Accelerate Drug Development of GLP-1 & -2 Receptor Analogs with Ready-to-Use Cell Based Assays

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Abstract

There is an increasing need to generate therapeutics targeting metabolic and gastrointestinal diseases to address the global burden of metabolic diseases. By targeting β-protein-coupled receptor (GPCR) such as glucagon-like peptide-1 (GLP-1) and GLP-2 receptors, therapeutics can be developed to address these global metabolic disorders. In particular, engineered recombinant agonists analogs targeting the GLP-1 receptor are FDA approved for managing type-2 diabetes, obesity, and weight disorders, while GLP-2 analogs have been under therapeutic focus for the treatment of short bowel syndrome, a serious unmet medical disorder. Several other novel GPCR analogs, including biologics, are in clinical development; hence, existing assays for characterizing their action (MOA) are complex and require extensive development time.

Eurofins DiscoverX® offers a comprehensive portfolio of fit-for-purpose products targeting GLP-1 and GLP-2 receptors. Based on the industry-validated Enzyme Fragment Complementation (EFC) technology, the GLP-1 and GLP-2 product lines are offered with different molecular MOA, such as cAMP accumulation or β-galactosidase activity.

In this poster, we share example data of marketed therapeutics to qualify cell-based potency assays (bioassays) targeting the GLP-1 and GLP-2 receptors. These ready-to-use bioassays are functional assays qualified with marketed drugs such as liraglutide, exenatide, and teduglutide for the therapeutic action of these glucagon-like peptide analogs. We demonstrate that these bioassays are fit-for-purpose for implementation in quality control (QC) lot-release testing, helping to accelerate the time-to-market for therapeutic development by 6 to 9 months.

Significance of GLP-1 and GLP-2 in Metabolic Disorders

Insulin secretion
Satiety
Cardioprotection
β-Glucagon secretory activity

Insulin secretion
Satiety
Cardioprotection
β-Glucagon secretory activity

β-Glucagon secretion
Calcium Mobilization
Ligand GPCR
G-Protein
Signal

Figure 2. Functional, cell-based assay formats for glucose metabolism targets for Multiple MOAs

A. Enzyme Fragment Complementation (EFC)
B. G-Protein-Coupled Receptor (GPCR)

Figure 3. Functional, cell-based assay formats for glucose metabolism targets for Multiple MOAs

A. Enzyme Fragment Complementation (EFC)
B. G-Protein-Coupled Receptor (GPCR)

Relative Potency Data Using the GLP-2R Bioassay with Teduglutide

Figure 4. Relative potency data for PathHunter® GLP-2R bioassay using Teduglutide. A, Preliminary relative potency data for 100% nominal concentrations (IC50) of Gattex® (Teduglutide) in the PathHunter GLP-2R Bioassay. Three independent assessments of IC50 were performed using the recommended assay conditions. Data shown are the mean standard deviation (mean ± standard deviation) from three IC50 curves fit by the BLUP (best linear unbiased predictor) model for the nominal 100% nominal concentration of teduglutide. B. Statistics calculated by PLA 3.0. Last column shows whether the two curves in the restricted model pass F-tests for linearity and parallelism. While further optimization is not underway, these data suggest suitability for development of fit-for-purpose assays to assess relative potency of teduglutide.

Figure 5. Qualification data for the semaglutide (GLP-1R) bioassay kit. A. Qualification study design. Five nominal concentrations (IC50) of semaglutide over a range of 50% to 150% were evaluated (8 ± 4 for each IC50). Replicate was evaluated using the 100% IC50 by a single analyst over 3 days. Intermediate precision incorporated 2 analysts, multiple lots, and evaluation of 2 different lots of bioassay cells. For this study, no plates failed pre-established system and sample suitability criteria for the assay. B. Qualification study results, also summarized in Table 6 in Figure 6, demonstrating good accuracy, repeatability, intermediate precision, and dilutional linearity for the semaglutide bioassay kit.

Figure 6. Summary of the assay performance of the bioassay kit (GLP-1R) with innovator drugs. The bioassay GLP-1R bioassay kit was qualified with innovator drugs, Ozempic (semaglutide), Victoza® (liraglutide), and Byetta® (exenatide), over a range of 50% to 150%, using two analysts. A., B., and C. depicted the relative potency with respect to the standards of liraglutide, edeglutide, and exenatide, respectively. Each graph shows the % potency with respect to the standard, while the 95% confidence interval is shown with each graph. Statistics calculated by PLA 3.0. Last column shows whether the two curves in the restricted model pass F-tests for linearity and parallelism. While further optimization is not underway, these data suggest suitability for development of fit-for-purpose assays to assess relative potency of teduglutide.

Qualification Data for Semaglutide (GLP-1R) Bioassay Kit Demonstrating Suitability for Relative Potency Applications

Figure 6. Summary of the assay performance of the bioassay kit (GLP-1R) with innovator drugs. The bioassay GLP-1R bioassay kit was qualified with innovator drugs, Ozempic (semaglutide), Victoza® (liraglutide), and Byetta® (exenatide), over a range of 50% to 150%, using two analysts. A., B., and C. depicted the relative potency with respect to the standards of liraglutide, edeglutide, and exenatide, respectively. Each graph shows the % potency with respect to the standard, while the 95% confidence interval is shown with each graph. Statistics calculated by PLA 3.0. Last column shows whether the two curves in the restricted model pass F-tests for linearity and parallelism. While further optimization is not underway, these data suggest suitability for development of fit-for-purpose assays to assess relative potency of teduglutide.

Summary

• Eurofins DiscoverX offers a portfolio of GLP-1 and -2 cell lines and ready-to-use bioassays for characterization through QC lot release. These cell-based MDA-reflective, functional assays are robust and sensitive.
• Evaluating targets (GLP-1R and GLP-2R) for a comprehensive understanding of therapeutic MOAs through QC lot release. These cell-based MDA-reflective, functional assays are robust and sensitive.
• Eurofins DiscoverX GLP-1 and -2 qualified bioassays have been validated at CRO’s and pre-commercially available for therapeutic development.
• Development of a qualified bioassay with the innovator drug Gattex (Teduglutide) is in progress, but preliminary relative potency data suggests the PathHunter GLP-2R bioassay may be suitable for development of a fit-for-purpose method to assess relative potency of teduglutide.
• IND-enabling characterization and assay qualification studies with the clinical molecules can be performed through Eurofins DiscoverX custom development program.
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