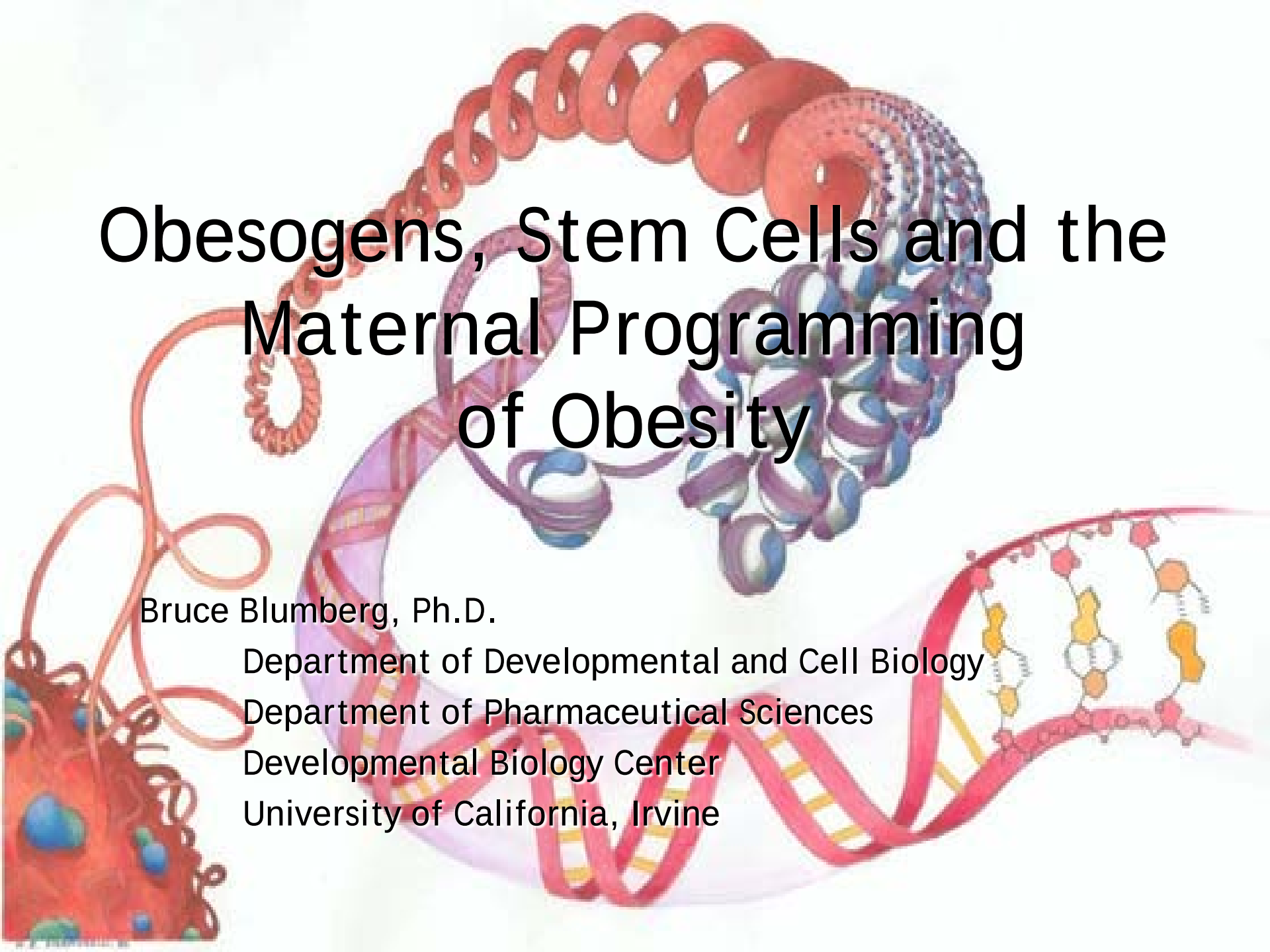

Obesogens, Stem Cells and the Maternal Programming of Obesity

