

# Endocrine disrupting chemicals and the programming of adipogenesis and obesity

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Group for Reproductive, Endocrine and  
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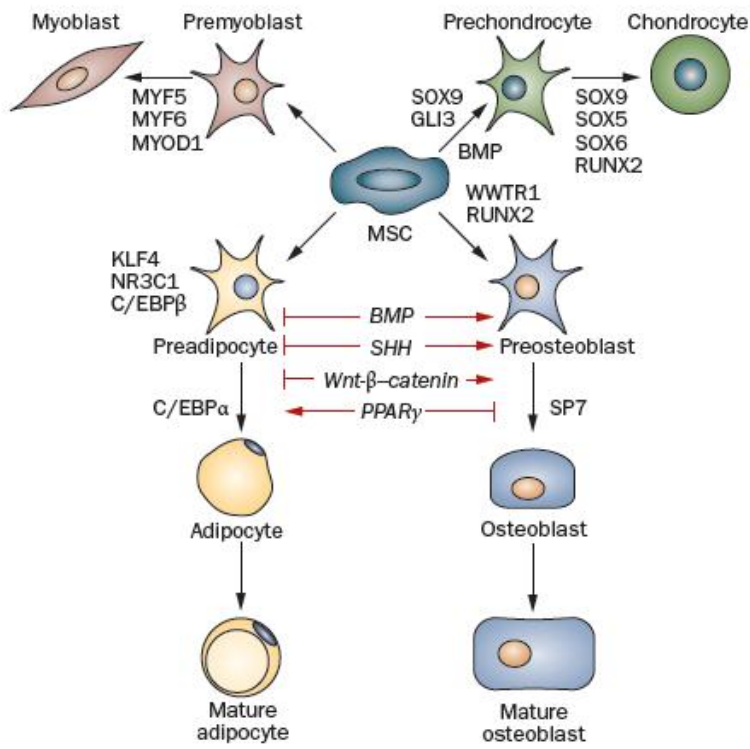
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# EDCs and the obesogen hypothesis

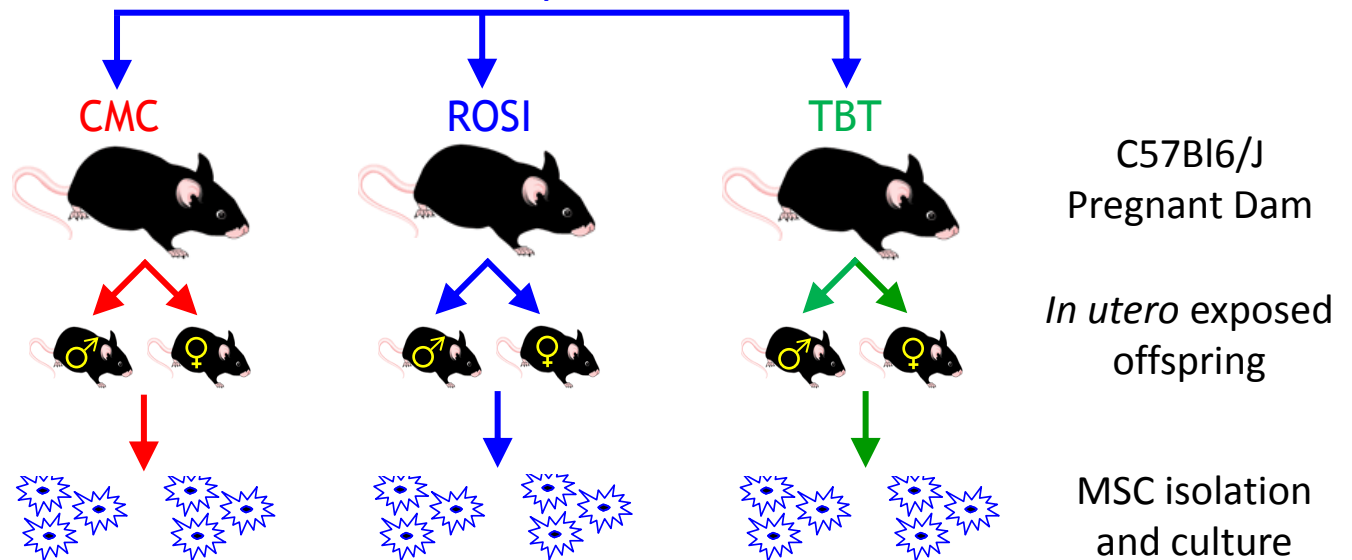
- **Obesogens** - chemicals that inappropriately stimulate adipogenesis and fat storage, disturb adipose tissue homeostasis, or alter control of appetite/satiety to lead to weight gain and obesity
- Pre- and postnatal exposure to EDCs such as environmental estrogens (ER) increases weight
  - DES, genistein, bisphenol A
- Thiazolidinedione anti-diabetic drugs (PPAR $\gamma$ )
  - Increase fat storage and fat cell number at all ages in humans
- Urinary phthalates correlate with waist diameter and insulin resistance in humans
  - Many chemicals linked with obesity in epidemiological studies
- Several compounds cause adipocyte differentiation in vitro (PPAR $\gamma$ )
  - phthalates, BPA, alkylphenols, PFOA, **organotins**
- Existence of obesogens is plausible



