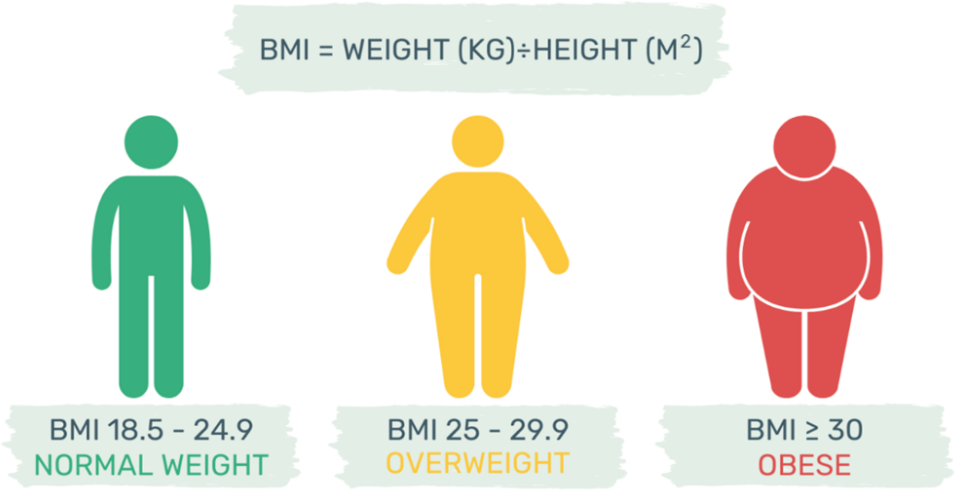
NK2R control of energy expenditure and feeding to treat metabolic diseases

Gerhart-Hines, Z. et al. Nature 2024, 635 (8040), 987–1000.

Liwenting

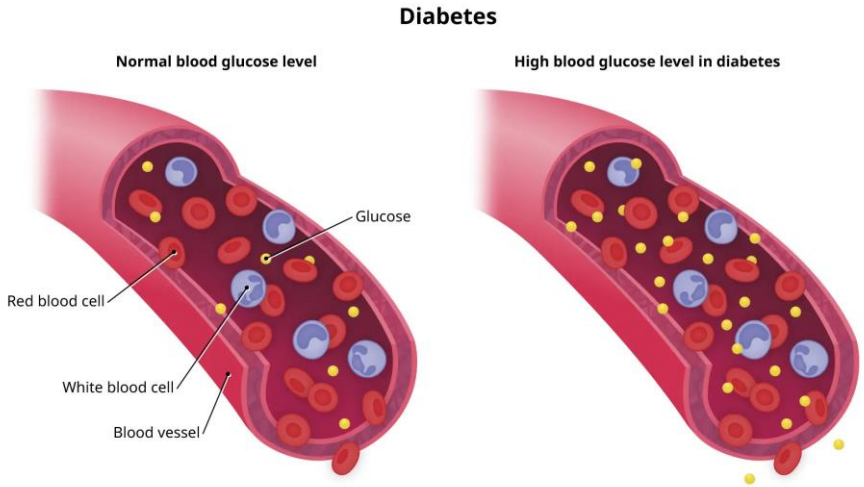
20250118

Background： The relationship between Obesity and Diabetes



Obesity

Insulin Resistance

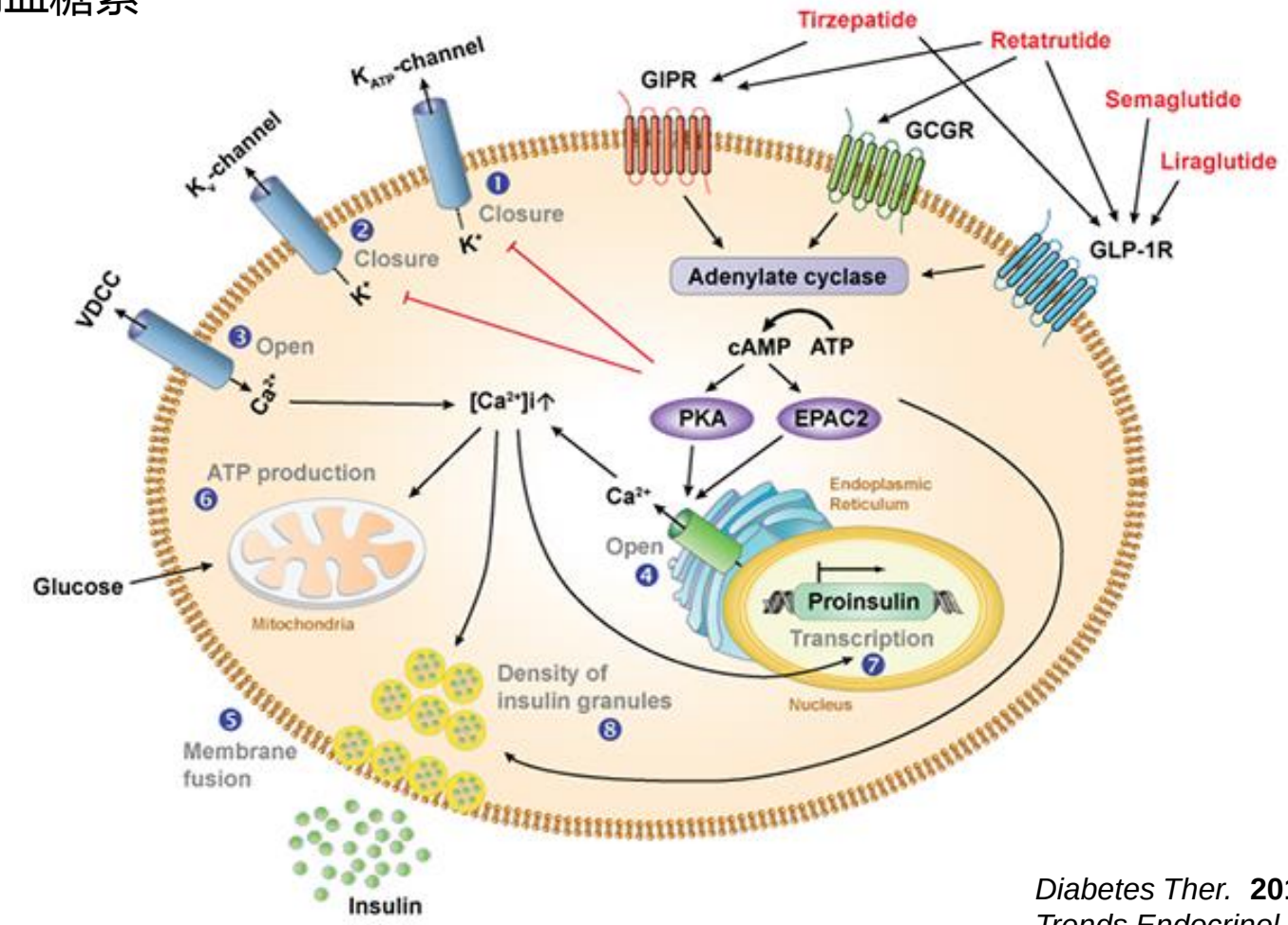


Diabetes
Type 2 Diabetes Mellitus（T2DM）

https://www.gleneagles.com.sg/conditions-diseases/diabetes/symptoms-causes

Background： Targeting GLP-1, GIP & GCG in Obesity and T2DM

- GLP-1（Glucagon-Like Peptide-1）,肠促胰岛素类激素
- GIP（Gastric Inhibitory Polypeptide） ,肠促胰岛素类激素
- GCG（Glucagon）,胰高血糖素



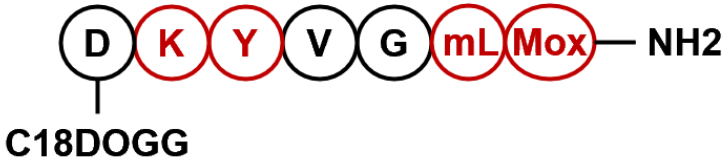
Diabetes Ther. **2019**, 10, 1645
Trends Endocrinol. Metab. **2020**, 31, 410

数据库
遗传筛选

NK2R

NK2R Agonists的开发

EB0002



NK2R Agonists核心特点

1. 提高能量消耗与抑制食欲的双重作用
2. 增强胰岛素敏感性
3.NK2R激动剂的临床前疗效和安全性评估

NK2R Agonists作用机理

1. EB1002激活NK2R的外周作用主要体现在能量消耗和胰岛素敏感性的改善。
2. EB1002 激活中枢机制主要通过DVC区域中的孤束核（NTS）调控食欲，并发现Glu3神经元对EB1002的响应最为敏感。
3. NK2R激动剂通过中枢多个神经元网络的协调作用，实现对食欲和代谢的系统性调控。