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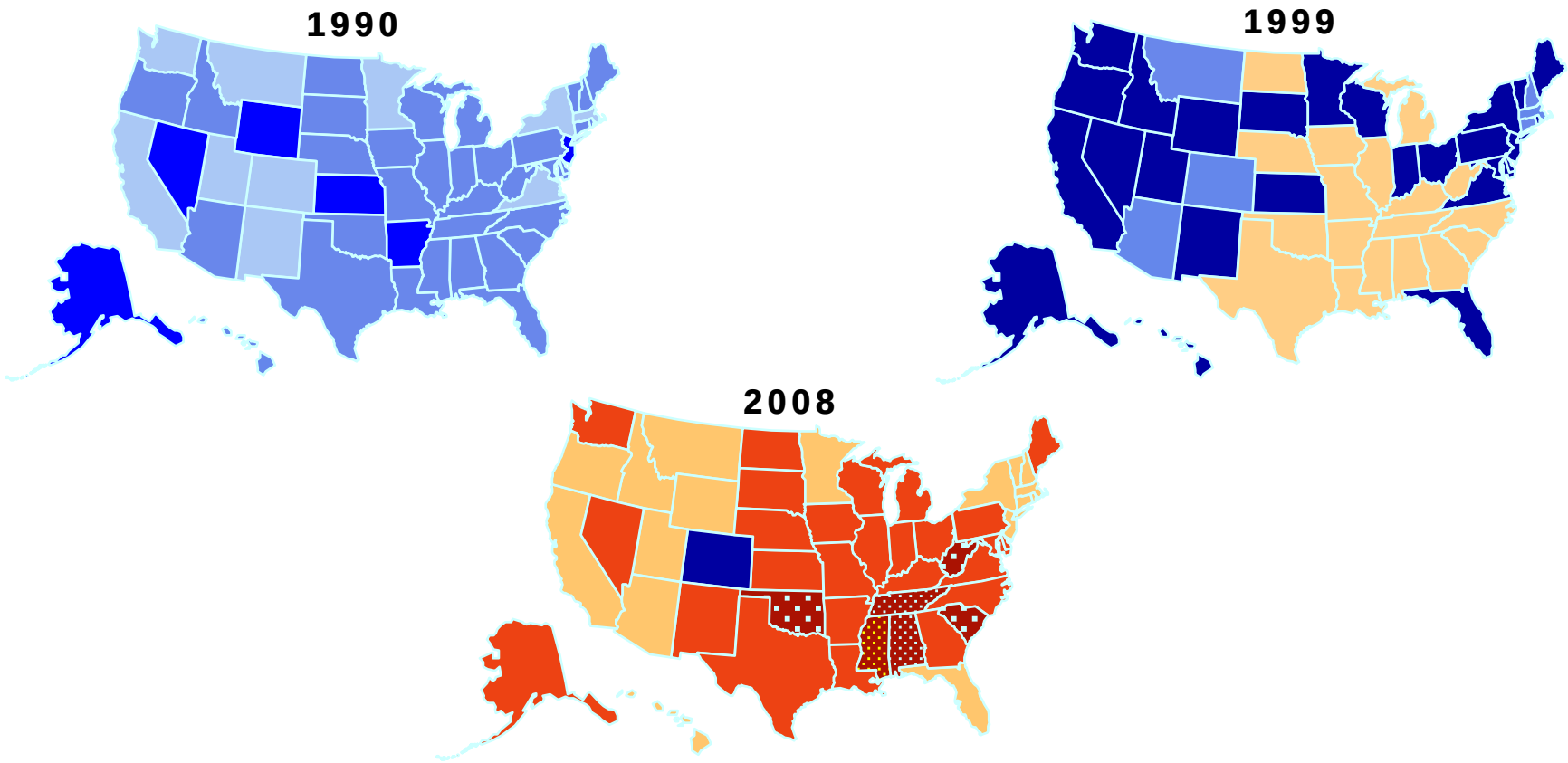
The Worldwide Obesity Epidemic

