



The Paradox of Progress:

Environmental Disruption of Metabolism and the Diabetes Epidemic

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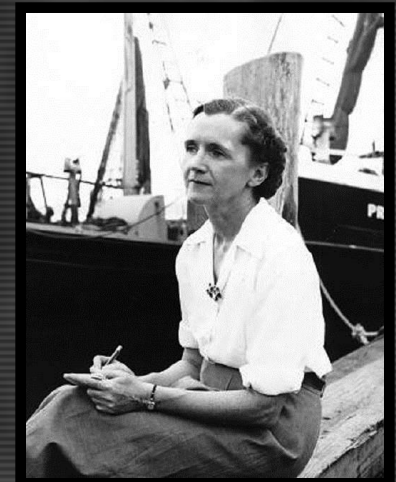
Conflicts of Interest

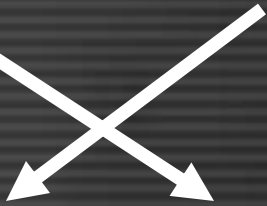
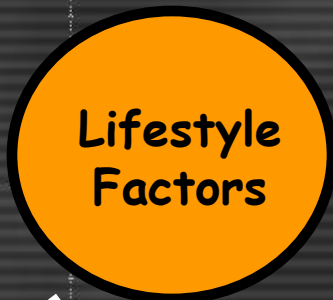