# MSCs can give rise to many cell types in vivo

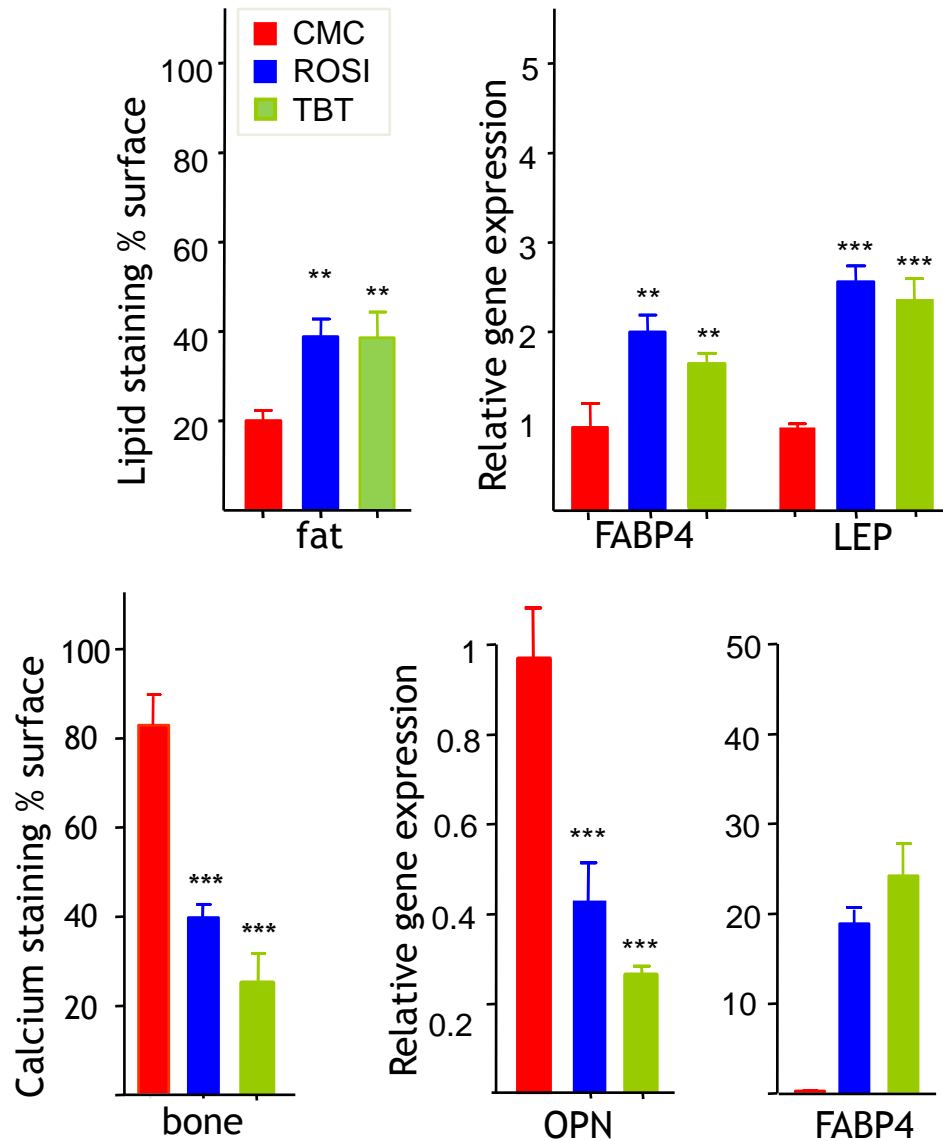
- PPAR $\gamma$  controls choice between fat and bone pathways
- Expression and activation of PPAR $\gamma$  favors the fat and inhibits bone formation.

