

[0013] In one embodiment, the GLP-1 receptor agonist is conjugated to the antibody or fragment thereof via a peptide linker comprising a sequence selected from the group consisting of (Gly₃Ser)₂, (Gly₄Ser)₂, (Gly₃Ser)₃, (Gly₄Ser)₃, (Gly₃Ser)₄, (Gly₄Ser)₄, (Gly₃Ser)₅, (Gly₄Ser)₅, (Gly₃Ser)₆, and (Gly₄Ser)₆.

5

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] FIG. 1. Reaction scheme for the generation of anti-GIPR/GLP-1 peptide conjugate

10 [0015] FIGS. 2A-2T. GLP-1 receptor agonist activity in CHOK1-GLP-1R H20 recombinant cells and GIPR antagonist activity in 293 HEK-GIPR #10 recombinant cells

[0016] FIGS. 3A-3C. GLP-1 agonist activity of 2G10 conjugate is more potent in cells expressing both GLP-1R and GIPR (CHOK1 hGLP-1R/hGIPR M1) compared to cells only expressing GLP-1R (CHOK1 hGLP-1R H20)

[0017] FIGS. 4A-4R. In vivo activity- glucose and body weight effects in db/db mice

15 [0018] FIGS. 5A-5D. GLP-1 receptor agonist and GIPR Antagonist In vivo Activity of 5G12 and 2G10 Chemical Conjugates in C57Bl6 mice (glucose tolerance test)

[0019] FIGS. 6A-6B. GLP-1 receptor agonist and GIPR Antagonist In vivo Activity of 5G12 and 2G10 Chemical Conjugates in DIO mice (plasma glucose and change in body weight)

20 [0020] FIG. 7. GLP-1R-GIPR bispecific conjugate 1273 reduces body weight in male spontaneously obese cynomolgus monkeys (% change from baseline)

[0021] FIG. 8. GLP-1R-GIPR bispecific conjugate 1273 reduces total energy intake in male spontaneously obese cynomolgus monkeys (% change from baseline)

[0022] FIG. 9. GLP-1R-GIPR bispecific conjugate 1273 reduces fasting insulin in male spontaneously obese cynomolgus monkeys (% change from baseline)

25 [0023] FIG. 10. GLP-1R-GIPR bispecific conjugate 1273 reduces fasting triglycerides in male spontaneously obese cynomolgus monkeys (% change from baseline)

[0024] FIG. 11. GLP-1R-GIPR bispecific conjugate 1273 reduces fasting total cholesterol in male spontaneously obese cynomolgus monkeys (% change from baseline)

30 [0025] FIG. 12. GLP-1R-GIPR bispecific conjugate 1264 reduces body weight in male spontaneously obese cynomolgus monkeys (% change from baseline)

[0026] FIG. 13. GLP-1R-GIPR bispecific conjugate 1264 reduces total energy intake in male spontaneously obese cynomolgus monkeys (% change from baseline)

- [0027] FIG. 14. GLP-1R-GIPR bispecific conjugate 1264 reduces fasting insulin in male spontaneously obese cynomolgus monkeys (% change from baseline)
- [0028] FIG. 15. GLP-1R-GIPR bispecific conjugate 1264 reduces fasting triglycerides in male spontaneously obese cynomolgus monkeys (% change from baseline)
- 5 [0029] FIG. 16. GLP-1R-GIPR bispecific conjugate 1264 reduces fasting total cholesterol in male spontaneously obese cynomolgus monkeys (% change from baseline)
- [0030] FIG. 17. GLP-1R-GIPR bispecific conjugates 1248 and 1257 reduce body weight in male spontaneously obese cynomolgus monkeys (% change from baseline)
- [0031] FIG. 18. GLP-1R-GIPR bispecific conjugates 1248 and 1257 reduce total energy
10 intake in male spontaneously obese cynomolgus monkeys (% change from baseline)
- [0032] FIG. 19. GLP-1R-GIPR bispecific conjugates 1248 and 1257 reduce fasting insulin in male spontaneously obese cynomolgus monkeys (% change from baseline)
- [0033] FIG. 20. GLP-1R-GIPR bispecific conjugates 1248 and 1257 reduce fasting triglycerides in male spontaneously obese cynomolgus monkeys (% change from baseline)
- 15 [0034] FIG. 21. GLP-1R-GIPR bispecific conjugates 1248 and 1257 reduce fasting cholesterol in male spontaneously obese cynomolgus monkeys (% change from baseline)
- [0035] FIGS. 22A-22B. Binding affinity of anti-GIPR/GLP-1R bispecific conjugates
- [0036] FIG. 23. Anti-GIPR/GLP-1R bispecific conjugate 1248 promotes strong GLP-1R and GIPR internalization in cells expressing both GLP-1R and GIPR
- 20 [0037] FIGS. 24A-24B. Time course and dose response of anti-GIPR/GLP-1R bispecific conjugates in GLP-1R internalization assay
- [0038] FIGS. 25A-25D. GLP-1R, GIPR and bispecific conjugate are co-localized upon internalization
- [0039] FIGS. 26A-26B. Inhibition of receptor internalization reduces 1248-induced cAMP
25 generation
- [0040] FIGS. 27A-27C. Bispecific conjugates show binding to GLP-1R and GIPR in FACS analysis
- [0041] FIG. 28. Anti-GIPR/GLP-1R bispecific conjugates stimulate calcium flux
- [0042] FIGS 29A-29B. Anti-GIPR/GLP-1R bispecific conjugate 1248 promotes beta-arrestin
30 recruitments through both GLP-1R and GIPR pathways
- [0043] FIG. 30. Anti-GIPR/GLP-1R bispecific conjugate 1248 stimulates insulin secretion in human pancreatic microislets