Results： Genetics of NK2R

Database:

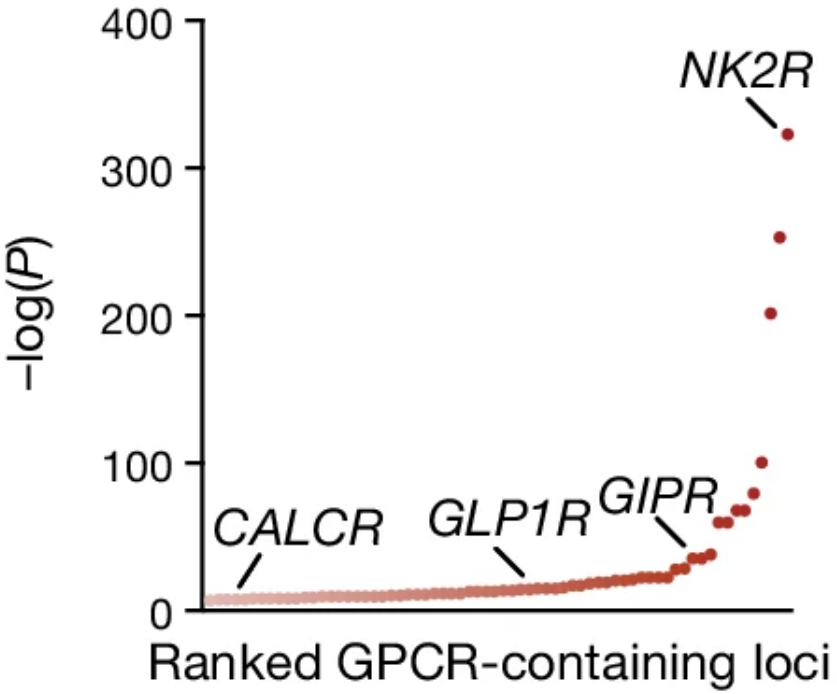
T2D-KP

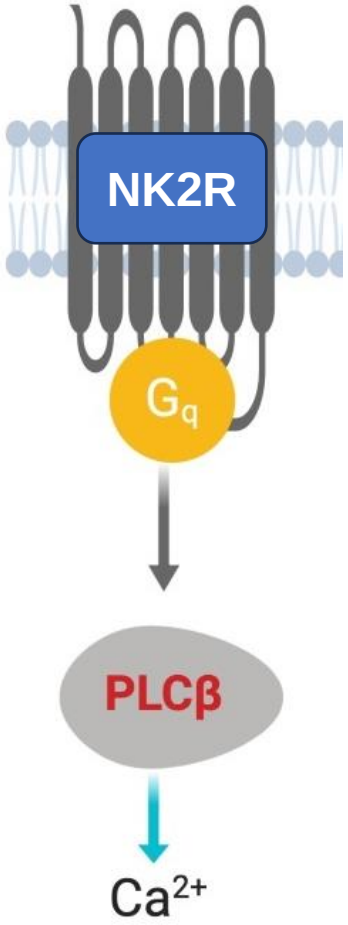
(HugeAMP Type 2

Diabetes Knowledge Portal)

Methods:

筛选与HbA1c水平显著相关的380多个非嗅觉类的GPCR基因





糖化血红蛋白 (HbA1c) 水平是血糖控制和糖尿病进展的主要临床指标。

https://encyclopedia.pub/entry/2907

Results： Genetics of NK2R

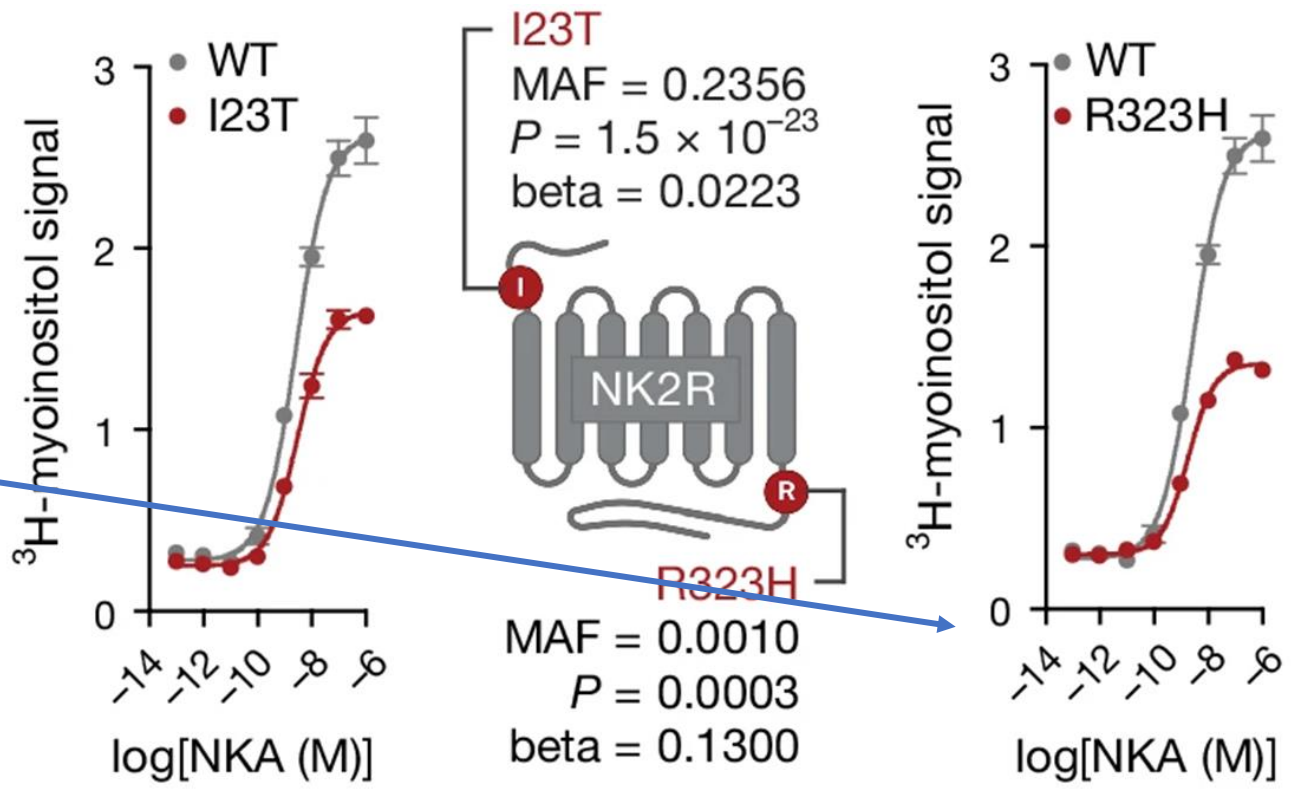
Four missense variants：

I23T (rs5030920; MAF = 23.6%)