- **CVS Caremark: National Pharmacy and Therapeutics Committee**
- **No scientific conflicts**



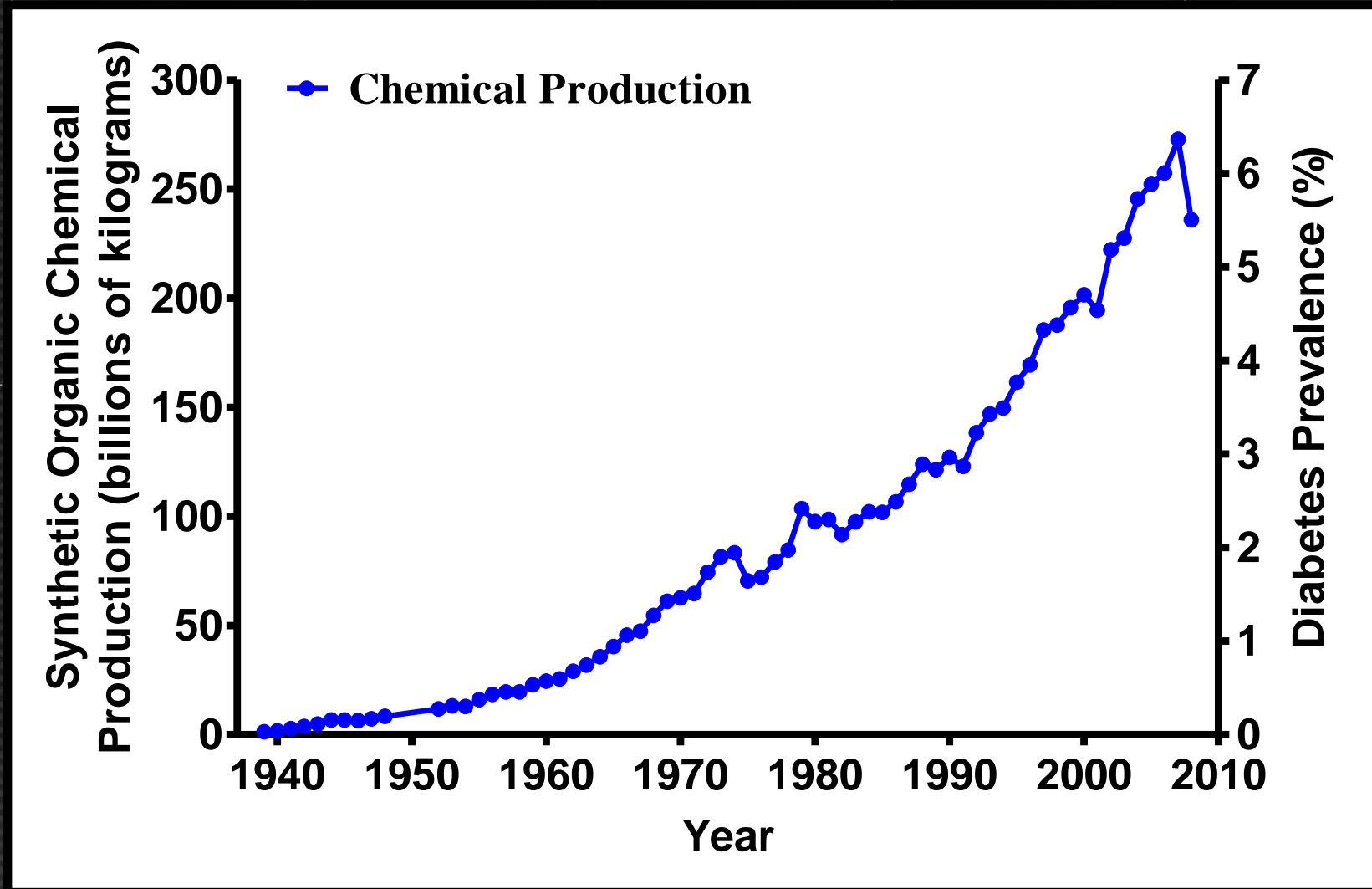
As the tide of chemicals born of the Industrial Age has arisen to engulf our environment, a drastic change has come about in the nature of the most serious health problems.