- 34% of the US population are clinically obese (BMI > 30)
  - Double worldwide average (Flegal et al. JAMA 2010;303:235-241)
- 68% are overweight (BMI > 25) – 86% estimated by 2020
- Obesity accounts for 8% of healthcare costs in Western Countries
  - $75 billion annually in US (2005), $147 billion (2009)
- Obesity is associated with "metabolic syndrome" -> type 2 diabetes and cardiovascular disease
  - Central (abdominal obesity)
  - Atherogenic dyslipidemia (high triglycerides, high LDL, low HDL)
  - Hypertension
  - Insulin resistance
  - Prothrombotic state
  - Pro-inflammatory state (elevated CRP)

Obesity Trends* Among U.S. Adults

BRFSS, 1990, 1999, 2008

(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)

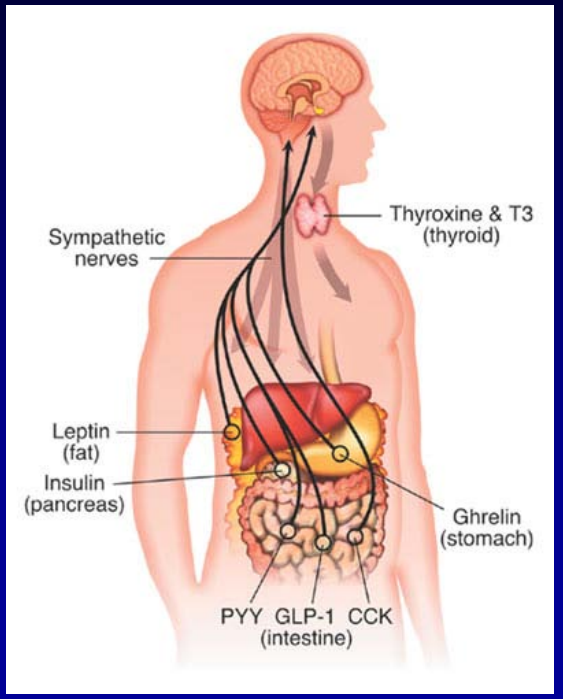


How does obesity occur ?

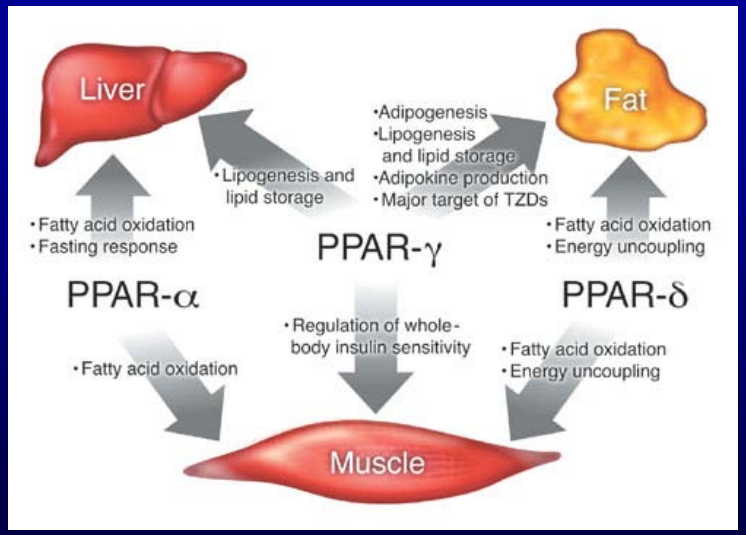
- Prevailing wisdom – "couch potato syndrome"
  - Positive energy balance, i.e., too much food, too little exercise
- Are there other factors in obesity ?
  - Stress (elevated glucocorticoids)
  - Inadequate sleep (stress?)
  - "Thrifty" genes which evolved to make the most of scarce calories
  - Viruses, gut microbes, SNPs
- What about role of prenatal nutrition or in utero experience?
  - Southampton studies
  - Maternal smoking decreases birth weight and increases obesity
- What about the role of industrial chemicals in rise of obesity?
  - Baillie-Hamilton (2002) postulated a role for chemical toxins
  - obesity epidemic roughly correlates with a marked increase in the use of chemicals (plastics, pesticides, etc.)
- **Many chemicals have effects on the endocrine system**

Hormonal control of weight

- Hormonal control of appetite and metabolism
  - Leptin, adiponectin, ghrelin are key players
  - Leptin, adiponectin – adipocytes
  - Grehlin – stomach
  - Thyroid hormone/receptor
    - Sets basal metabolic rate