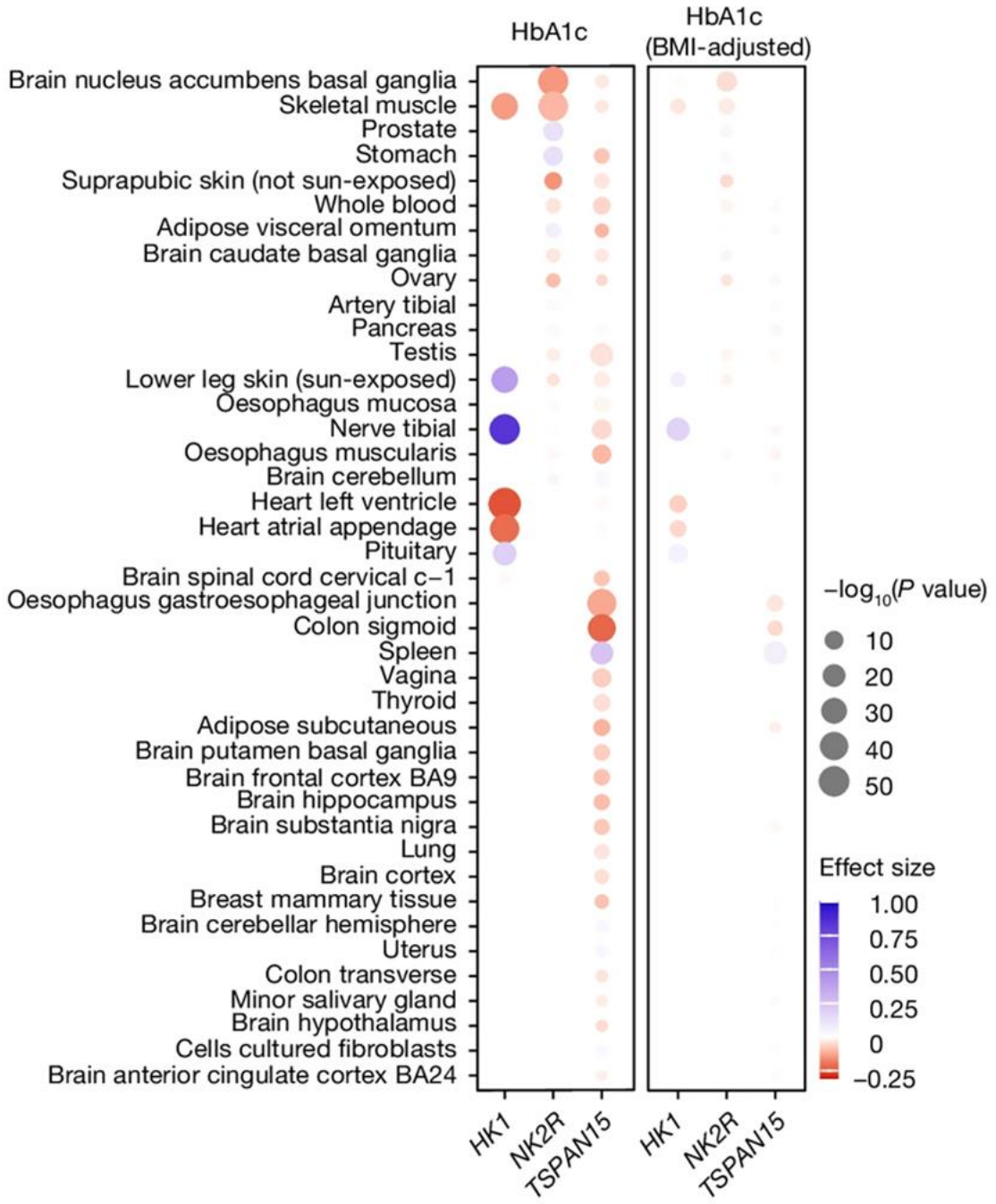
R323H (rs61732393; MAF = 0.10%)

V54I (rs151093941; MAF = 0.025%)

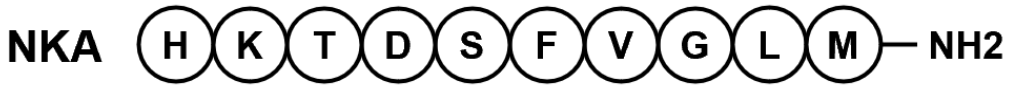
A161T (rs148031991; MAF = 0.102%)

