Novel Oral Small Molecule GLP1 Agonist Reduces Body Weight and Improves Glucose Control in DIO Mice

*David J Bearss[1], Chenyu Lin[1], Kyle Medley[1], Hariprasad Vankayalapati[1]
[1]Biolexis Therapeutics, Inc., Lehi, UT

obesityweek | The Obesity Society
November 3-6, 2024 • San Antonio
11/04/24 2:30-3:30 PM

ABSTRACT

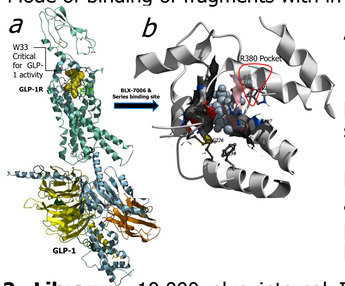
Background:
Oral, small-molecule agonists of the GLP-1 receptor hold significant promise for treating obesity and type 2 diabetes. By activating the GLP-1 receptor improved long-term outcomes for those living with obesity. They may also enhance patient compliance by eliminating the need for injections. We present key metabolic parameters in High-Fat Diet (HFD) Obese mouse models.

Methods
An Obese model was induced in C57BL/6J mice by providing a HFD for 17 weeks (60%) before treatment. Six groups, 10 mice per group were (vehicle, Orforglipron) dosed daily for 4 weeks. Body weight was measured 3 times weekly, and plasma metabolic parameters were measured at terminal 28th day. In-vitro studies includes 1. Ca^{2+} mobilization in Min6-c4 cells 2. cAMP accumulation 3. LANCE Ultra cAMP and 4. β-arrestin recruitment assays performed.

Results
BLX-7006 (26 pM in cAMP and 202 nM in Ca2+ influx assays) dosed for 4 weeks resulted in a dose-dependent reduction in body weight compared to vehicle doses. Dose-dependent decreases of key metabolic parameters by week 3, were significant for BLX-7006. Similarly, their sensitivity, fasting insulin, and fasting glucose was significant. Histological liver weight, liver triglyceride, lipid content, and fraction of hepatocytes presented.

MOLECULERN FRAGMENT-BASED DISCOVERY

1. Discovery of Oral Small Molecule GLP-1 Agonist - Structural Biology: Figure 1: (a) GLP-1R in complex with lead BLX-7006 and (b) Mode of binding of fragments with in catalytic GLP-1R (PDB ID: 6X1A).

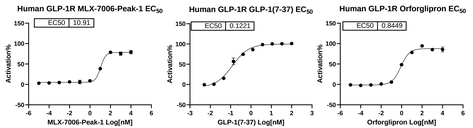


Approach: MolecuLern Fragment Library with the use of on-the-fly LigEdit computation at the polar/acid sites, privileged scaffold library search, properties, 1 ns MD, MMGBSA methods for binding energies/ΔΔG & in addition, generation of physiological conformational state by Quenched MD.

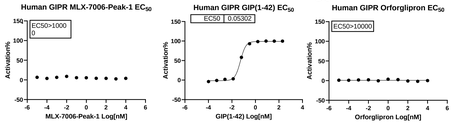
2. Library: 10,000 plus internal IP rich fragments (RO3) Library, 13,822 Synthesized NCEs (RO5) Library, 8.8 Million Biolexis Virtual NCE Library, Isoelectronic/Isosteric/Bioisosteric replacements mimicking hot-spot sites of GLP-1 catalytic site at W33, R380 and other key residues. On demand synthesis of 74 novel agents led to the identification of BLX-7006 – Orally available, developable, and clinically ready candidate.

IN VITRO RESULTS

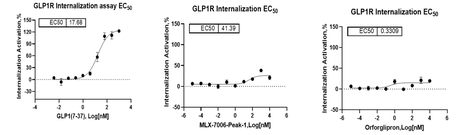
3. GLP-1R HTRF cAMP Assay EC_{50} GLP-1R CHO:



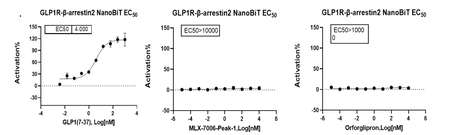
4 GIPR HTRF cAMP Assay EC_{50} GIPR CHO:



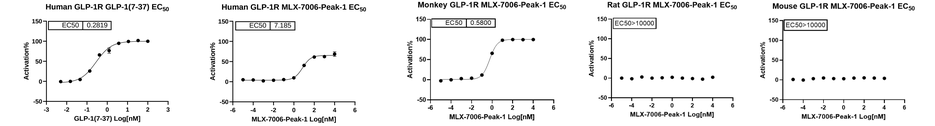
5. GLP1R Internalization Assay *(EC_{50} HEK293T GLP1R Turbo GFP)*:



6. GLP1R NanoBiT Assay *(EC_{50} HEK293T β-Arrestin2 GLP1R)*:



7. Human, Monkey, Rat & Mouse GLP-1R HTRF cAMP Assay EC_{50} GLP-1R CHO:



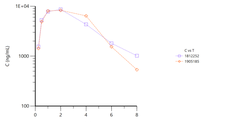
8. GLP-1R SPR binding Assay to assess the binding affinity to GLP-1R protein:

