Modified Glucagon-like Peptide-1 Receptor Agonist Producing Bacteriophages for the Treatment of Type 2 Diabetes Mellitus

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Introduction

Type 2 Diabetes Mellitus (T2DM) is a common metabolic disorder, affecting over 38 million Americans, with 90–95% of cases classified as type 2 [1]. Primarily driven by insulin resistance, T2DM leads to complications like cardiovascular and kidney disease, which in 2019 accounted for approximately 1.5 million deaths globally and an additional 460,000 deaths from related complications [2]. While GLP-1 receptor agonists (GLP-1RAs) enhance insulin secretion and beta-cell survival, their application is limited by side effects, including gastrointestinal disturbances, acute kidney injury, and immunogenic reactions [3,4].

To address these limitations, we propose an innovative, single-infection phage system capable of delivering and sustaining GLP-1 production directly in the gut. This approach promises reduced risk of adverse effects, minimal dependency on patient compliance, and long-term glucose regulation. By modifying GLP-1RA for stability, our solution enables effective, localized production within the gut, avoiding industrial production complications and discomfort associated with injectable formulations. Our engineered phage system, designed to undergo only a single replicative cycle, prevents uncontrolled phage proliferation, ensuring safe and controlled GLP-1RA release for managing T2DM.

Mission Statement

Our mission is improve Type 2 diabetes care and patient outcomes through the development of advanced biological technologies through innovation, teamwork, and continuous learning.

Project Timeline

Project Gantt Chart: The following chart outlines the timeline of this project with intermediate milestones and task completion tracking.

Customer Needs/Metrics

Needs/Metrics	Target Value
Treatment Effectiveness	Decrease of 2.5% in A1C levels
Ease of Use (5 pt. scale)	5
Frequency of Dosage	Once per week
Patient Compliance	80% Regimen Adherence after 12 months
Cost of Production	$15 per dose
Risk of Abuse	<2% incidence
Immunogenicity	<5% of patients show immune response to phage and microbiome change
Product Half-Life	> 2 days

Product Benchmarking
Comparison of competitors in Type 2 Diabetes treatment

House of Quality (HoQ)
Relationship between customer needs, metrics, and target specifications

Device Concept and Design

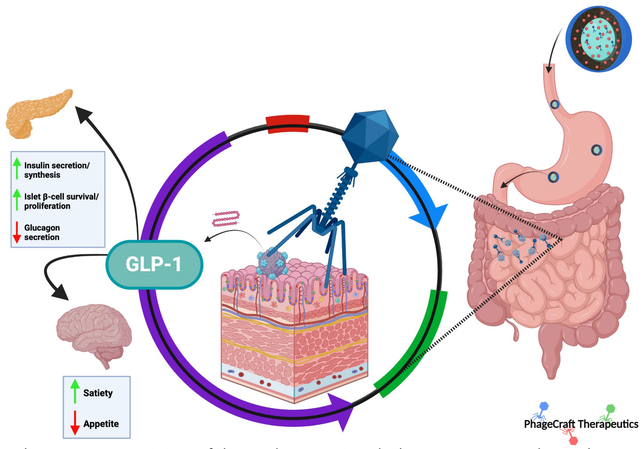

Figure 1. A schematic representation of the product is pictured where enteric-coated capsules carry modified phages through the GI tract to reach the distal small intestine. The phage-host interaction depicts integration of the phage genome to induce GLP-1RA production in the target microbe. Downstream effects of GLP-1 that are most relevant to T2DM management are pictured with depictions of effector functions on the pancreas and brain.

Modeling

Enteric Coating pH Dependent Degradation:	$D(pH) = \frac{100}{1 + e^{-k(pH - pH_0)}}$
Bacteriophage Shelf Life/Stability	$SL = \frac{ln(\frac{M_0}{M})}{e^{72.87 - \frac{23037}{T}}}$
GLP-1RA Degradation in Bloodstream	$[GLP1\ RA]\ (t) = [GLP1\ RA]_0 * e^{-k_d * t}$

Table 2. Equations of three primary models that are critical to quality for the product design.

