GLP-1R Agonist Antibodies for Weight Management, Primed for Clinical Development

Antibodies with best-in-class potential for addressing the growing need in obesity and diabetes

The Unmet Medical Need

Obesity is a global medical concern and its prevalence has nearly tripled in the last 50 years. Worldwide, 39% of adults (>1.9B) are overweight, while 13% of adults (650M) are obese. Effective therapeutic options are needed, as obesity puts patients at a higher risk of developing insulin resistance and serious comorbidities:

- **Diabetes**: A metabolic disorder that affects 1 in 10 Americans. 90 to 95% of diabetes patients have type 2 diabetes (T2D) and obese patients are 80 times more likely to develop T2D.
- **Non-alcoholic steatohepatitis (NASH)**: Excess production of lipids in the liver leads to the accumulation of lipotoxic metabolites and affects 37% of patients with severe obesity.

Target Rationale: Glucagon-Like Peptide 1 Receptor (GLP-1R) for Obesity and Diabetes

Weight gain induces dysregulation of the GLP-1R signaling pathway, resulting in reduced insulin secretion, hyperglycemia, exacerbation of obesity, and increased risk of diabetes. The development of a GLP-1R antibody agonist is a promising, next-generation therapeutic strategy and offers several advantages over peptide agonists, such as greater specificity, improved half-life, and more favorable biodistribution, potentially leading to fewer side effects.

Twist’s GLP-1R Agonist Antibody: TB59-2

Twist's team has developed TB59-2, a high-affinity, fully human GLP-1R-specific IgG2 antibody. The GLP-1 (7-36) peptide is fused to the N-terminus of the light chain of a GLP-1R-specific antibody, discovered using Twist's expertly designed and proprietary GPCR library. TB59-2 has been extensively characterized and effectively stabilizes blood glucose concentrations in a glucose tolerance test (Figure 1), suggesting promise for further pre-clinical development. Twist has discovered 2 additional GLP-1R agonists that, like TB59-2, exhibit a robust cAMP and β-arrestin response and are ready for further testing.

Additional Advantages

- Potent nM antagonist; EC₅₀ = 15.5 nM
- Dose-dependent cAMP response, similar to GLP-1 (7-36)
- Long half-life of 54 hours (in rats)
- Promising pre-clinical efficacy

![Figure 1. TB59-2 is a GLP-1R agonist that stabilizes blood glucose concentrations in a glucose tolerance test using different doses and dosing regimens.](image-url)

If you are interested in learning more or licensing Twist antibodies, please contact biopharma@twistbioscience.com

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