- Hormonal control of fat cell development and lipid balance
  - Regulated through nuclear hormone receptors RXR, PPARγ
  - PPARγ – master regulator of fat cell development
    - increased fat cell differentiation
    - Increased fat storage in existing cells
    - Increased insulin sensitivity



From Nature Medicine 10, 355 - 361 (2004)

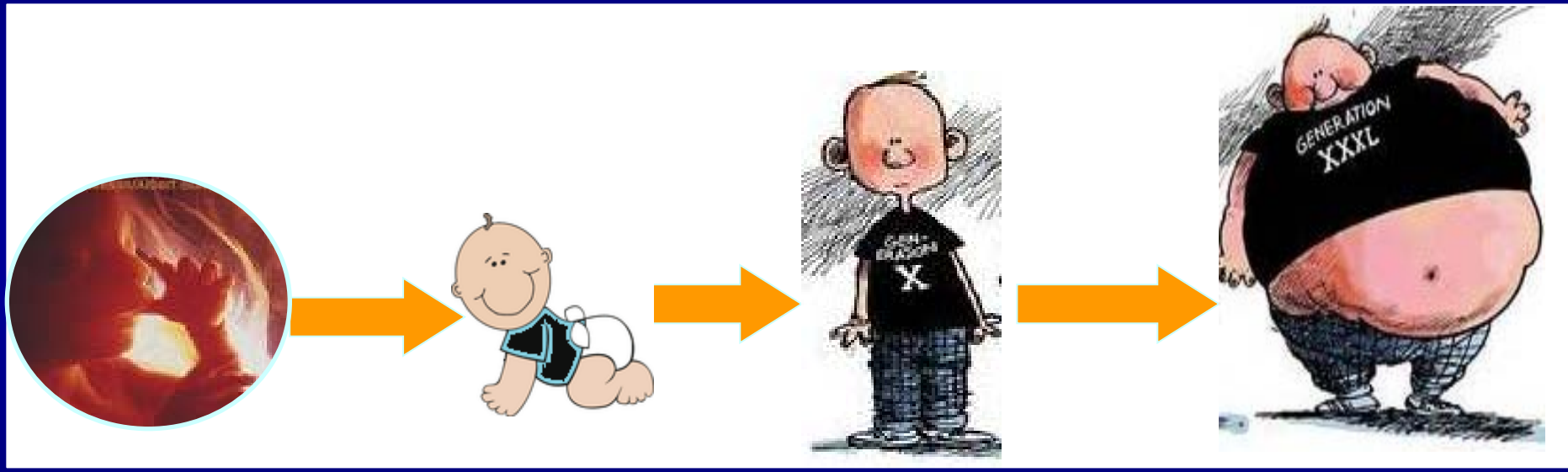
Endocrine Disrupting Chemicals (EDCs)

- *Endocrine disrupter* - a compound that mimics or blocks the action of endocrine hormones, either directly or indirectly
  - Often persistent pollutants or dietary components that disturb development, physiology and homeostasis

- Frequently act through nuclear hormone receptors
  - Environmental estrogens
  - Anti-androgens
  - Anti-thyroid

- Recent white paper from the Endocrine Society - Diamanti-Kandarakis, et al, Endocrine Reviews 30 (4): 293-342 (2009)
  - Details scientific support for existence and effects of EDCs
  - Endorsed by American Medical Association
  - Led to H.R.4190 - Endocrine Disruption Prevention Act of 2009
  - Moves responsibility for research from EPA to NIEHS

Endocrine Disrupting Chemicals (EDCs)



- Are EDC-mediated disturbances in endocrine signaling pathways involved in adipogenesis and obesity

