Designing long-acting potent Y2 agonists

Soren Ostergaard

Research Chemistry III, Novo Nordisk, 2760 Maaloev, Denmark
sq@novonordisk.com

Peptides are notoriously known to display very short in vivo half-lives often measured in minutes, which in many cases greatly reduces or eliminates sufficient *in vivo* efficacy. To obtain long half-lives allowing for up to once-weekly dosing regimen, fatty acid acylation (lipidation) have been used to non-covalently associate the peptide of interest to serum albumin thus serving as a circulating depot[1].

In the design of potent PYY_{3-36} analogues[2,3] we performed a deep mutational analysis of PYY_{3-36} with the aim to identify hot spots that could improve potency and selective of Y_2 versus Y_1, Y_4 and Y_5 receptors, while at the same time display long half-life and excellent formulation properties. Highly potent and selective analogues were identified and in combination with GLP-1 demonstrate superior weight loss in animal studies

The knowledge gained from the SAR activities furthermore led to the design of potent dual GLP-1/PYY agonists, that displayed improved in vivo activity compared to their mono-agonist counterparts[4].

[1] P. Kurtzhals, S. Østergaard, E. Nishimura, T. Kjeldsen, Nature Rev. Drug Disc, **2022**, doi.org/10.1038/s41573-022-00529 (in press)
[2] S. Østergaard, J. Kofoed, J. F. Paulsson, K. G. Madsen, R. Jorgensen and B. S. Wulff, *J. Med. Chem*, **2018**, *61*, 10510-10530.
[3] S. Østergaard, J. F. Paulsson, J. Kofoed, F. Zosel, J. Olsen, C. B. Jeppesen, J. Spetzler, L. Ynddal, L.G. Schleiss, B.O. Christoffersen, K. Raun, U. Sensfuss, F.S. Nielsen, R. Jorgensen, B.S. Wulff, Scientific Reports, **2021**, 11, 21179.
[4] S. Østergaard, J. F. Paulsson, M. Kjærgaard Gerstenberg and B. S. Wulff, *Angew. Chem. Int. Ed*., **2021**,*60*, 8268-8275.