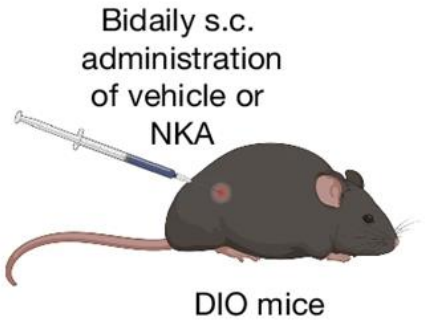


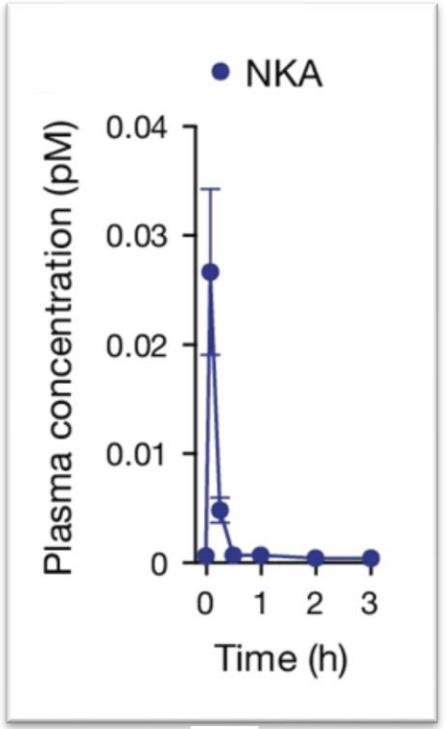
Results： Genetics of NK2R

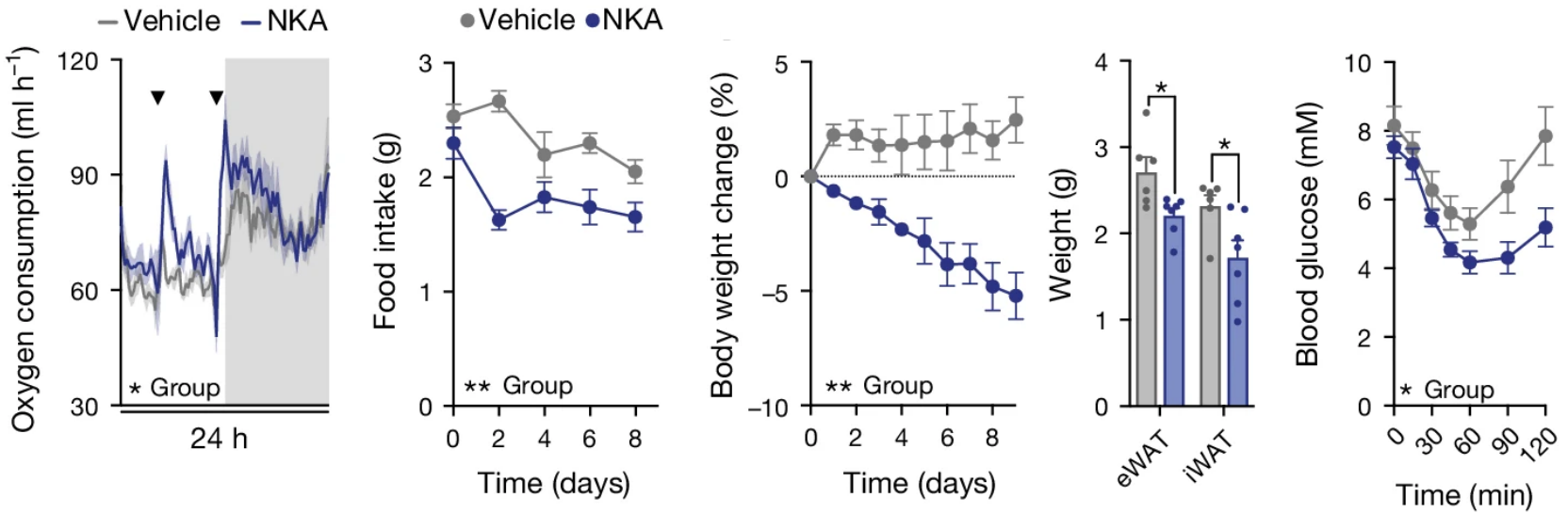


Results： Development of NK2R Agonists

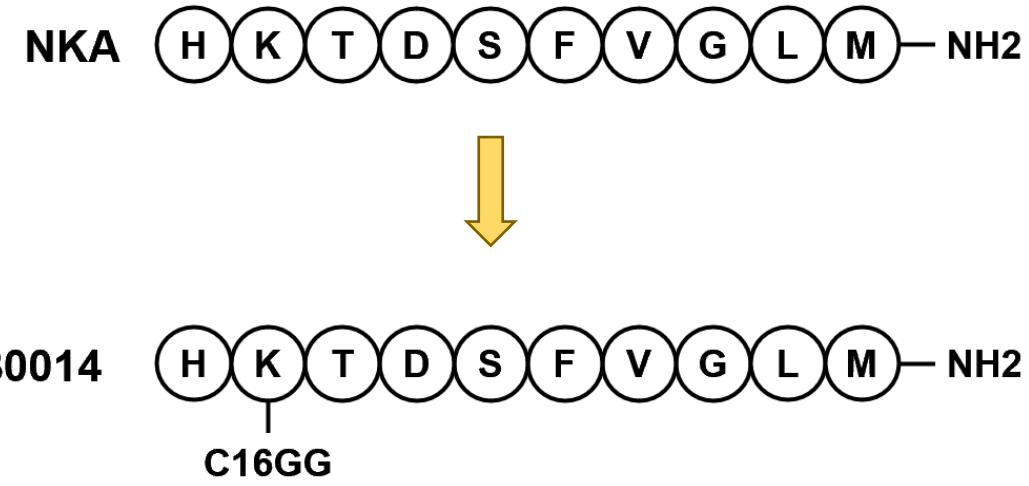




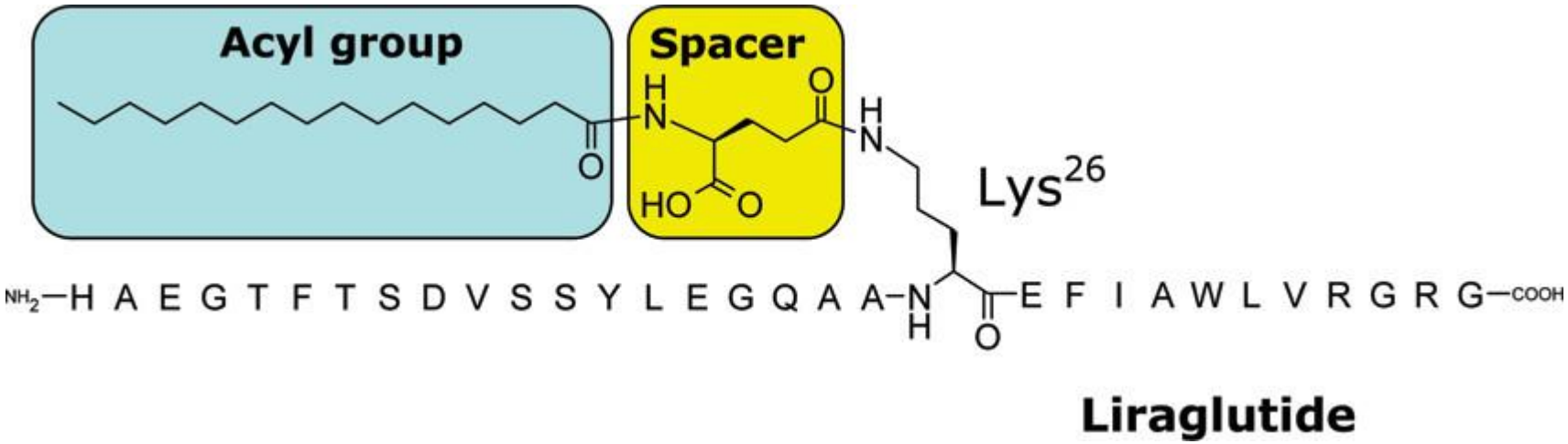




Results： Development of NK2R Agonists

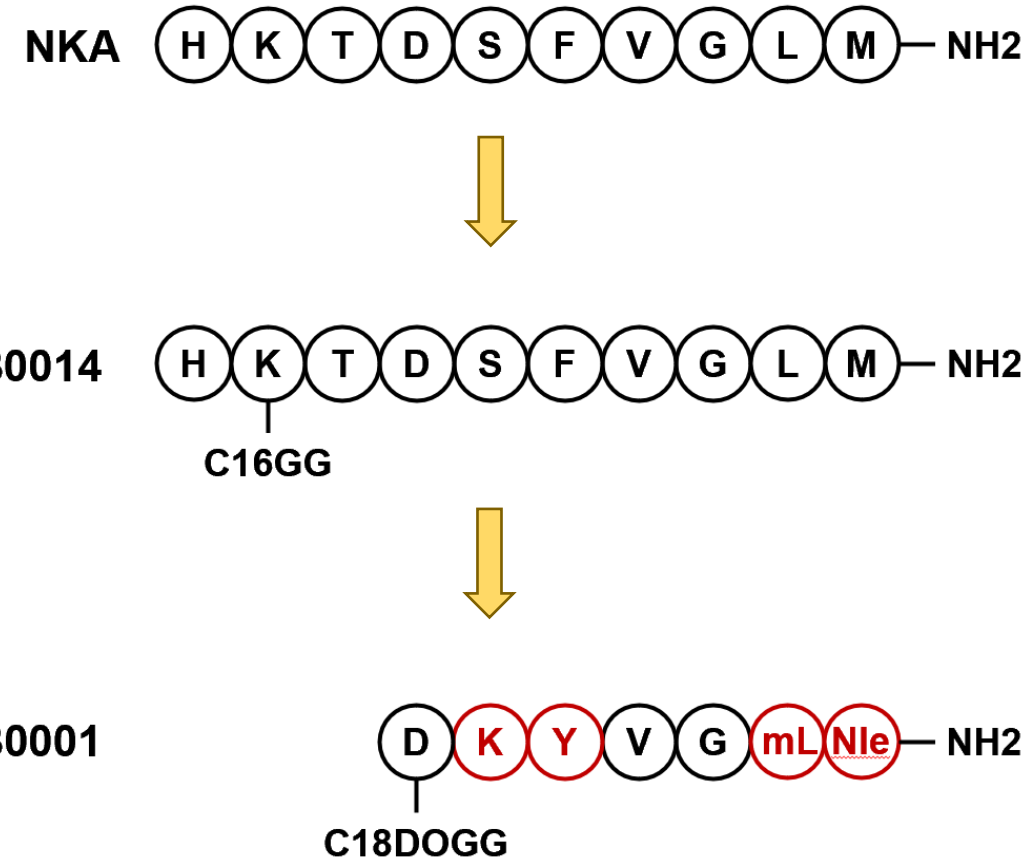


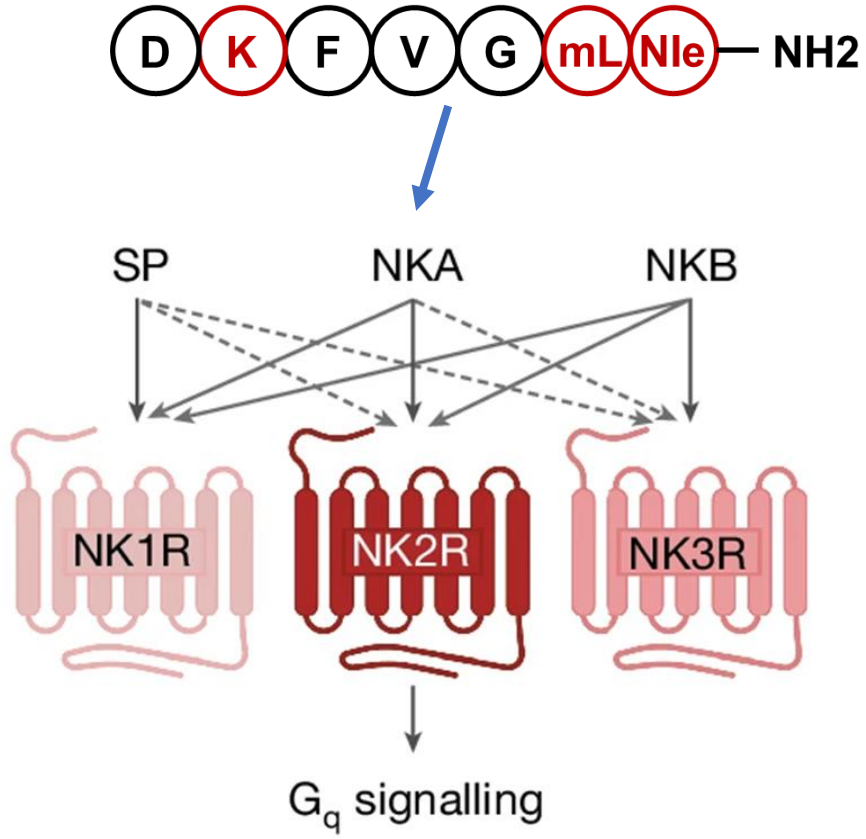
Transient loose stools

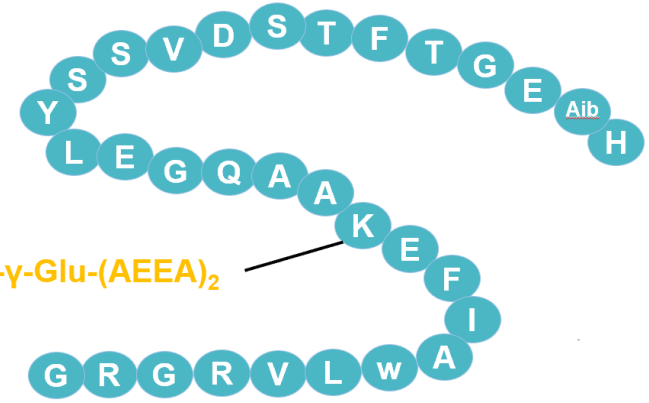


Liraglutide

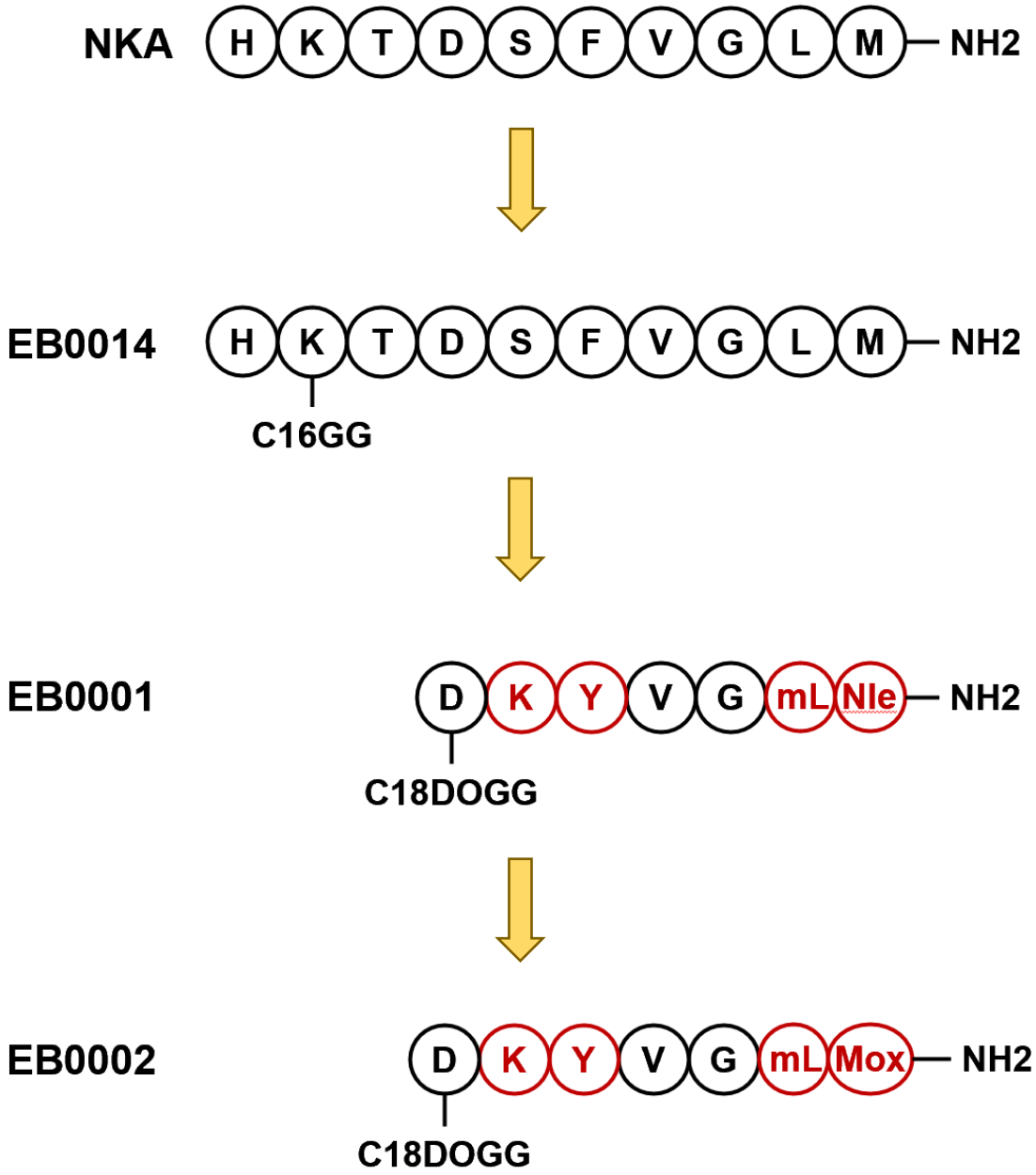