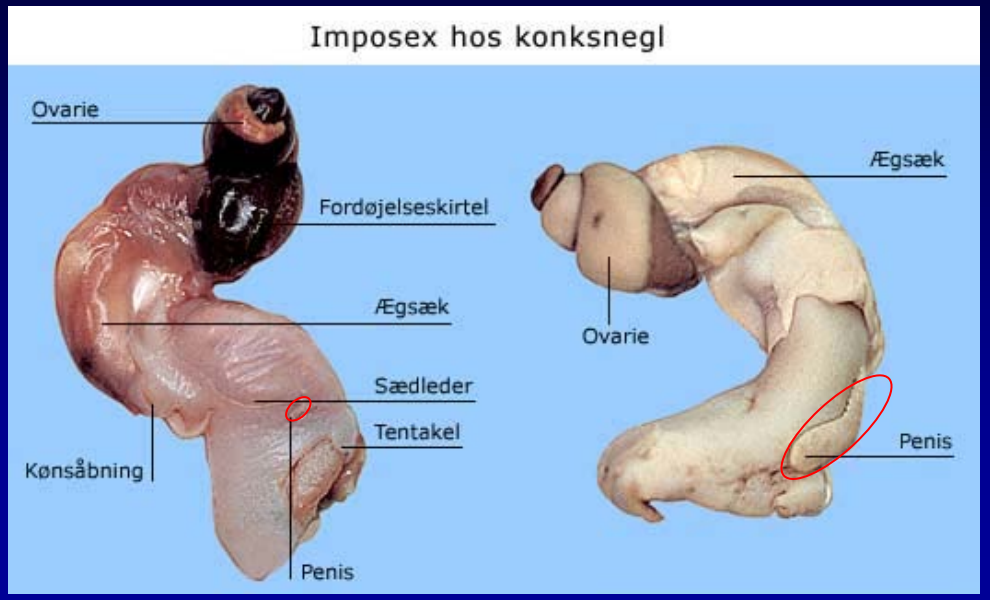
EDCs and the obesogen hypothesis

- ***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 (PPARγ)
  - Increase fat storage and fat cell number at all ages in humans

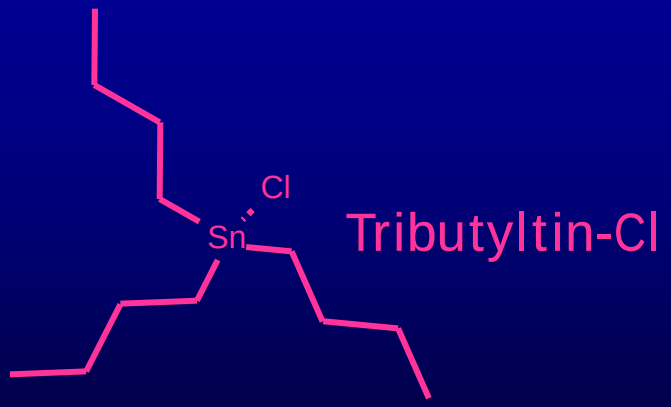
- Urinary phthalates correlate with waist diameter and insulin resistance in humans
- several compounds cause adipocyte differentiation in vitro (PPARγ)
  - phthalates, BPA, aklylphenols, PFOA, **organotins**
- Existence of obesogens is plausible

Endocrine disruption by organotins

- Organotins -> imposex in mollusks
- Sex reverses genetically female flounder and zebrafish -> males
- Which hormone receptors might be organotin targets?

