tmem27 polypeptide. .

In a further embodiment, the antibody is a monoclonal antibody, preferably a humanized antibody.

In a further embodiment, the antibody has been produced by immunizing suitable animals with whole cells expressing the Tmem27 polypeptide, preferably human Tmem27 polypeptide.

In a further preferred embodiment, the antibody comprises a CDR3 of a V_H domain of an antibody obtainable from hybridoma cell line TMEM27-8/9 (DSM ACC2995) and a CDR3 of a V_L domain of an antibody obtainable from hybridoma cell line TMEM27-8/9 (DSM ACC2995).

In a further preferred embodiment, the antibody comprises CDR1 to CDR3 of the V_H domain of an antibody obtainable from hybridoma cell line TMEM27-8/9 (DSM ACC2995) and CDR1 to CDR3 of the V_L domain of an antibody obtainable from hybridoma cell line TMEM27-8/9 (DSM ACC2995).

In a further preferred embodiment, the antibody is a chimeric antibody comprising a V_H domain and a V_L domain of an antibody obtainable from hybridoma cell line TMEM27-8/9 (DSM ACC2995).

In a further preferred embodiment, the antibody is produced by hybridoma cell line TMEM27-8/9 which was deposited with the DSMZ (German Collection of Microorganisms and Cell Cultures) on May 27, 2009 and received the deposit number DSM ACC2995.

In a second aspect, there is provided the antibody as defined herein for use as a medicament.

~~In a second object, t~~The present disclosure also~~invention~~ relates to the use of the antibody of the present invention for the manufacturing of a medicament for the treatment of a disease involving modulation of TMEM27 cleavage and its signaling pathway. The disease is preferably diabetes. In a third aspect, there is provided the use of the antibody as defined herein for the manufacturing of a medicament for the treatment of diabetes. In a fourth aspect, there is provided the antibody as defined herein for use in treating diabetes.

In a further embodiment, the antibody of the present disclosure~~invention~~ is used as a tool for the intracellular delivery of active compounds. The active compound is preferably covalently coupled to the antibody. The "active compound" can be any suitable molecule, including DNA, RNA, siRNA, a protein, a peptide, or a pharmaceutically active agent, such as, for example, a toxin, an antibiotic, an antipathogenic agent, an antigen, an antibody, an antibody fragment, an immunomodulator, an enzyme, or a therapeutic agent. The antibody of the present disclosure~~invention~~ is suitable for intracellular delivery of active compounds since the antibody allows a targeted intracelluar delivery of the active compounds by specifically targeting pancreatic beta-cells.

In a further embodiment, the antibody of the present disclosure~~invention~~ can be used for *in vivo* imaging of beta cell islet and beta-cell mass in a pancreas of a animal, preferably a human being. In a fifth aspect, there is provided the use of the antibody as defined herein for the *in vivo* imaging of beta cell islet and beta-cell mass in a pancreas of an animal.

A suitable method for *in vivo* imaging is e.g. Immuno-PET (Positron Emission Tomography).. Immuno-PET is based on the coincidental detection of a mononclonal antibody labelled with a positron-emitting radionuclide. The following positron emitters can be used for immuno-PET: gallium-68 (^{68}Ga; $t_{1/2}$, 1.13 hours), fluorine-18 (^{18}F; $t_{1/2}$, 1.83 hours), copper-64 (^{64}Cu; $t_{1/2}$, 12.7 hours), yttrium-86 (^{86}Y; $t_{1/2}$, 14.7 hours), bromine-76 (^{76}Br; $t_{1/2}$, 16.2 hours), zirconium-89 (^{89}Zr; $t_{1/2}$, 78.4 hours), and iodine-124 (^{124}I; $t_{1/2}$, 100.3 hours) [The Oncologist, Vol. 12, No. 12, 1379-1389, December 2007)].

The distribution of a PET conjugate in a patient can be monitored by detection of the annihilation photon pairs with a PET camera. A PET camera consists of a ring of detectors placed around the body of the patient. If two photons are registered by detectors on opposite sides of the body within a very short time interval (typically 5–15 nanoseconds), it is assumed that somewhere along the line between the two detectors an annihilation event has taken place. By calculating the crossing of all lines, the location of the radiation source (radiolabelled mAb) can be determined.

In a sixth aspect, there is provided a conjugate comprising an antibody as defined herein and an active compound covalently linked to the antibody.

In a seventh aspect, there is provided a hybridoma cell line TMEM27-8/9 which was deposited with the DSMZ (German Collection of Microorganisms and Cell Cultures) on May 27, 2009 and received the deposit number DSM ACC2995.

In an eighth aspect, there is provided a nucleic acid molecule comprising a sequence encoding a V_H domain of an antibody obtainable from hybridoma cell line TMEM27-8/9 (DSM ACC2995).

In a ninth aspect, there is provided a nucleic acid molecule comprising a sequence encoding V_L domain of an antibody obtainable from hybridoma cell line TMEM27-8/9 (DSM ACC2995).

In a tenth aspect, there is provided a nucleic acid molecule comprising a sequence encoding an antibody produced by hybridoma cell line TMEM27-8/9 which was deposited with the DSMZ (German Collection of Microorganisms and Cell Cultures) on May 27, 2009 and received the deposit number DSM ACC2995.

In an eleventh aspect, there is provided a vector comprising the nucleic acid sequence as defined herein.

In a twelfth aspect, there is provided a host cell comprising the vector as defined herein.