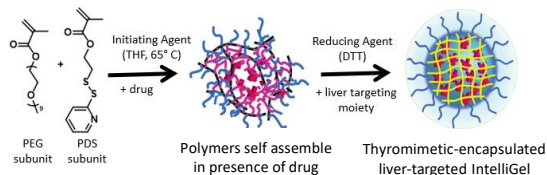


# Liver-targeted IntelliGel system for the delivery of thyromimetics in the treatment of obesity

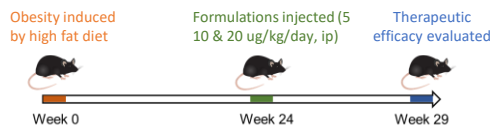
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- Obesity is a multi-factorial disorder, which is often associated with diseases such as diabetes, hypertension and other cardiovascular diseases, non-alcoholic steatohepatitis (NASH) and certain cancers.
- Over the past 50 years, obesity has become a major worldwide epidemic; in the US, more than one third of adults and 20% of adolescents are obese.
- We have developed an IntelliGel™ polymeric platform in which a potent thyromimetic drug is encapsulated and specifically targets the liver.
- Inside the liver cells, the IntelliGels degrade and release drug, which activates the thyroid hormone beta receptor (TR $\beta$ ), which modulates lipid homeostasis, including cholesterol metabolism.

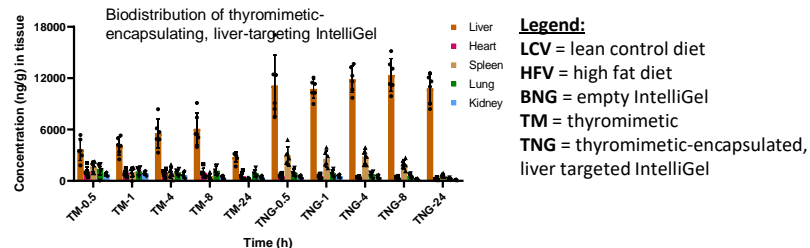
## Preparation of liver-targeting IntelliGels



## Experimental protocol

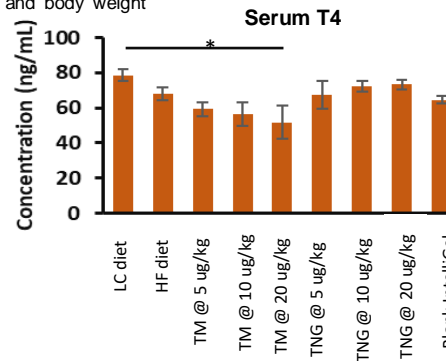
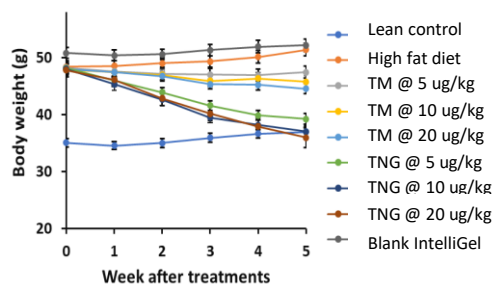


## Thyromimetic-encapsulating IntelliGels specifically target the liver



## Thyromimetic-encapsulating, liver-targeting IntelliGels reverse body weight gain in HFD treated mice in the diet-induced obesity (DIO) mouse model without changes in serum T4 levels

- Mice are fed high fat diet or lean control diet for 24 weeks. TM, TNG and BNG are dosed in mice via ip administration for 5 weeks and body weight measured each week.



## CONCLUSION

A novel IntelliGel formulation that selectively delivers a potent thyromimetic drug to the liver has been developed. At concentrations of 5-20  $\mu\text{g}/\text{kg}$ , a thyromimetic-encapsulating, liver-targeting IntelliGel formulation completely reverses body weight gain in a DIO mouse model. This is due to activation of the liver TR $\beta$  receptor by selective delivery of the encapsulated thyromimetic to the liver, with no involvement of thyroid hormone receptors in the periphery.

**This is the first time a liver-specific thyromimetic has shown this level of body weight reduction, which equals the efficacy seen with Glp1 agonists in DIO mouse models.**

In addition to body weight loss, we also see marked reduction of liver fat, cholesterol, triglyceride and reversal of ALT/AST elevation at levels greater than or equal to other thyromimetics.

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> Serum T4 is not changed with thyromimetic-encapsulated IntelliGel (TNG), showing that the thyromimetic is not systemically available and is acting through the liver. T4 level is changed in TM alone dose, showing some systemic exposure.