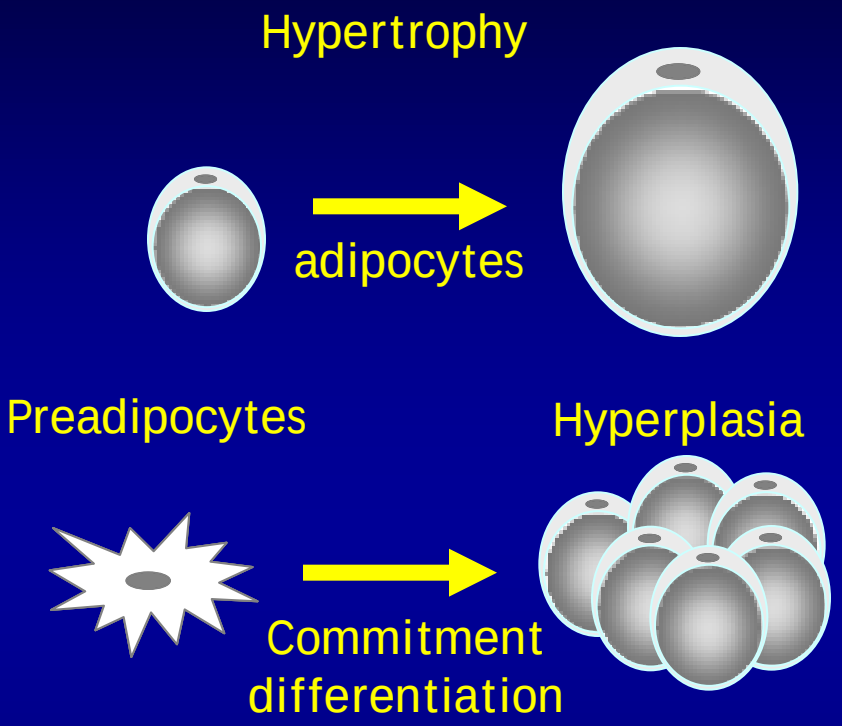


- We found that tributyltin (TBT)
  - Binds and activates at ppb (low nM) to two nuclear receptors, RXR and PPARγ critical for adipogenesis
  - TBT induced adipogenesis in cell culture models (nM)
  - Prenatal TBT exposure led to weight gain in mice, in vivo



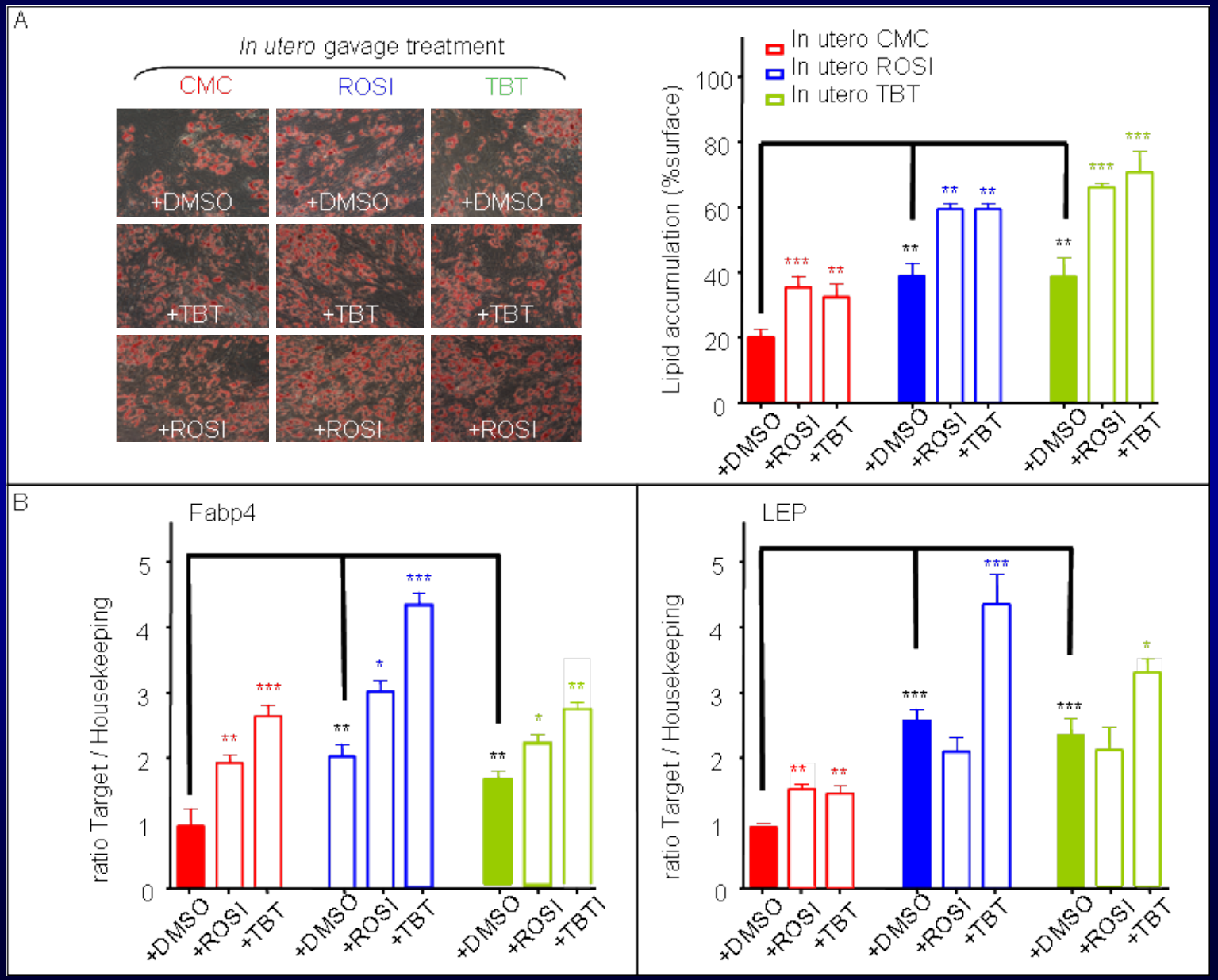
How does TBT exposure cause weight gain?