## Prenatal Exposure

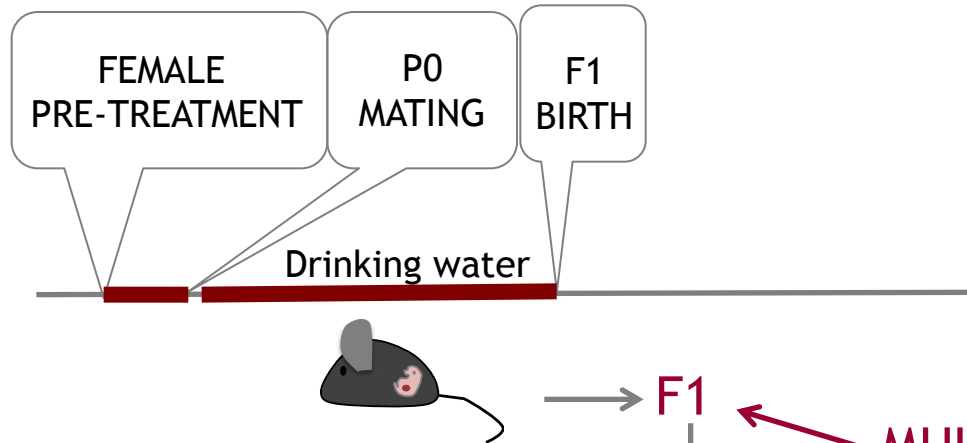


Kirchner S et al. Molecular Endocrinology 2010;24:526-39.

