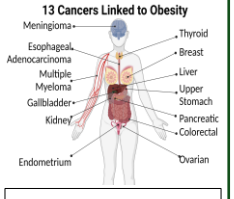
Triple incretin receptor agonist induced weight loss delays tumor latency in obesity-associated breast cancer

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Introduction

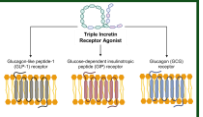
- Obesity increases risk of multiple cancers, including breast cancer (BC).
- Weight loss strategies like bariatric surgery reduce the risk of obesity-associated cancers
- GLP-1R agonists are widely used weight loss dugs.
- GLP-1R agonists promote weight loss, improve metabolic dysfunction, reduce risk and progression in pancreatic and lung cancer[1].
- The effects of GLP-1R agonists on spontaneous BC are unknown.



[1]Marathe et al., 2025 *npj Metabolic Health And Disease*

Hypothesis

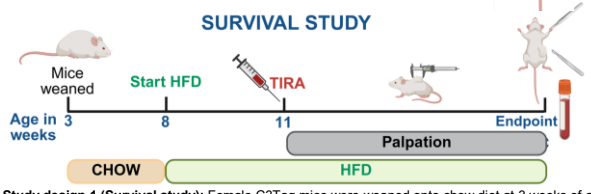
Incretin-agonism induced weight loss by triple incretin receptor agonist (TIRA) will delay tumor latency in a pre-clinical murine model of BC.



Methods and study design

Pre-clinical mouse model of BC
C3(1)-Tantigen ("C3Tag")
Genetically Engineered Mouse Model (**GEMM**)
Background strain FVB/N
Develop spontaneous BC





Study design 1 (Survival study): Female C3Tag mice were weaned onto chow diet at 3 weeks of age and were fed 60% high fat diet (HFD) starting at 8 weeks of age. At week 11, the mice were randomized by average body weight and injected subcutaneously with vehicle (VEH) or triple incretin receptor agonist (TIRA, 15 nmol/Kg BW) every other day. A control group of mice was weight matched (WM) to TIRA-mediated weight loss by caloric restriction. All mice remained on HFD. Mice were palpated every other day to record tumor latency and progression until IACUC defined endpoint.

TIRA induced weight loss long term and improved hyperglycemia

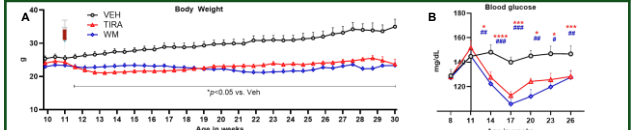


Figure 1: TIRA induced long term weight loss and improved metabolic dysfunction. (A) VEH mice increased body weight throughout the course of HFD feeding. TIRA-injected mice showed significant weight loss through week 11 to 14, after which BW stabilized. BW in WM mice closely matched TIRA mice by design. (B) Blood glucose (4- hour fasted) was reduced in TIRA and WM mice vs. VEH mice. n = 12 per group. Data is shown as Mean ± SEM with two-way ANOVA with Fisher's LSD test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$.

TIRA reduced adiposity while maintaining muscle mass

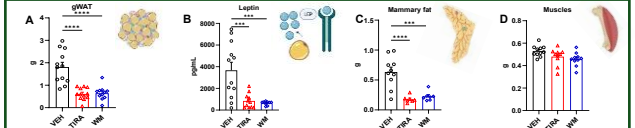


Figure 2: TIRA reduced adipose tissue while preserving lean mass in long term exposure. (A) Gonadal white adipose tissue (gWAT), (B) leptin, and (C) mammary fat pad was reduced in TIRA and WM mice vs. VEH mice. (D) Pooled muscle mass was not affected. Data is shown as Mean ± SEM with one-way ANOVA with Posthoc Tukey test. ***$p < 0.001$, ****$p < 0.0001$.

TIRA delayed tumor latency

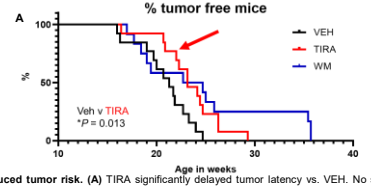


Figure 3: TIRA reduced tumor risk. (A) TIRA significantly delayed tumor latency vs. VEH. No significant difference was observed between WM vs VEH or TIRA mice. Logrank (Mantel-Cox) test. *$p < 0.05$.

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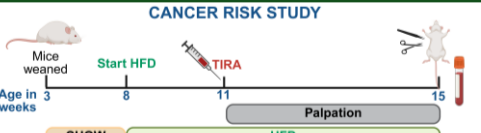
Questions?
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This poster contains unpublished data.

Study design- Cancer risk & Pre-neoplasia



Study design 2 (Risk study): The study design for risk evaluation is identical to study design 1 for survival except that sacrifice occurred at week 15 (a time point prior to average tumor latency when mice have attained stabilized BW)

TIRA induced weight loss, improves hyperglycemia, and reduces adiposity

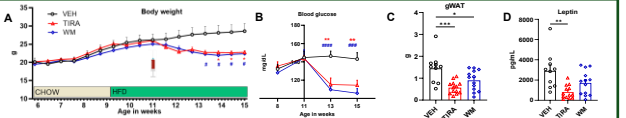


Figure 4: TIRA induced short term weight loss and improved metabolic dysfunction. (A) Body weight in VEH mice increased over time throughout the course of HFD feeding. The TIRA injected mice showed significant weight loss through week 11 to 15 compared to VEH. BW in WM mice was matched to TIRA mice by design. (B) Blood glucose (4- hour fasted) was reduced in TIRA and WM mice as compared to VEH mice. n = 10-12 per group. Data is shown as Mean ± SEM with two-way ANOVA with Fisher's LSD test. (C) Gonadal white adipose tissue (gWAT) and (D) leptin were reduced in TIRA and WM vs. VEH. Data is shown as Mean ± SEM with one-way ANOVA with Posthoc Tukey test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$.

TIRA reduced circulating lipids including ceramides and elevated bile acids

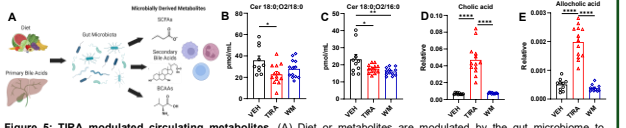


Figure 5: TIRA modulated circulating metabolites. (A) Diet or metabolites are modulated by the gut microbiome to produce metabolites that impact anti-tumor immunity. (B-C) Ceramides were reduced in TIRA treated mice while (D-E) bile acids were elevated in TIRA mice. n = 10-12 per group. Data is shown as Mean ± SEM with one-way ANOVA with Posthoc Tukey test. *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$.

Conclusions

- Triple incretin receptor agonist TIRA induced significant weight loss and improved metabolic dysfunction despite mice remaining on high fat diet.
- TIRA significantly delayed tumor onset compared to vehicle.
- TIRA's anti-tumor function could be through circulating mediators including ceramides, bile acids and other metabolites under investigation.

Acknowledgements

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