- Changes in the hormonal control of appetite and satiety?
- Altered ability of adipocytes to process and store lipids?
- Increased number of adipocytes or pre-adipocytes?



- Mesenchymal stem cells (MSCs) (now called multipotent stromal cells) precursors to many lineages including bone, cartilage, and adipose.
  - MSCs differentiate into adipocytes following rosiglitazone exposure
  - MSCs may (or may not) home to adipose depots after induction
- ***Hypothesis:*** TBT induces adipogenesis in MSCs

Prenatal TBT exposure increases MSC differentiation into adipocytes



Kirchner et al., 2010 Molec Endocrinol, 24, 526-539

Effects of prenatal TBT on MSC pool

- TBT exposure biases the MSC compartment toward adipocytes
  - 7-15% more pre-adipocytes in TBT-treated than control animals
- Increased expression of adipocyte markers reflects increased number of pre-adipocytes
  - Decreased potential to form osteoblasts
- This suggests that the setpoint for fat cell number has been permanently altered by TBT exposure
  - Implications for obesogen exposure in general?
- TBT is an obesogen that acts through PPARγ to increase fat deposition and body weight while predisposing MSCs to be adipocytes

Conclusions and 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, environmental estrogens (BPA, DEHP), PFOS
- Prenatal obesogen exposure reprograms exposed animals to be fat
  - Epigenetic changes alter fate of stem cell compartment -> more preadipocytes and more cells committed to adipocyte lineage
- Obesogens shift paradigm from treatment to prevention during pregnancy, childhood and puberty
  - Reduced exposure to obesogens, optimized nutrition
  - Obesity is intractable once established

Obesogens - Just the Tip of the Iceberg ?

TBT/TPT
Phthalates
PFOA

DES
Bisphenol A
Genistein

Nicotine
Air pollution
BaP

fructose
COX2 inhibitors
PCBs ?, PBDEs ?
Organophosphate pesticides

- What don't we know yet?
  - How many obesogens are out there
  - What are the body burdens in populations
  - Molecular targets of action beyond RXR-PPARγ
  - Critical windows of exposure
  - How does prenatal exposure alter adult phenotype ?
  - How does diet interact with obesogen exposure?
  - Is the prenatal reprogramming epigenetic?

Human Studies Supporting the Obesogen Hypothesis

- Prenatal & early life exposures to low levels of PCBs and DDE are associated with increased weight in boys and girls at puberty (Gladen et al, J. Pediatr., 2000).
- Childhood obesity is associated with maternal smoking in pregnancy (Toschke et al, Eur J Pediatr 2002)
- Soy-based formula in infancy is a potential risk factor for overweight later in life (Strom et al., JAMA, 2001; Stettler et al., 2005).
- Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult US males (Stahlhut et al, EHP, 2007)
- Exposure to hexachlorobenzene during pregnancy increases the risk of overweight in children aged 6 years (Smink et al, Acta Paediatrica, 2008)
- Intrauterine exposure to environmental pollutants (POPs) and body mass during the first 3 years of life (Verhulst et al EHP, 2009)
- Prenatal exposure to DDE is associated with rapid weight gain in the first 6 months and elevated BMI later (Mendez et al EHP, 2011)