Results： Development of NK2R Agonists

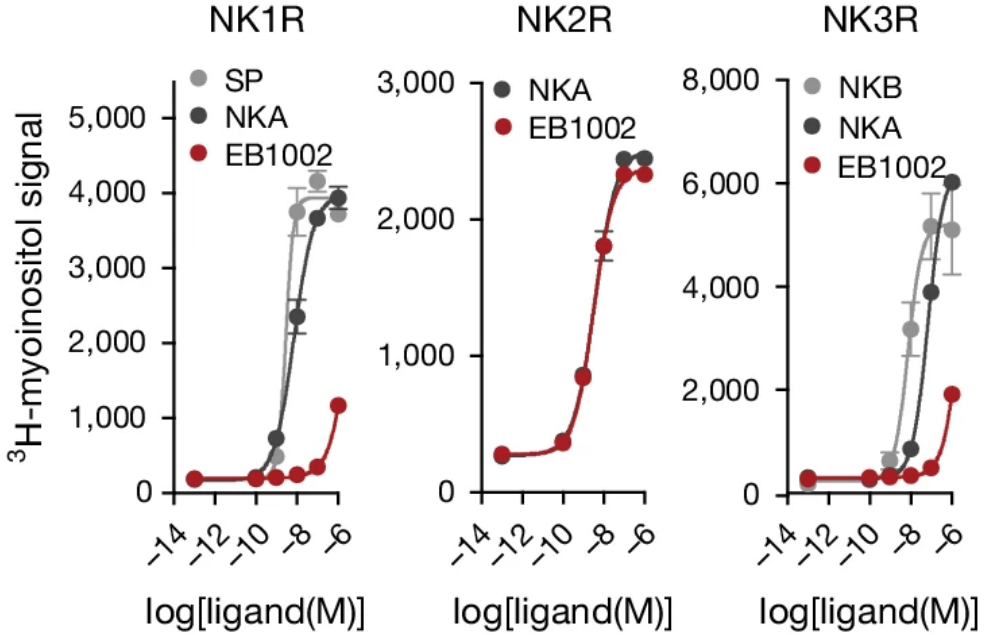


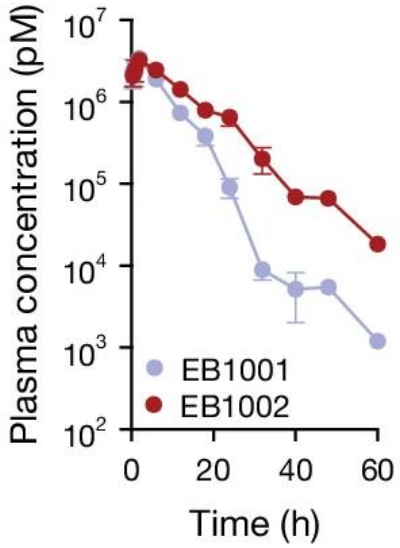




Results： Development of NK2R Agonists







Results： Biological Activity of NK2R Agonists

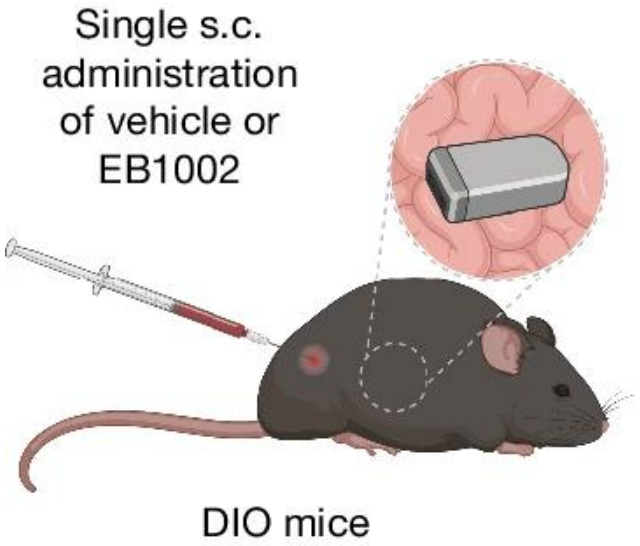
NK2R Agonists

1. 提高能量消耗与抑制食欲的双重作用

氧消耗量
Oxygen consumption ↑

脂肪酸氧化
Fatty acid oxidation ↑

核心体温
Body temperature ↑



呼吸交换比率
(RER) ↓

食物摄入量
Food intake ↓

NK2R KO ✗

NK2R antagonist- Saredutant ✗

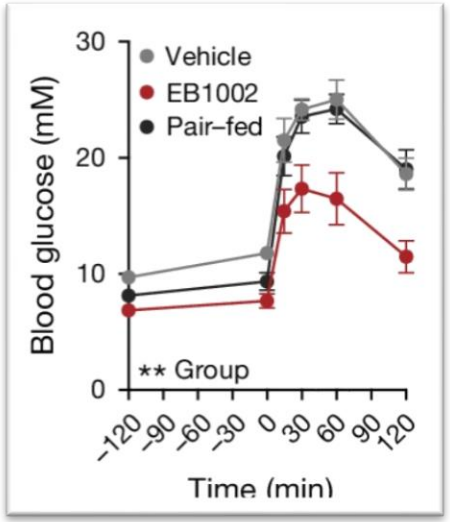
Results： Biological Activity of NK2R Agonists

