Anti-diabetic/obesity agents

Technology Overview

- Anti-diabetic agent: Non systemic approach of GPR119 agonist
- Anti-obesity agent: TAZ modulator

Core Technologies

- Non-systemic GPR119 agonist (small molecule)
- - KRI60209: lead compound, good in vitro potency, in vivo acute efficacy
- non-systemic property, druggability, toxicity profile
- TAZ modulator (small molecule)
- - KR64105: lead compound, good in vitro anti-adipogenic effect, drugability,
- in vivo efficacy

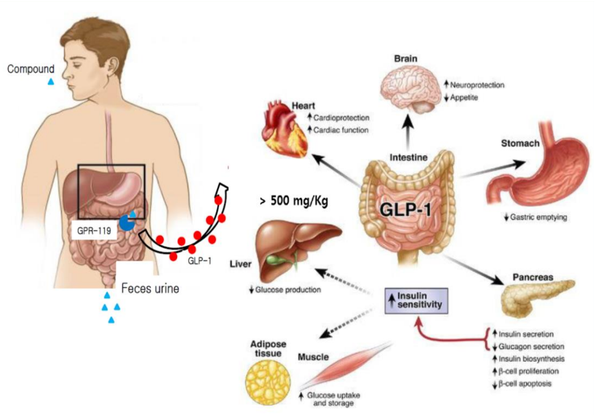
Application Area and Advantages

- Non-systemic GPR119 agonist : anti-diabetes
- TAZ modulator: anti obesity/diabetes

Accomplishments

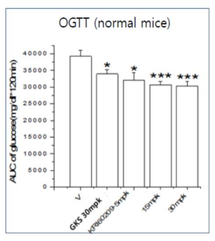
- Strong IP Portfolios
- Looking for licensing & collaborative research opportunities

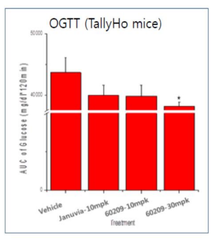
Non systemic GPR119 strategy



Scaffold 1

KR-code	In vitro activity (EC50 value)	Liver Microsomal Stability (% remaining after 30 min)	CYP (5 subtypes) % inh at 10 uM	hERG (binding)
KRI60209	14 nM	Human 99%	1A2= 8.2 %, 2C9 =56.2 % 2C19 =0.0 % 2D6 =6.5 %, 3A4 =0.0 %	21.3% inhibition at 10 uM
Stability (37°C, 24 hr, Water)	**Solubility (equilibrium)**	**PAMPA Permeability**	**LD50 in ICR mice**	
99 %	20uM in FeSSIF (simulated intestinal fluid in fed state)	5.12± 0.157 (grade : low) Suitable for non systemic approach	> 500 mg/Kg	





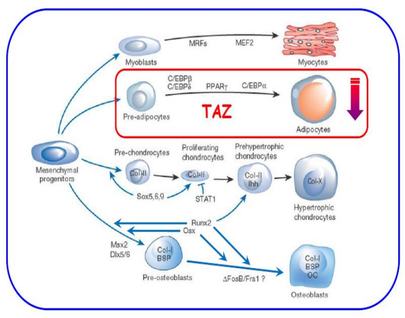
In vivo PK in rat

Table 1. Pharmacokinetic parameters in male rats

Parameters	IV, 5 mg/kg	PO, 5 mg/kg
T_{max} (hr)	-	1.33 ± 0.577
C_{max} (μg/mL)	-	0.0143 ± 0.0117
$T_{1/2}$ (hr)	4.22 ± 3.05	4.65 ± 2.72
AUC$_t$ (μg·hr/mL)	7.01 ± 3.17	0.114 ± 0.0795
AUC$_\infty$ (μg·hr/mL)	7.15 ± 3.5	0.135 ± 0.0759
CL (L/kg/hr)	0.809 ± 0.395	-
V_d (L/kg)	1.03 ± 0.418	-
F (%)	-	1.63

TAZ: Transcriptional Co-Activator with PDZ-Binding Motif

- Original articles: *Science* **2005**, *309*, 1074; *Brit J Pharmacol* **2012**, *165*, 1584



- The transcriptional co-activator with PDZ-binding motif (TAZ) is characterized as a transcriptional modulator of mesenchymal stem cell differentiation into osteoblasts and adipocytes.
- Increased TAZ activity in the nucleus suppresses adipocyte development

➡ Small molecule TAZ modulator could be anti-obesity drug candidate

TAZ modulator KR64105 (in vitro, in vivo efficacy)

KRI64105				
structure	In vitro activity Anti-adipogenic effect 3T3L1	Liver microsomal stability 30 min incub.	hERG (Patch clamp)	Permeability (PAMPA)
	active	>99.9 (h) 86 (m)	IC_{50} = 79 uM	4.42±0.243 (medium)
Cytotoxicity (IC_{50} (uM))	Micronucleus, Chromosomal aberration	PK (10 mpk, rat)	In vivo efficacy (long term, DIO) 50 mpk, 8주	In vivo efficacy (long term, DIO) 50 mpk
NIH 3T3: = 35.6 L929: = 33.1 VERO: = 36.6 HFL-1: = 76.2 CHO-K1: = 38.9	negative	$T_{1/2}$ 37.3 h AUC 2.36 (ug.hr/mL) CL 0.09 (L/kg/hr) F = 52 %	Weight gain reduction (> 10%)	(OGTT, ITT) OGTT (AUC reduction) ITT (AUC reduction)

○ In vivo long term study 50 mpk, 10 weeks in DIO model