Rachel Carson, Silent Spring, 1962

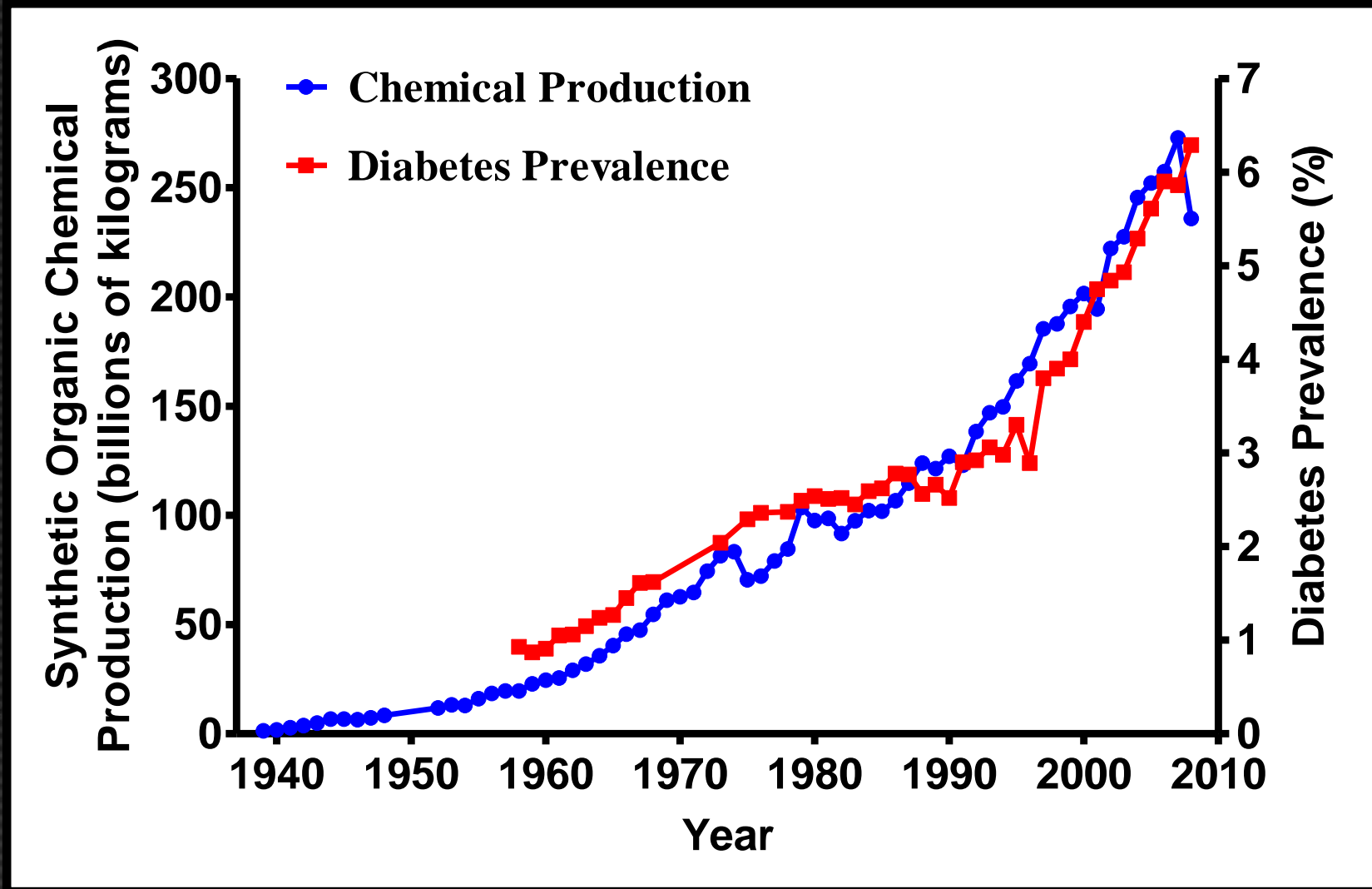




U.S. Synthetic Chemical Production



Diabetes Rates





Agricultural Chemicals
Food Additives
Packaging
Phytochemicals

Industrial Chemicals and By-Products
Air Pollutants



Waste Products

Pharmaceutical Products



Personal Care Products
Flame Retardants
Solvents & Coatings

Animal Models of Pollutant-Induced Dysglycemia

Insulin Resistance/Hyperinsulinemia

BPA (Alonso-Magdalena et al., 2010)

Arsenic (Paul et al., 2011)

Air pollution (Xu et al., 2010; Yan et al., 2011)

Maternal smoking/nicotine (Somm et al., 2008; Oliveira et al., 2010)

POPs (Ruzzin et al., 2010)

PBDE (Nash et al., 2013)

Glucose Intolerance

Arsenic (Hill et al., 2009)

Triphenyltin (Ogino et al., 1996)

DEHP (Martinelli et al., 2006)

Maternal smoking/nicotine (Bruin et al., 2007; Bruin et al., 2008; Holloway et al., 2005)

PCBs (Baker et al., 2013)

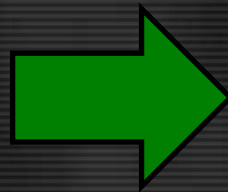
Hyperglycemia

Triphenyltin (Matsui et al., 1984)

Hypoglycemia/Increased Glucose Tolerance

BPA (Miyawaki et al., 2007)

DEHP (Sakurai et al., 1978; Feige et al., 2010)