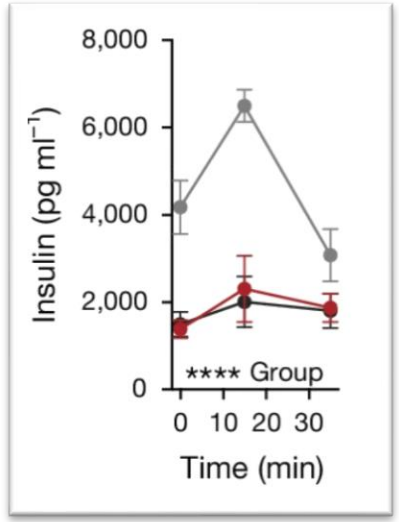
NK2R Agonists

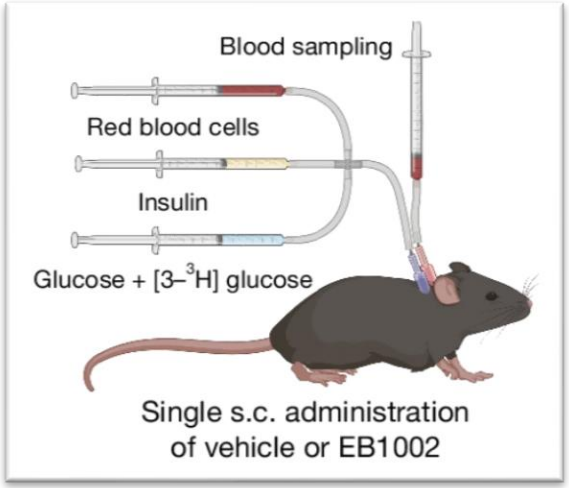
1. 提高能量消耗与抑制食欲的双重作用

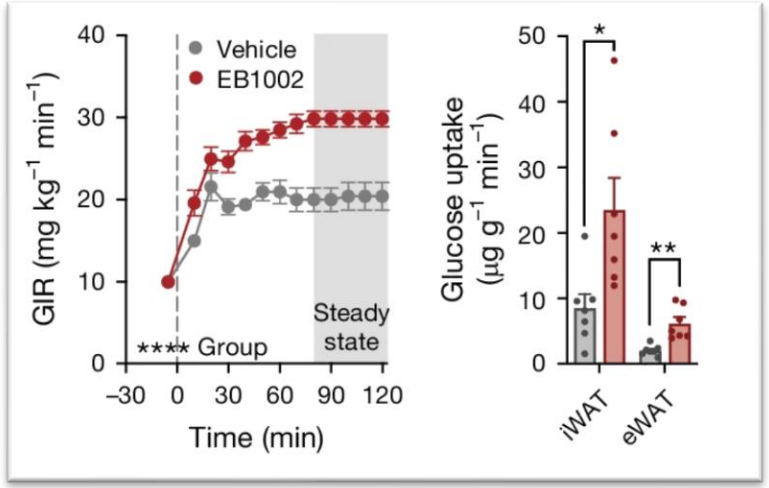
2. 增强胰岛素敏感性

- 配对喂养实验 (pair-feeding)
- 高胰岛素正常血糖钳夹研究 (hyperinsulinaemiceuglycaemic clamp study)





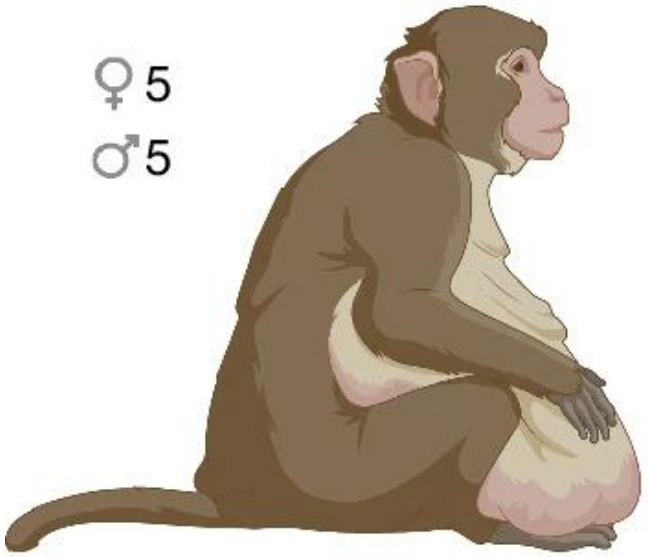




Results： Biological Activity of NK2R Agonists

NK2R Agonists

1. **提高能量消耗与抑制食欲的双重作用**
2. **增强胰岛素敏感性**
3. **NK2R激动剂的临床前疗效和安全性评估**



最高剂量 480 nmol/kg

体重

食物摄入量

空腹血糖浓度

胰岛素水平

甘油三酯

总胆固醇和LDL

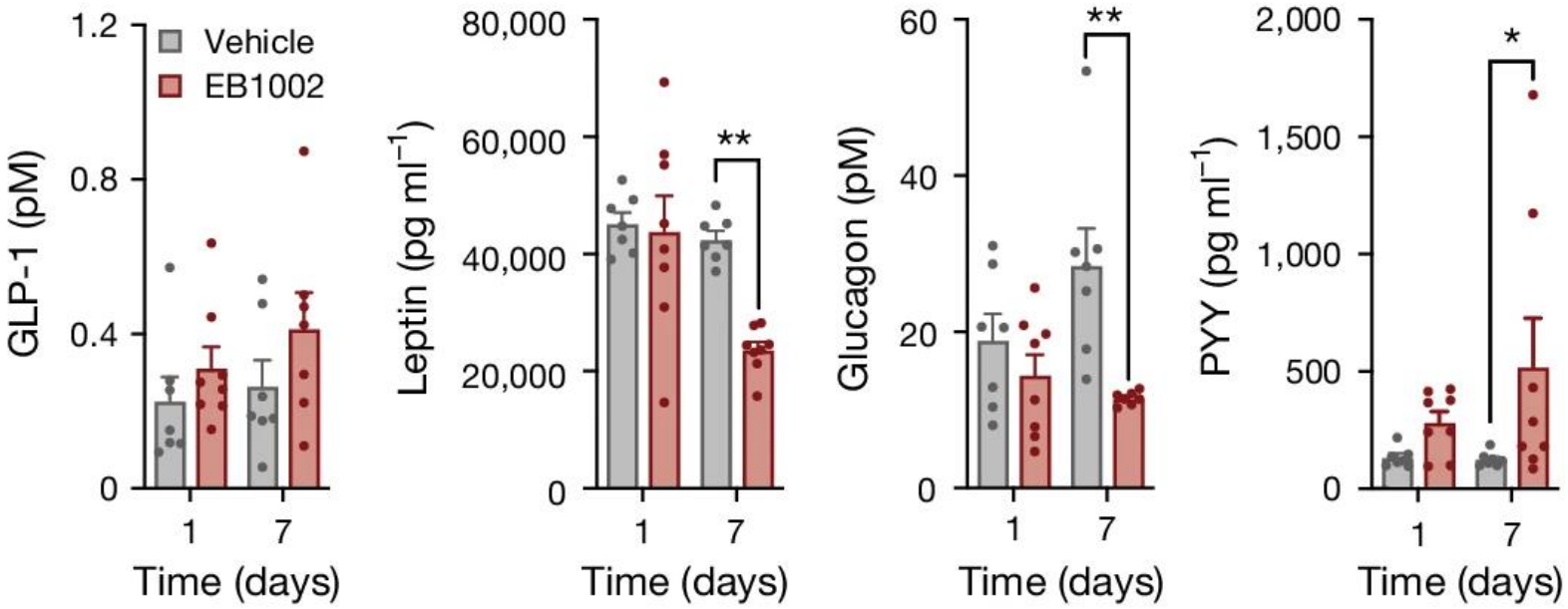
无恶心、呕吐或者腹泻

未出现焦虑或焦虑样行为

心肺、肝脏、肾脏安全

Results： Mechanism of Action of NK2R Agonists (Energy homeostasis)

