Preliminary study of efficacy and duration of an mRNA based GLP-1R agonist in diabetic monkeys

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BACKGROUND

HFG1 is an mRNA based GLP-1R agonist encoding a fusion protein of a GLP-1 analogue and a pH sensitive binder of human FcRn. The mRNA is encapsulated inside lipid nano-structures (LNPs) designed for subcutaneous gene delivery and local transfection, and the proteins expressed would be secreted and distributed into systemic circulation. In order to characterize the HFG1 activities in vivo, five monkeys with naturally occurred diabetes (FPG≥9.69 mg/dl, HbA1c≥5.6%) were selected to receive one subcutaneous injection of LNPs of slightly variable compositions containing about 0.5-1.0mg mRNA. The monkeys were closely monitored for 60 days and no behavior changes were observed except that they all had greatly reduced food uptake on the first few days after injection. By D56 they lost an average of 0.22kg each. Blood samples were collected at various time points and assayed in a GLP-1R/CRE Luciferase Reporter Cell system for GLP-1 equivalent activities. Figure 1 plotted the individual measurements (solid dots) and average value changes (solid line). The HbA1c% levels were assayed by Suzhou Xihua Scientific Co. and shown as open squares. Even though some time points are missing (TBD), the trend of HbA1c% reduction after a single HFG1 injection is significant.

METHODS

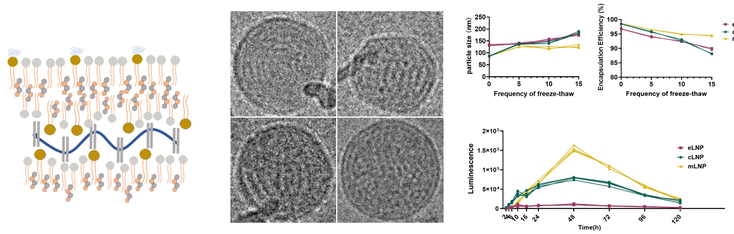

Figure 1. LNPs with membrane stabilized structures (mLNP) were developed. Unlike traditional LNPs for mRNA vaccination, mLNPs are more stable both under storage stress conditions and in physiological medium. The resulted transgene production is higher and longer lasting compared to other LNPs.

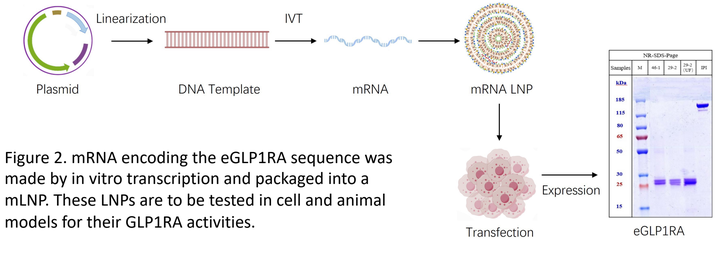

Figure 2. mRNA encoding the eGLP1RA sequence was made by in vitro transcription and packaged into a mLNP. These LNPs are to be tested in cell and animal models for their GLP1RA activities.

PRELIMINARY RESULTS

GLP1RA activities of the mRNA LNP transfection products

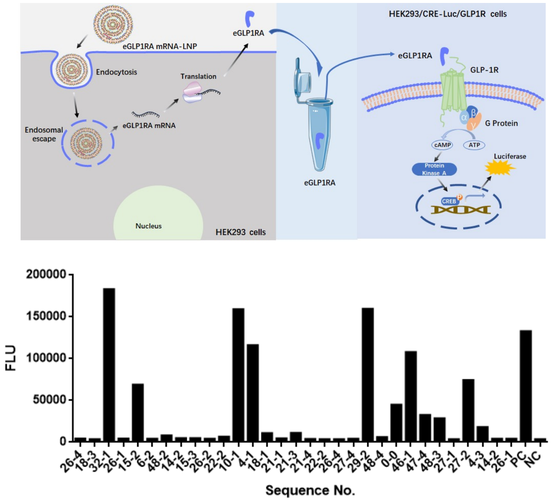

Figure 3. The various mRNA sequences were used to transfect HEK293 cells using mLNPs. The resulted gene products were tested for GLP1RA activities using a HEK293/CRE-Luc/GLP1R assay. The sequences with the highest activities were selected for further development.