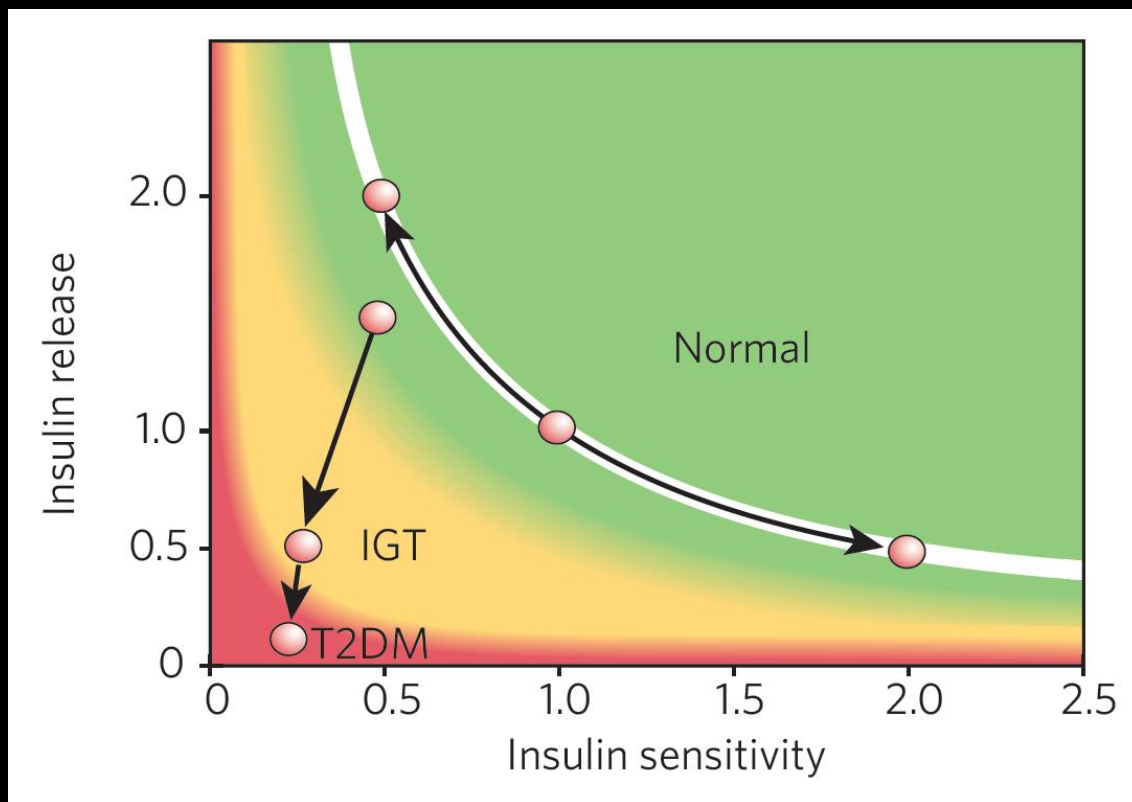
These data are generally supportive of epidemiological studies.

Search for Biological Mechanisms



Mission: To understand the molecular mechanisms by which environmental contaminants disrupt energy homeostasis.

Maintenance of Glucose Homeostasis



Insulin Resistance: Environmental factors (diet, physical inactivity, etc.), obesity, NAFLD, susceptibility genes

β -cell Dysfunction: ER stress, oxidative stress, genetic susceptibility, apoptosis, de-differentiation

Decreased β -Cell Function

Arsenic (Douillet et al., 2013; Fu et al., 2010; Diaz-Villasenor et al., 2008)

Cadmium (Chen et al., 2009; El Muayed et al., 2012)

Mercury (Chen et al., 2010)

Vacor (Kenney et al., 1981)

Maternal smoking/nicotine (Bruin et al., 2007)

TCDD (Kurita et al., 2009; Novelli et al., 2005; Piaggi et al., 2007)

Altered β -Cell Structure/Status

PCBs (Wassermann et al., 1975)

TCDD (Ebner et al., 1993)

Disruption of Calcium-Dependent Signaling

Arsenic (Diaz-Villasenor et al., 2008)

PCBs (Fischer et al., 1999)

Triphenyltin (Miura and Matsui, 2006)

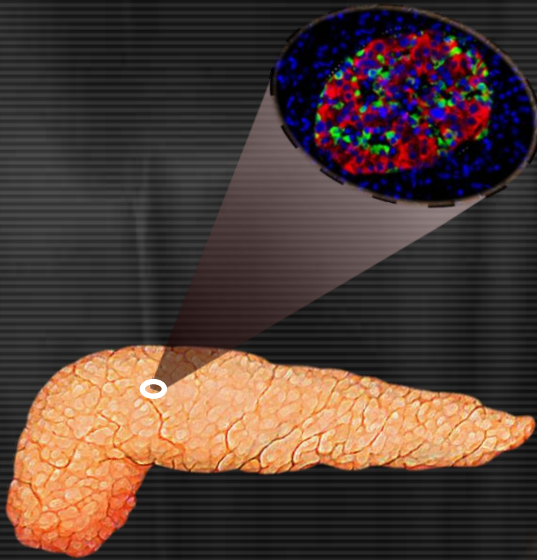
BPA (Alonso-Magdalena et al., 2006; Nadal et al., 2000)