# Prenatal TBT exposure reprograms MSCs to become fat cells instead of bone cells

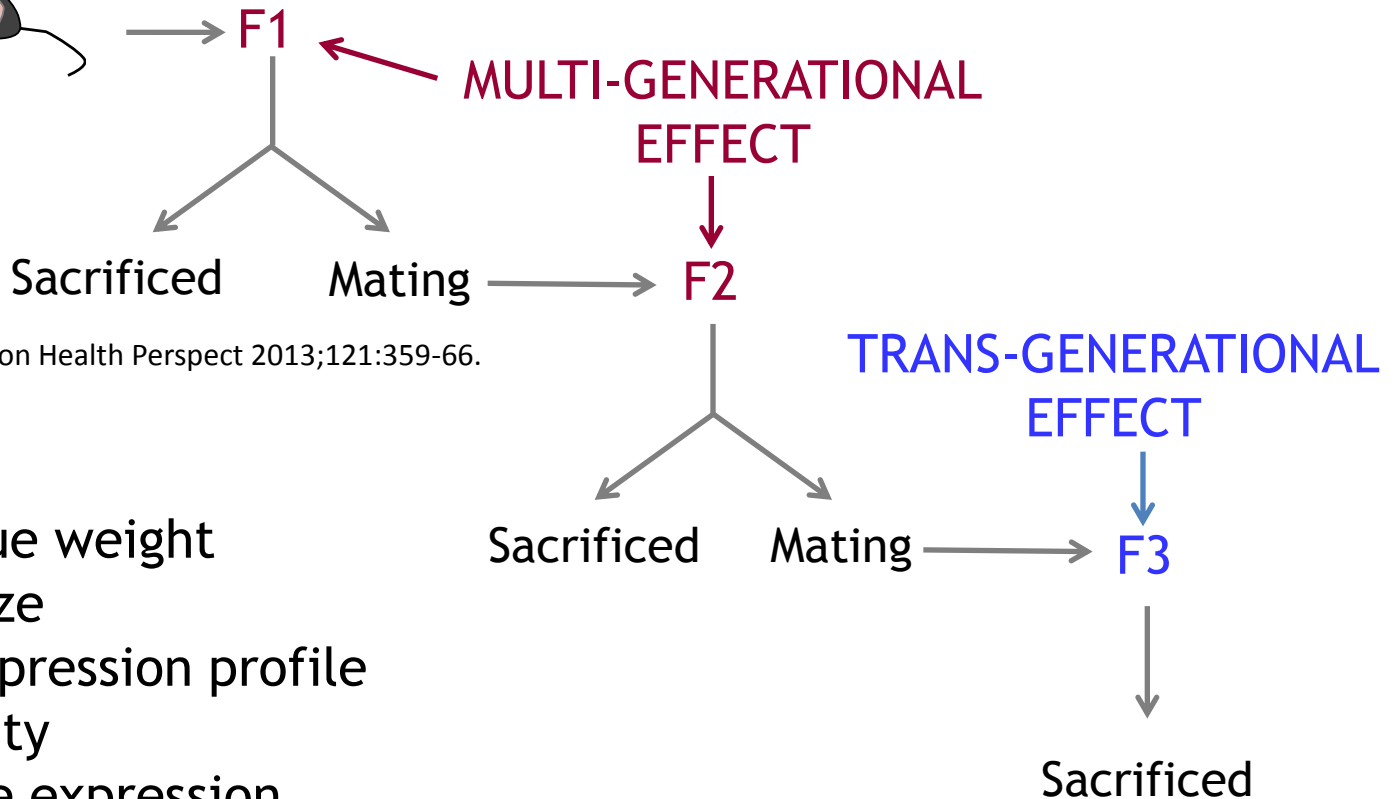


# Are effects of TBT exposure transgenerational? (i.e., permanent)



## TREATMENTS

DMSO  
 ROSI 0.5  $\mu$ M  
 TBT 5.42 nM (50x < NOAEL)  
 TBT 54.2 nM (5x < NOAEL)  
 TBT 542 nM



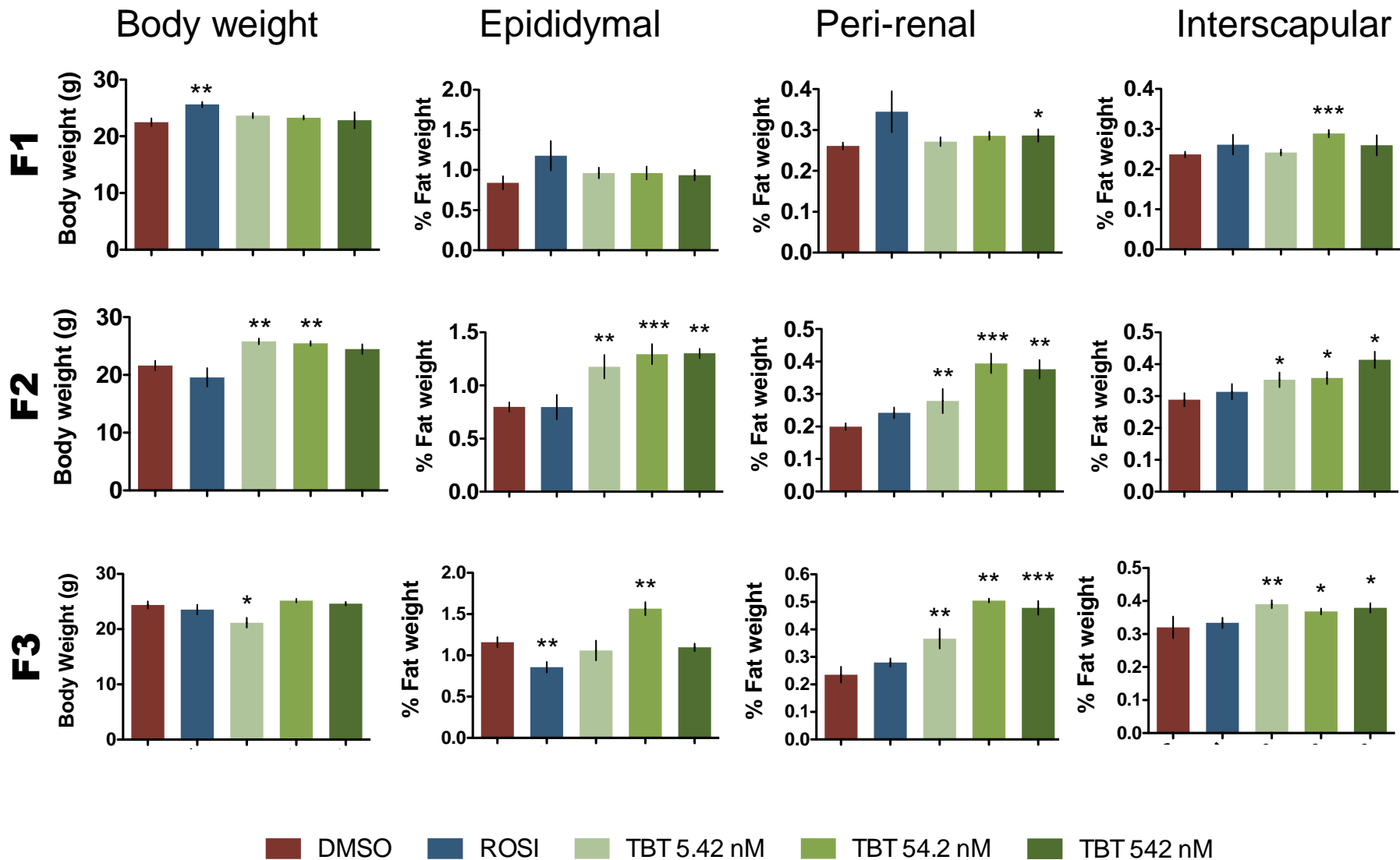