GLP-1R SPR Assay Results

Target	Compound ID	Kinetics						Affinity			
		ka (1/Ms)	kd (1/s)	KD (M)	KD (nM)	Rmax (RU)	Chi ^{2} (RU^2)	KD (M)	KD (nM)	Rmax (RU)	Chi ^{2} (RU^2)
GLP-1R	Semaglutide	1.15E+06	2.12E-01	1.84E-07	184.0	62.4	5.20E+01	1.36E-07	136.0	59.5	2.91E+00
	BLX-7006	3.18E+04	5.70E-03	1.79E-07	179.0	4.8	4.50E-01	7.30E-07	730.0	5.4	1.41E-01

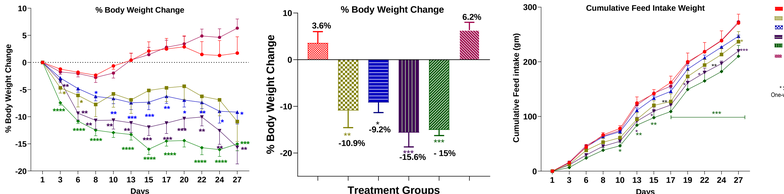
9. Oral Bioavailability Study of BLX-7006 in Cynomolgus Monkeys:

The C_{max} of BLX-7006 in plasma after single oral administration of 10 mg/kg (two monkeys) was 8650 ng/mL, 8290 ng/mL respectively. The AUC_{0-t} was 34503.8 ng·h/mL, 37119.8ng·h/mL. The C_{max} in plasma after intravenous administration of 5 mg/kg was 95000 ng/mL & AUC_{0-t} was 307241.5 ng·h/mL.

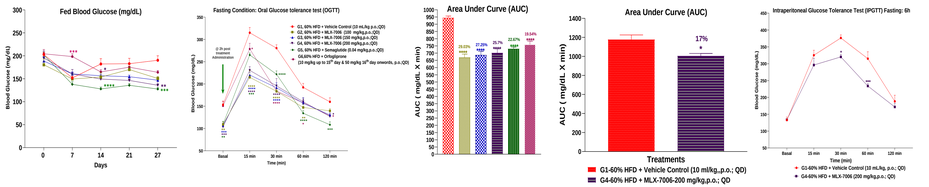


MOUSE DIO - EFFICACY RESULTS

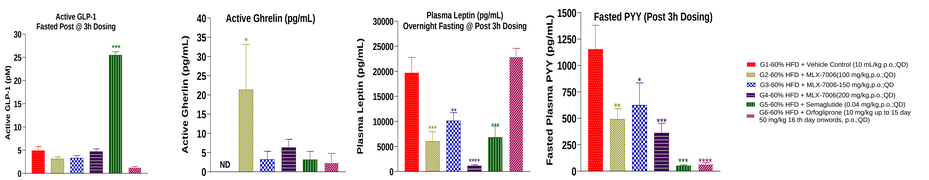
10. Results of % Body Weight Change & Cumulative Food Intake (g) of DIO Mice:



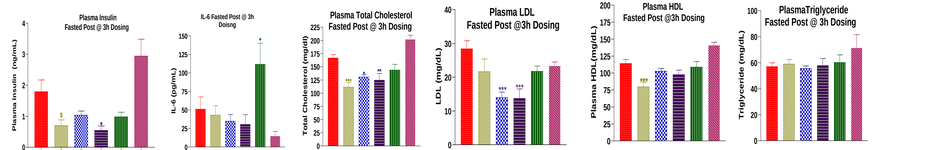
11. Fed/Fasting, OGTT, IVGT & AUC Results of DIO Study:



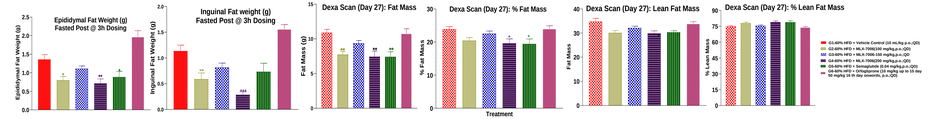
12. Active GLP-1, Ghrelin, Plasma Leptin and Fasted PYY:



13. Plasma Insulin, IL-6 & Metabolic Parameters of BLX-7006



14. Epididymal and Inguinal Fat Weights and Day 27th DEXA Scans



DISCUSSION AND CONCLUSIONS

- BLX-7006 showed on target efficacy in cAMP, Internalization, NanoBiT in cell, active in humans, primates and in cell free SPR binding assays.
- Significant exposure in mouse, rat, and NHP species with low CL and half-life greater than 3 hours.
- 28 days C57B/6 DIO mouse model study demonstrated significant % body weight changes greater than 15%, and consistent food intake effects across all dose groups were noted.
- DEXA Scan results on day 27 demonstrated significant changes in Epididymal and Inguinal fat weights, that are well correlated with % body weight changes.
- BLX-7006 effect was significant in reducing Plasma Leptin levels over Semaglutide.
- All metabolic parameters, OGTT, IVGT and AUCs results show significant dose dependent effect.
- BLX-7006 IND enabling studies are in progress with anticipated FIH trials in Q2, 2024.