TCDD (Fischer et al., 1999; Kim et al., 2009)

Increased Insulin Secretion

BPA (Alonso-Magdalena et al., 2006)

PCBs (Fischer et al., 1996)



- Integrator of metabolism
- Lipid-rich tissue



Brain

- Responsible for ~10% of gluconeogenesis
- Site of elimination



Kidneys

- Accounts for ~80% of post-prandial glucose uptake



Skeletal Muscle

- Central organ of metabolism
- Site of detoxification



Liver

- Insulin and glucagon production



Pancreas

- Incretin hormones
- Site of absorption

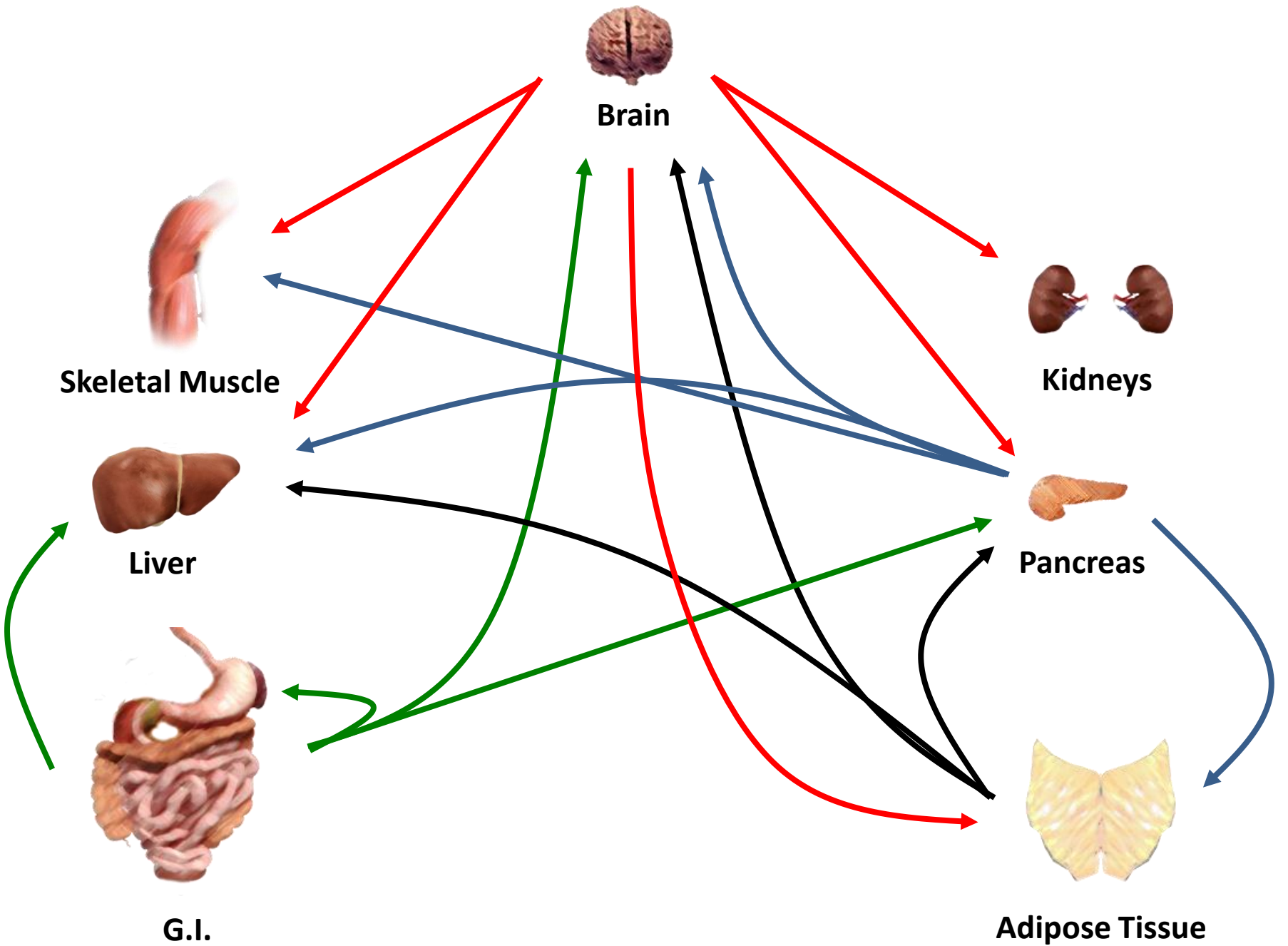


G.I.