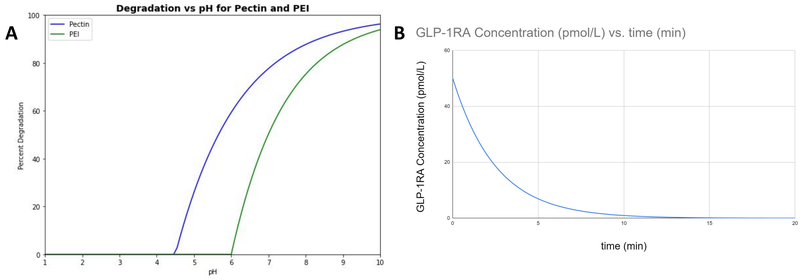

Figure 2. (A) The pH dependent degradation of pectin and polyethylenimine (PEI) is reported as percent degradation vs pH. (B) Curve depicting GLP-1RA degradation in the bloodstream.

Design for Manufacturing

Engineered bacteriophages will be enclosed within an enteric capsule made from an inexpensive layer-by-layer(LbL) process covering film-coated alginate beads with alternating polyethylenimine and pectin layers. The Bacteriophages will be produced in an E. coli based system in which E. coli are transformed with a phage vector construct containing a modified GLP-1RA with capsid knockout and a helper phage construct. The phage vector construct will be created utilizing MEGAWHOP with a custom DNA oligonucleotide and a covalently closed circular DNA form of the bacteriophage genome.

Product Architecture

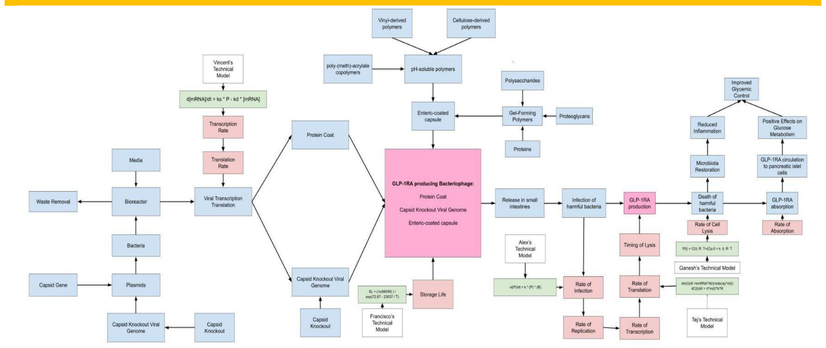

Figure 3. Product architecture is depicted with all subsystems relevant to the design.

Final Product Specifications

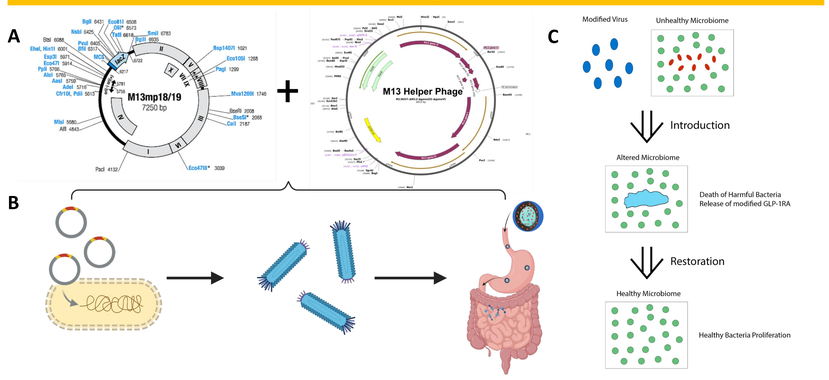

Figure 4. (A) Phage vector construct with the helper phage construct are introduced to an (B) E. coli host system that will produce functionally modified phages capable of GLP-1RA secretion in a single infectious cycle. The approach for clinical implementation is depicted with (C) engineered phage targeting of pro-inflammatory microbes implicated in T2DM, leading to restoration of the native gut microbiota.

Design Status and Future Work

After conducting market research, problem identification, concept generation, and concept screening, our team selected a GLP-1RA producing bacteriophage to be our most promising design. Our solution aims to treat Type 2 Diabetes Mellitus using an oral capsule containing engineered bacteriophages that will destroy pro-inflammatory bacteria within the human gut after utilizing their machinery to produce a modified GLP-1RA for absorption. Our team is currently performing technical modeling of critical product subsystems. After technical modeling has been completed, materials can be ordered and prototyping can begin. Finally, validation and verification of critical product specifications can be tested utilizing our prototype.

Acknowledgments

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