Chamorro-Garcia R et al. Environ Health Perspect 2013;121:359-66.

8 weeks old

- Body weight
- Adipose tissue weight
- Adipocyte size
- MSC gene expression profile
- Liver adiposity
- Hepatic gene expression

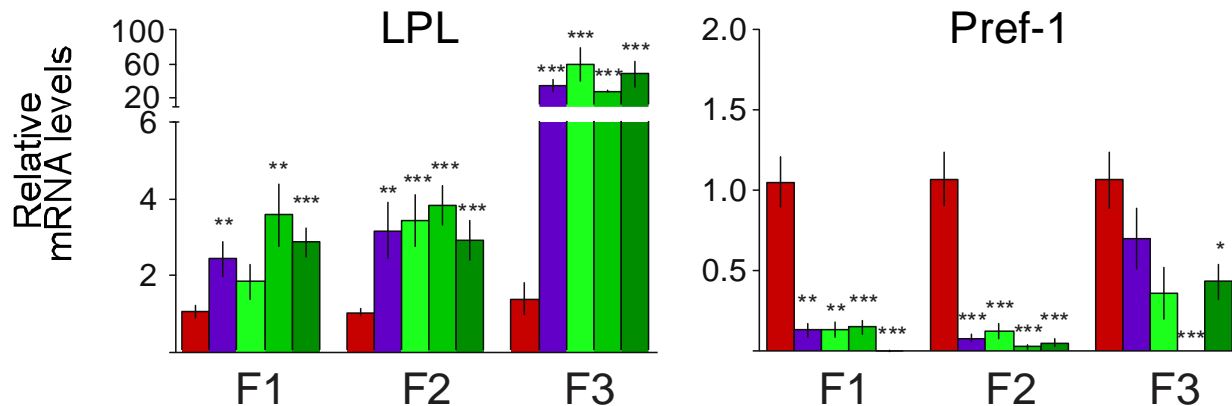
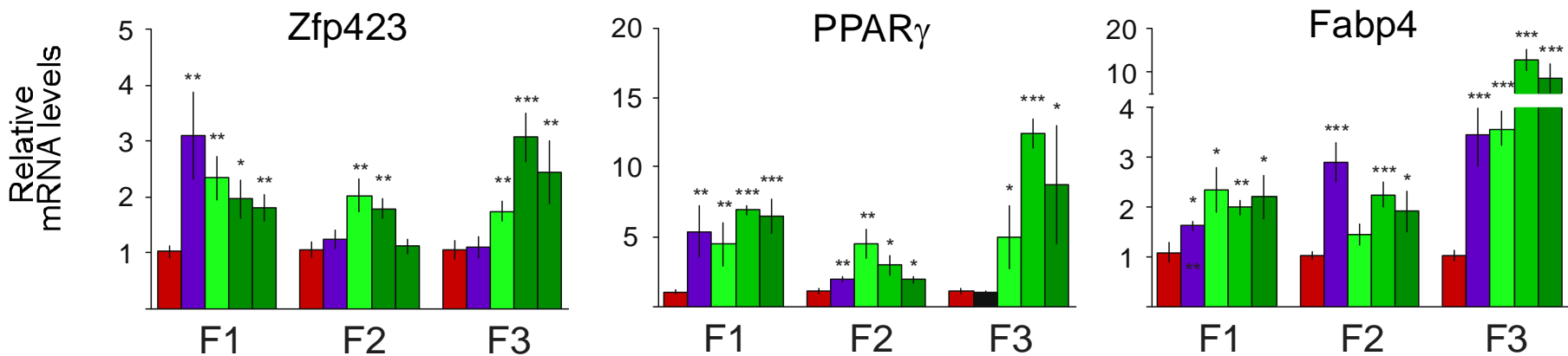
# TBT exposure has transgenerational effects