- Energy storage depot
- Hormone production
- Storage of lipophilic compounds

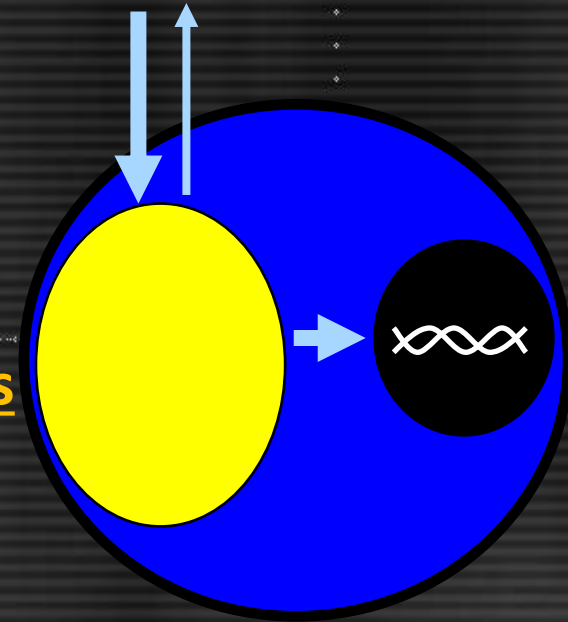


Adipose Tissue



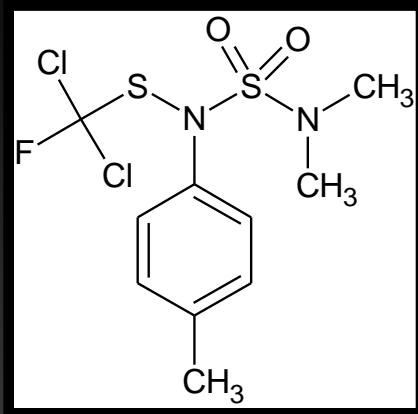
Adipocytes: Perfect EDC Targets

- By and large, EDCs are lipophilic compounds; thus, they are likely to bioaccumulate in the lipid droplet of the adipocyte.
- Slow leaching of EDCs from the lipid droplet may provide a continuous source of local exposure in the fat pad.
- Cell differentiation and signaling in adipocytes is driven by several nuclear hormone receptors with lipophilic compounds as their endogenous ligands.
 - For example: PPAR γ , glucocorticoid receptor
- Adipose tissue secretes a number of factors (adipokines) that regulate systemic energy metabolism.

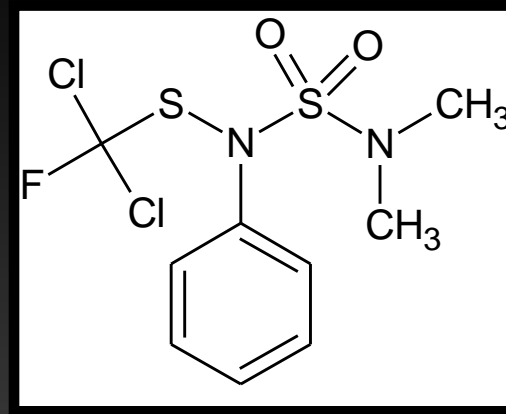


What are the effects of EDCs on adipocyte development and metabolism?