Kinetics of mLNPs and the gene products after s.c. injection

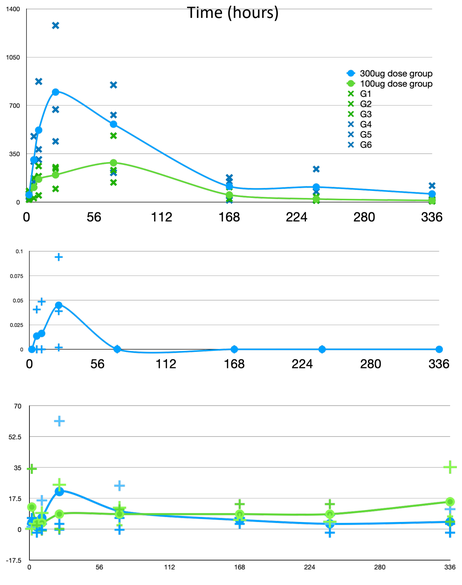

Figure 4. The mLNPs were administered by s.c. injection. There were two dose groups containing 3 monkeys each. G1-G3 received a 100ug mRNA dose (green dots and line) and G4-G6 received 300ug (blue dots and line). The plasma cationic lipid concentration (top figure), mRNA concentration (middle figure), and estimated eGLP1RA concentration (bottom figure) at various time points after injection were assayed and plotted. (Y axis marks are relative scale numbers that have not yet been validated.)

Longer term PK/PD observations after a single HFG1 injection

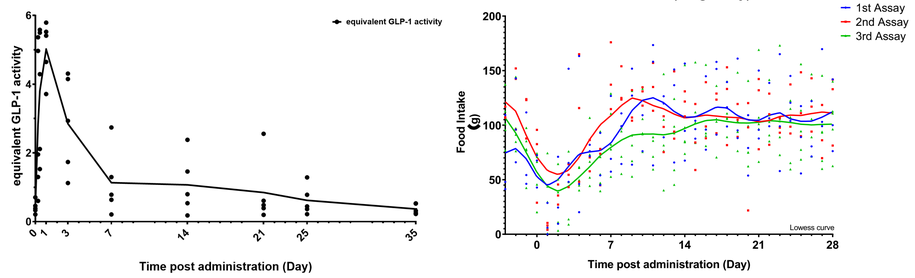

Figure 5. Blood samples were collected at various time points and assayed in a GLP-1R/CRE Luciferase Reporter Cell system for GLP-1 equivalent activities (left panel). Daily food consumption values were recorded (right panel).

Pharmacodynamics after multiple HFG1 injections

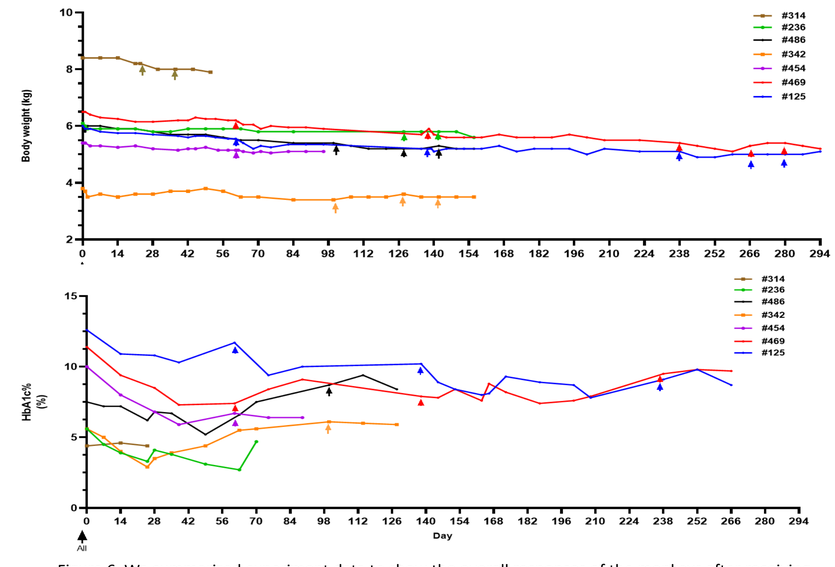

Figure 6. We summarized experiment data to show the overall responses of the monkeys after receiving multiple HFG1 injections. The different animals were color coded and the arrows indicated the time when injections were given.

DISCLOSURES

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