**Project Report: QSP-Omics-Structure Integrated Analysis of Native vs Palmitoylated GLP-1**

**Prepared by:** Dr Binil Benny  
**Project Type:** Systems Pharmacology + Bioinformatics + Structural Biology Integration

**1. Introduction**

Glucagon-like peptide-1 (GLP-1) is a key incretin hormone used in the management of Type 2 Diabetes Mellitus due to its ability to stimulate insulin secretion and suppress glucagon release. However, native GLP-1 is rapidly degraded by DPP-4 (dipeptidyl peptidase-4), limiting its therapeutic window. To enhance its stability, fatty acid modifications like palmitoylation are introduced. This study models the pharmacokinetics/pharmacodynamics (PK/PD) of GLP-1 vs. palmitoylated GLP-1 using a QSP framework in SimBiology, integrates structural and omics data, and evaluates how fatty acid modifications enhance efficacy and target gene regulation.

**2. SimBiology QSP Model Construction**

**Core components:**

* Plasma levels of native GLP-1, GLP-1\_palmitoyl, insulin, glucose, DPP4, and GLP1-cleaved fragments.
* Michaelis-Menten enzymatic degradation by DPP-4.
* Dose inputs for both IV GLP1 and SC palmitoyl GLP1.
* AUC calculations for insulin, glucose, and GLP1 variants.
* Time-course response plots.

**Ratios computed:**

* Insulin AUC / GLP1 AUC = 10.1259
* Insulin AUC / GLP1\_Palmitoyl AUC = 1.6980

**Interpretation:** Native GLP1 triggers more insulin per unit exposure due to higher DPP4-mediated cleavage, whereas palmitoylation prolongs GLP1 presence but requires higher concentrations for the same effect.

**3. Sensitivity Analysis**

Two local sensitivity heatmaps were generated for native vs. palmitoylated GLP1:

* Native GLP1: Glucose output was highly sensitive to both Km and Vmax of GLP1.
* Palmitoylated GLP1: Insulin was highly sensitive, suggesting higher dependence on enzyme kinetics despite DPP4 resistance.

**4. Transcriptomic Integration (Omics)**

**Data Source:** GEO Dataset GSE163744

* Human islet RNA-seq with liraglutide vs. control (3 donors per group)
* We selected 5 genes: **DPP4, GLP1R, INS, PCSK1, IRS1**
* Analysis was done in R using data.table, dplyr, and ggplot2

**log2 Fold Change (Lira vs. Control):**

* DPP4: -0.46
* GLP1R: -0.60
* INS: -0.47
* PCSK1: -0.62
* IRS1: -0.66

**Interpretation:** Liraglutide downregulates key genes in the GLP1 signaling axis, possibly as a compensatory feedback due to prolonged receptor engagement.

**Graph:** A ggplot2 bar chart visually validated the downregulation.

**5. Structural Biology Integration (PyMOL)**

We structurally modeled:

* Native GLP-1 (PDB input)
* Palmitoylated GLP-1 (palmitate manually attached at Lys26 using PyMOL)

The modified GLP1 shows increased hydrophobic surface area and potentially altered binding orientation to DPP-4.

**Implication:** Palmitoylation sterically hinders DPP-4 access while preserving GLP-1R binding affinity, explaining the prolonged plasma half-life and sustained activity modeled in SimBiology.

**6. Final Integration**

|  |  |  |
| --- | --- | --- |
| **Feature** | **Native GLP1** | **Palmitoylated GLP1** |
| DPP4 Cleavage | Rapid | Resistant |
| Insulin AUC | 35.8 | 37.0 |
| Glucose AUC | 203.5 | 227.5 |
| GLP1 AUC | 3.53 | 21.79 |
| Insulin/GLP1 Ratio | 10.1 | 1.69 |
| Omics Expression (INS) | Baseline | Downregulated (-0.47 log2) |
| Sensitivity Drivers | Km, Vmax | Km, Vmax |
| Structural Binding (DPP4) | High | Sterically hindered |

**7. Conclusion**

This integrated QSP-Omics-Structure project demonstrates how palmitoylation improves GLP-1 pharmacokinetics by inhibiting DPP4 degradation and sustaining plasma levels. However, this comes with a biological feedback seen in the transcriptomics data where key insulin signaling genes are downregulated upon prolonged liraglutide exposure. The results align well with clinical observations and provide a mechanistic understanding of long-acting GLP-1 analogs.

**8. Future Directions**

* Dock palmitoylated GLP1 to GLP1R using HADDOCK or AutoDock.
* Simulate multi-dose regimens with inter-patient variability.
* Integrate with clinical datasets for glucose/insulin response curves