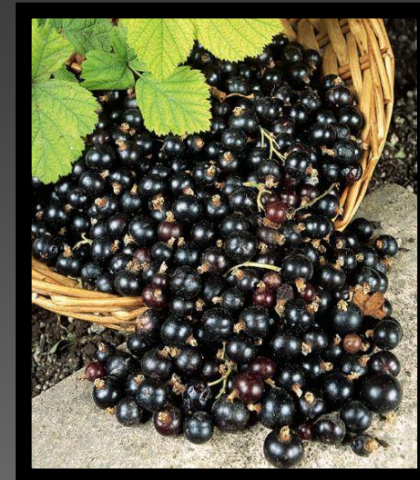
Phenylsulfamide Fungicides



Tolyfluanid



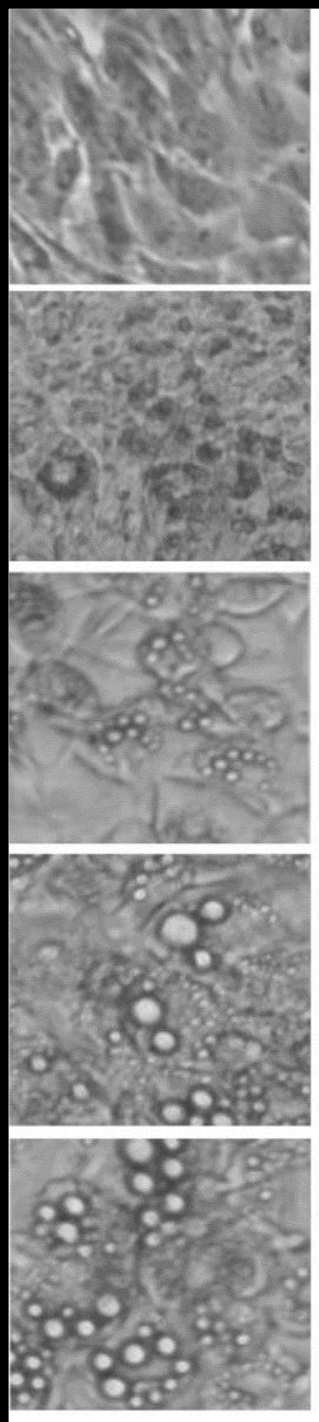
Dichlofluanid



Fungicides also used as booster biocides in marine paints.

Our Experimental Systems

- **3T3-L1 Cell Line**
 - Well-characterized model to assess preadipocyte-to-adipocyte differentiation (“adipogenesis”)
- **Primary Adipose (and Hepatocyte) Culture**
 - Interrogation of tissue-specific effects on insulin signaling and physiology
- **Animal Models**
 - Characterization of integrated whole-body energy homeostasis



Altered Cellular Development

- **Enhanced Adipocyte Differentiation**

- **Tolyfluanid** (Sargis et al., 2010)
- **Endrin** (Sargis et al., 2010)
- **Dicyclohexylphthalate** (Sargis et al., 2010)
- **Tributyltin** (Kanayama et al., 2005; Grun et al., 2006)
- **PCB-77** (Arsenescu et al., 2008)
- **TCDD** (Arsenescu et al., 2008)
- **BPA** (Masuno et al., 2005)
- **Triflumazole** (Li et al., 2012)