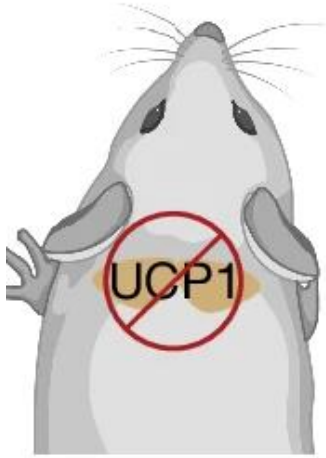
1. EB1002可能通过多种途径改善全身代谢健康



Results： Mechanism of Action of NK2R Agonists (Energy homeostasis)

1. EB1002可能通过多种途径改善全身代谢健康

2. EB1002诱导的代谢改善独立于典型的棕色脂肪活性



氧消耗量
Oxygen consumption

脂肪酸氧化
Fatty acid oxidation

核心体温
Body temperature

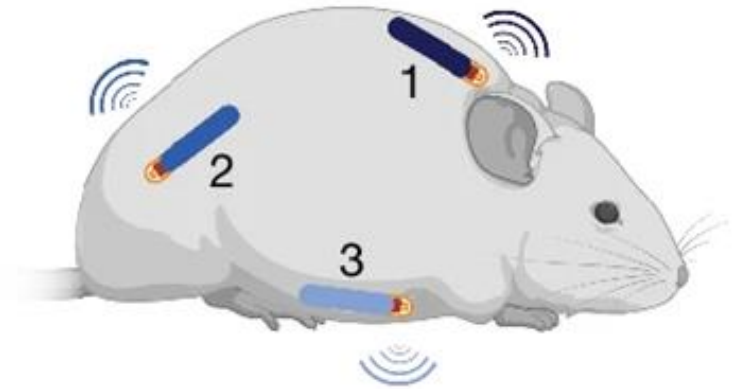
呼吸交换比率
(RER)

食物摄入量
Food intake

Results： Mechanism of Action of NK2R Agonists (Energy homeostasis)

EB1002诱导的代谢改善独立于典型的棕色脂肪活性，而是由多组织参与的动态能量消耗驱动。

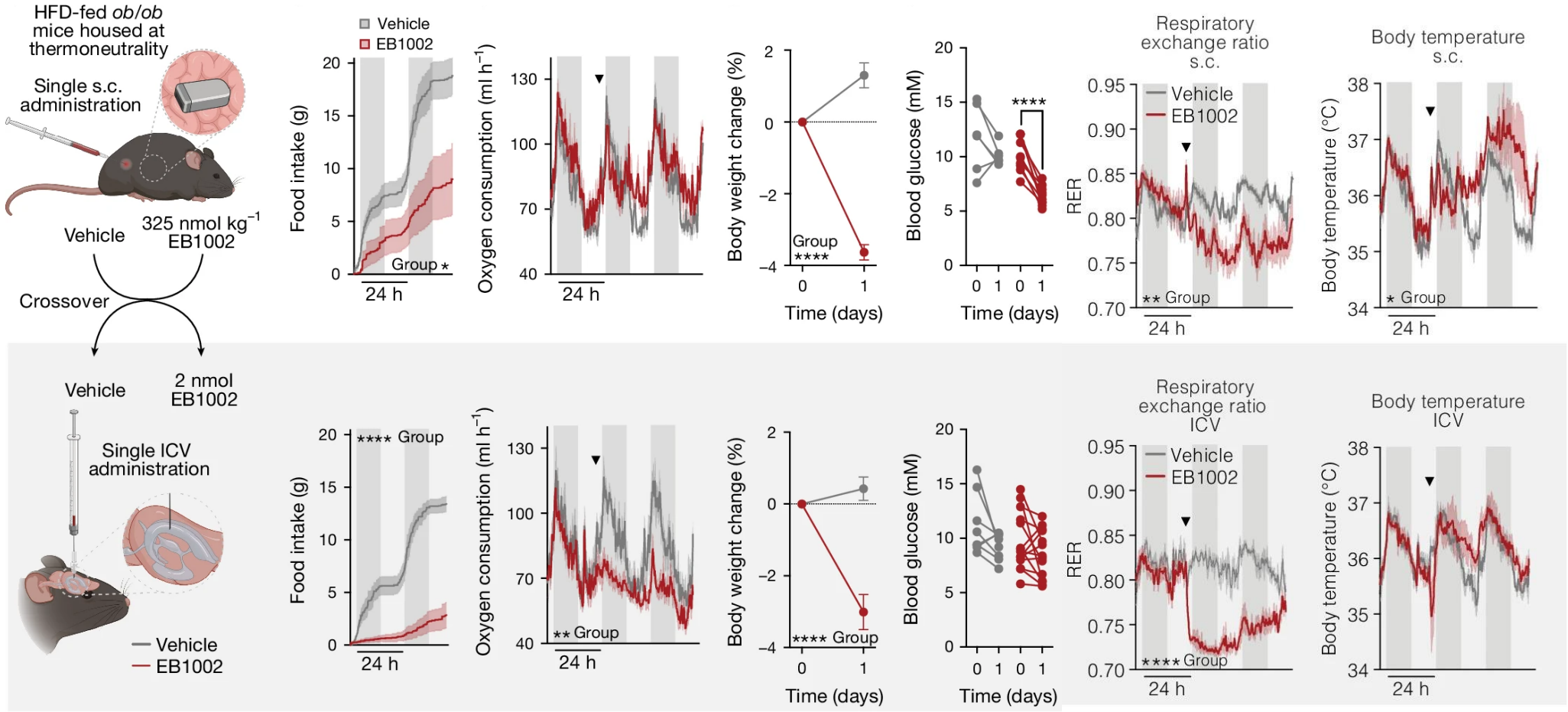
1. **EB1002可能通过多种途径改善全身代谢健康**
2. **EB1002诱导的代谢改善独立于典型的棕色脂肪活性**
3. **EB1002显著提高了肩胛骨间和后肢区域的温度，而腹部温度在药效结束前逐渐下降。**



