CASE STUDY

DISCOVERY OF A THERAPEUTIC ANTIBODY FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE AND TYPE I DIABETES

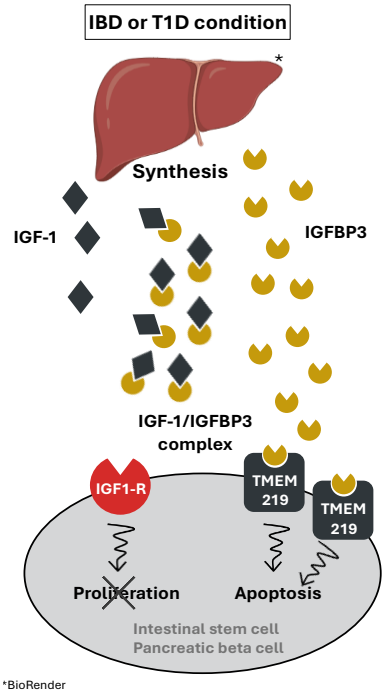

Figure 1. IGFBP3/TMEM219 axis in IBD and T1D

Increased free IGFBP3 levels in IBD and T1D patients cause TMEM219 activation in intestinal stem cells and pancreatic beta cells, thereby resulting in strong induction of the apoptotic pathway and massive cell loss.

THE NEED

Preventing apoptopic cell loss in IBD and insulin-dependent diabetes patients

Insulin-like growth factor binding-protein 3 (IGFBP3) binds to Transmembrane Receptor 219 (TMEM219) on intestinal stem cells (ISCs) and pancreatic beta cells and mediates cell death/apoptosis in an IGF1-independent way. Dysregulation of the IGFBP3/TMEM219 axis, due to increased levels of circulating free IGFBP3, plays a key role in the exaggerated apoptosis of intestinal stem cells and pancreatic beta cells occurring in conditions of chronic gastrointestinal inflammation, such as Inflammatory Bowel Disease (IBD) and Type 1 Diabetes (Figure 1).

Therefore, the inhibition of the TMEM219/ IGFBP3 axis may represent an appropriate strategy to protect ISCs and pancreatic beta cells from the IGFBP3-mediated detrimental effects observed in IBD and T1D.

THE SOLUTION

Development of a TMEM219 specific antibody with high affinity binding capacity

In cooperation with Enthera, YUMAB employed its proprietary fully human antibody platform and expertise to generate the lead candidate Ent001, a stabilized IgG4, without the need for bioinformatic engineering to reach an affinity to TMEM in the lower pM range. Ent001 specifically binds to TMEM219 inhibiting its interaction with IGFBP3 (Figure 2).

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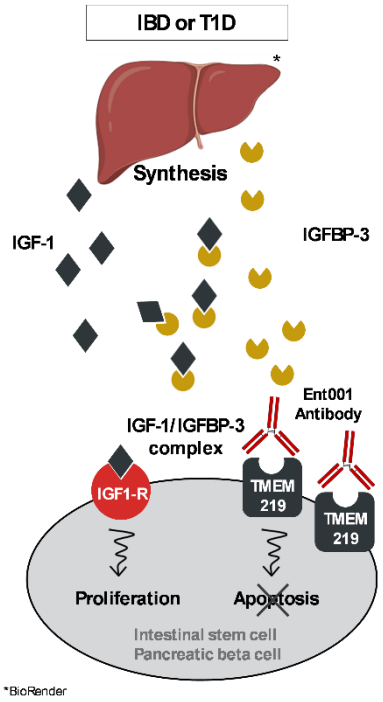

Figure 2. Interaction of Ent001 with its target TMEM219

Entheras Ent001 binds specifically to TMEM219 and inhibits the interaction of IGFBP-3 and TMEM219.

THE IMPACT

Antagonism of IGFBP3-binding to TMEM219 by Ent001 decreases apoptosis in preclinical models of IBD and T1D

With the lead antibody Ent001 YUMAB enabled Enthera to conduct successful preclinical development studies and to proceed with clinical trials in human.

Ent001 is a first-in-class antibody targeting the IGFBP-3-TMEM219 axis. To date, Enthera successfully completed the evaluation of Ent001 for safety and tolerability in a Phase 1a first-in-human (FIH) study in healthy volunteers. The study results showed a safe and tolerable response upon Ent001 application without any adverse reactions. Tolerability is one of the key features of YUMAB's fully human antibody platform.

Based on these results Enthera initiated a multiple ascending dose Phase 1b clinical trial in patients with moderate to severe acute ulcerative colitis.

"With their expertise and technological capabilities, team YUMAB has been the right match for the successful development of Ent001. Always tuned to our needs they guided us through the process, saving time and clearing the path for a first-in-class IBD drug candidate."

Dr. Virna Marin, Senior Project Manager R&D, Enthera

CONTACT US
+49 531 481170-0
info@yumab.com
www.yumab.com