## *Heavier fat depots*



# TBT exposure has transgenerational effects

## *Increased expression of fat-specific genes in MSCs*



■ vehicle   
 ■ ROSI   
 ■ TBT 5.4 nM   
 ■ TBT 54.2 nM   
 ■ TBT 542 nM

# Implications For Human Health

- Diet and exercise are insufficient to explain obesity epidemic particularly in the very young
- Obesogens inappropriately stimulate adipogenesis and fat storage
  - Prescription drugs
    - Thiazolidinedione anti-diabetic drugs (Actos, Avandia)
    - Atypical antipsychotics, anti-depressants
  - Environmental contaminants
    - organotins, estrogens (BPA, DEHP), PFOA/S, DDE, POPs
    - triflumizole, zoxamide, organophosphates, parabens
- Prenatal obesogen exposure reprograms exposed animals to be fat
  - Epigenetic changes alter fate of stem cell compartment -> more preadipocytes and more adipocyte progenitors
- Obesogens shift paradigm from treatment to prevention during pregnancy, childhood and puberty: **Reduced exposure to obesogens, optimized nutrition**



# Chemicals with transgenerational Effects

- Tributyl tin (RXR, PPAR $\gamma$ , estrogen) plastic, industrial use, water pipes) – increased fat mass, reprogram stem cells to produce more fat cells over time, fatty liver disease (Chamorro-Garcia R et al. Environ Health Perspect 2013;121:359-66).
- Vinclozolin (anti-androgen) – fungicide, impairs male reproductive function (Anway MD et al. Science 2005;308:1466-9).
- Plastics mixture, BPA, DEHP, DBP, (estrogen, anti-androgen) obesity, reproductive diseases, sperm epimutations (Manikkam M et al., PLoS One 2013;8:e55387).

## Chemicals with transgenerational Effects (2)

- Hydrocarbons, JP-8 jet fuel (?) obesity, reproductive diseases, sperm epimutations (Tracey R et al., *Reprod Toxicol* 2013;36:104-16).
- BPA, estrogen (plastics, thermal paper, recycled paper, food packaging), altered social interactions, modified gene expression (Wolstenholme JT et al., *Endocrinology* 2012;153:3828-38).
- DDT, estrogen (pesticide) – 50% of F3 males and female rats develop obesity (Skinner MK et al., *BMC Med* 2013;11:228).