Female DIO mice

Results： NK2R agonism in the CNS and periphery

1. EB1002激活NK2R的外周作用主要体现在能量消耗和胰岛素敏感性的改善。



Results： NK2R agonism in the CNS and periphery

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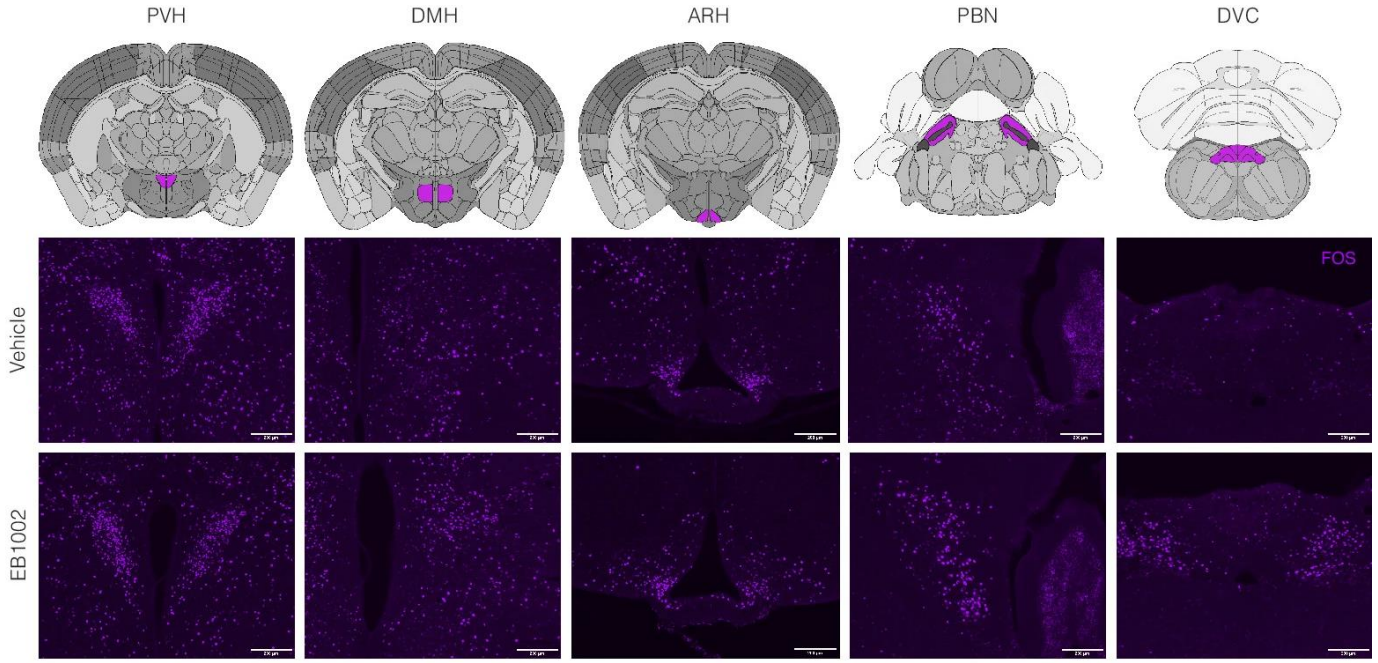
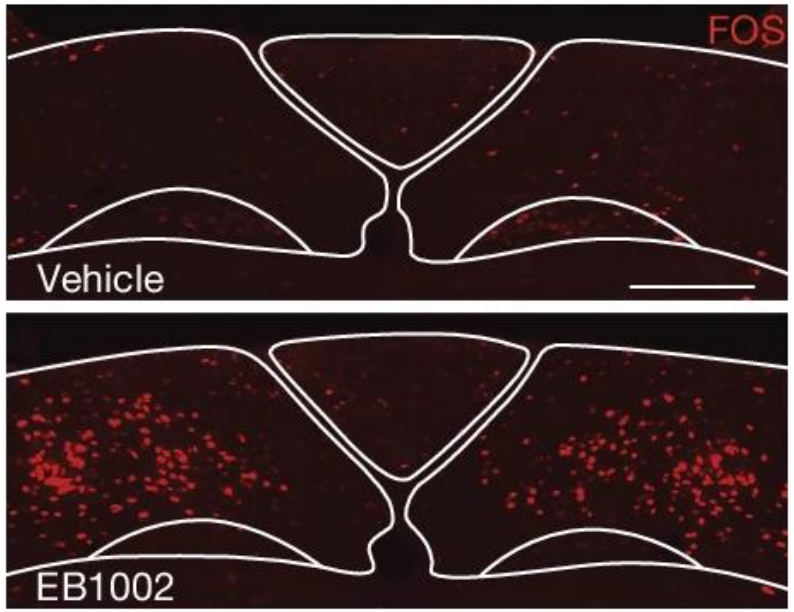
2. EB1002 激活中枢机制主要通过DVC区域中的孤束核（NTS）调控食欲，并发现Glu3神经元对EB1002的响应最为敏感。





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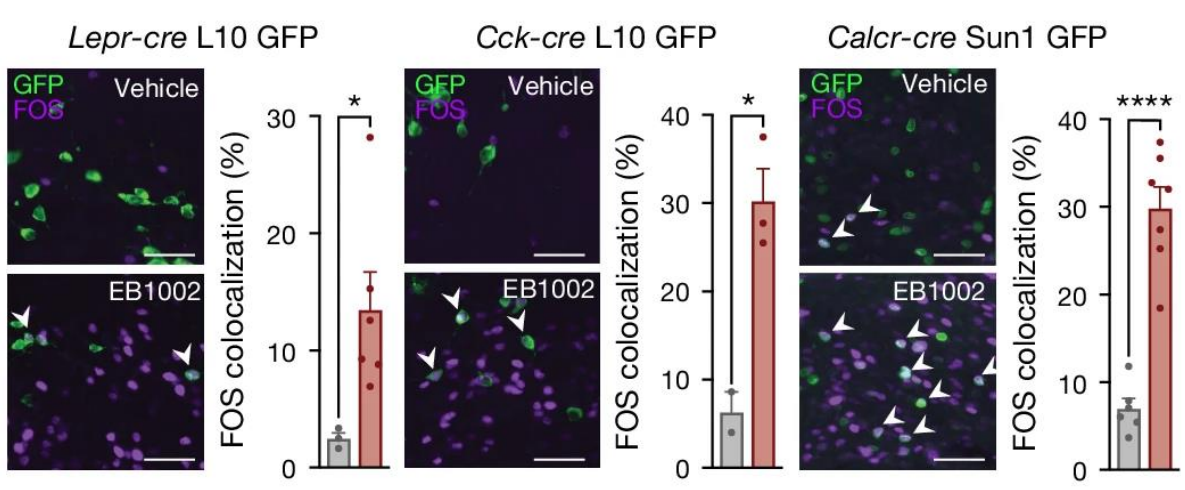

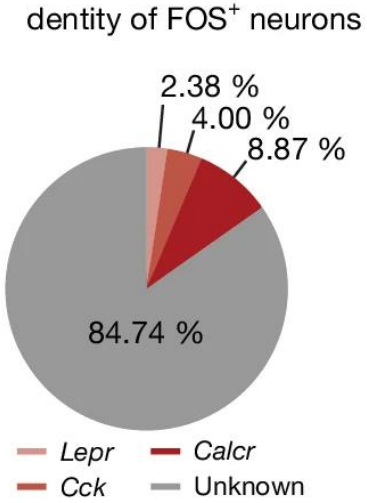

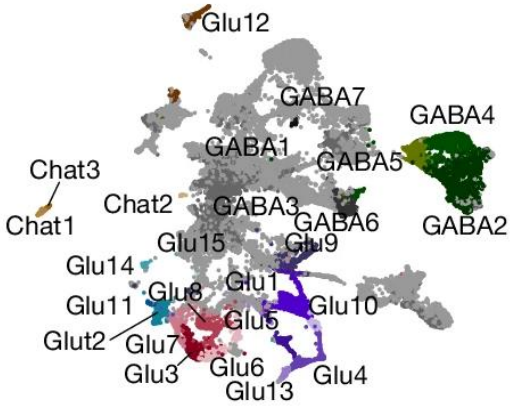

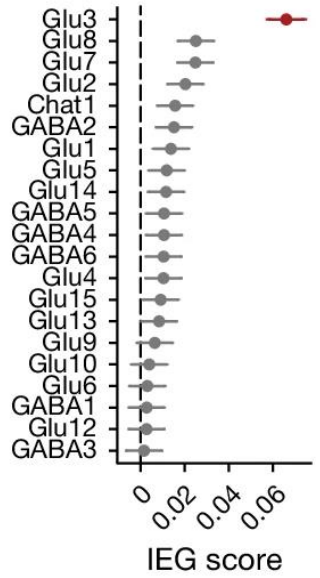

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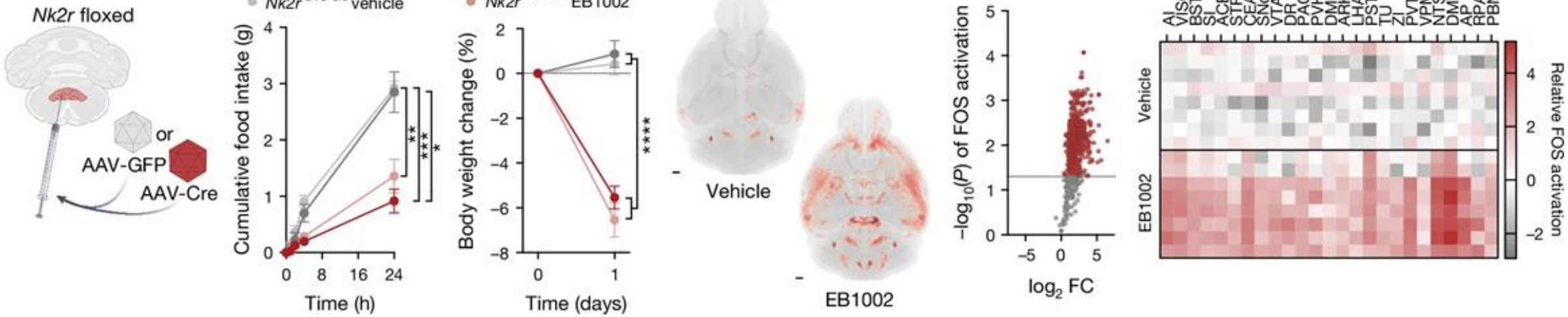

Zach Gerhart-Hines
丹麦NNF基础代谢研究中心

Zach Gerhart-Hines实验室的研究成果已经催生了三家生物技术公司的成立——Embark Biotech、Embark Laboratories 和 Incipiam Pharma。

2023 年8月，Embark Biotech 被诺和诺德以高达 4.56 亿欧元收购，并与新成立的 Embark Laboratories 的团队建立为期三年的合作关系，旨在开发针对心脏代谢疾病的下一代疗法。

Thanks For Your Attention!