- **Impaired Adipocyte Development**

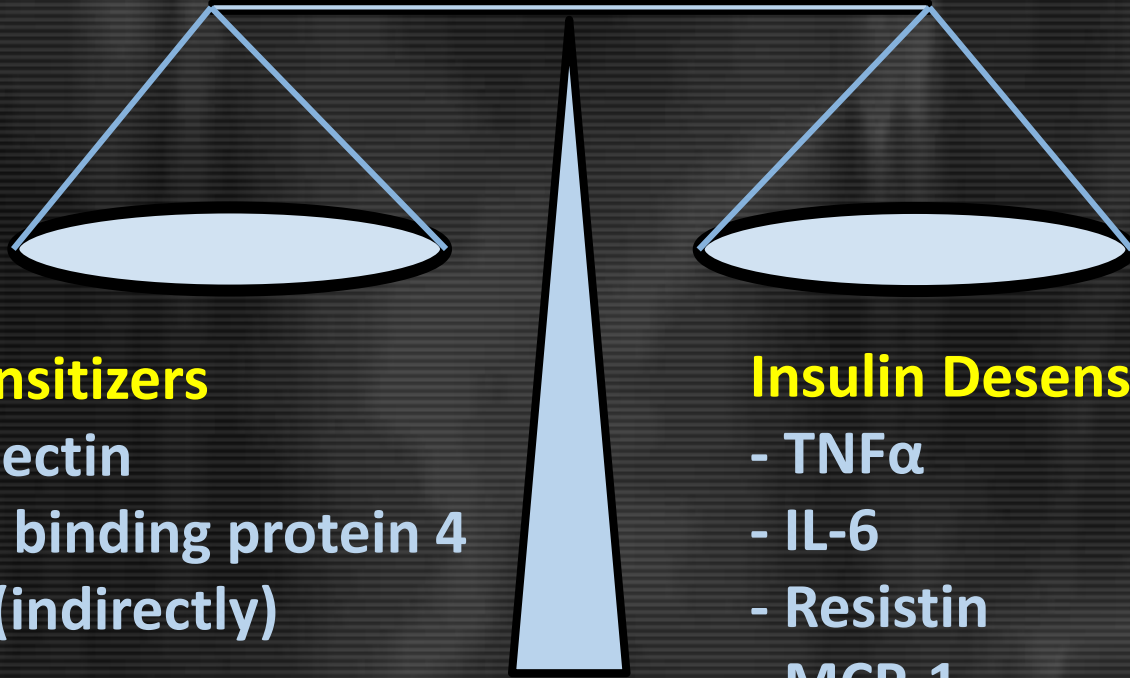
- **Endrin** (Moreno-Aliaga et al., 1999)
- **PCB-77** (Arsenescu et al., 2008)
- **TCDD** (Arsenescu et al., 2008; Hsu et al., 2010; Shimba et al., 2001)
- **Arsenic** (Wauson et al., 2002)

- **Impaired Myocyte Development**

- **Arsenic** (Steffans et al., 2010; Yen et al., 2010)



Adipocyte Mediators of Insulin Sensitivity



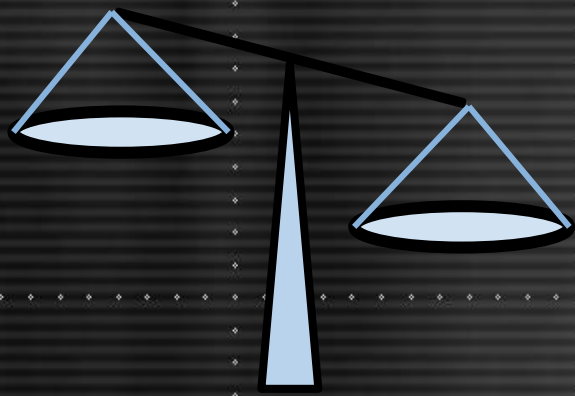
Insulin Sensitizers

- Adiponectin
- Retinol binding protein 4
- Leptin (indirectly)
- IL-10

Insulin Desensitizers

- TNF α
- IL-6
- Resistin
- MCP-1





Mediators of Insulin Sensitivity

Decreased Adiponectin

Cadmium (Kawakami et al., 2010)

Tributyltin (Zuo et al., 2009)

Air pollution/PM2.5 (Xu et al., 2011)

BPA (Kidani et al., 2010; Hugo et al., 2008)

Maternal Smoking (Pardo et al., 2005)

Nicotine (Holloway et al., 2007)

Increased Adiponectin

DDE (Howell & Magnum, 2011)

Decreased IL-10

Air pollution (Sun et al., 2009)

Increased IL-10

POPs (Sonne et al., 2007)

Increased TNF α

TCDD (Kern et al., 2002; Nishiumi et al., 2010)

POPs (Sonne et al., 2007)

PCB-77 (Baker et al., 2013; Arsenescu et al., 2008)

Air pollution/PM2.5 (Laing et al., 2010)

BPA (Ben-Jonathan et al., 2009)

Increased IL-6

Air pollution/PM2.5 (Laing et al., 2010; Sun et al., 2009)

PCB-77 (Wang et al., 2010)

BPA (Ben-Jonathan et al., 2009)

Increased Resistin

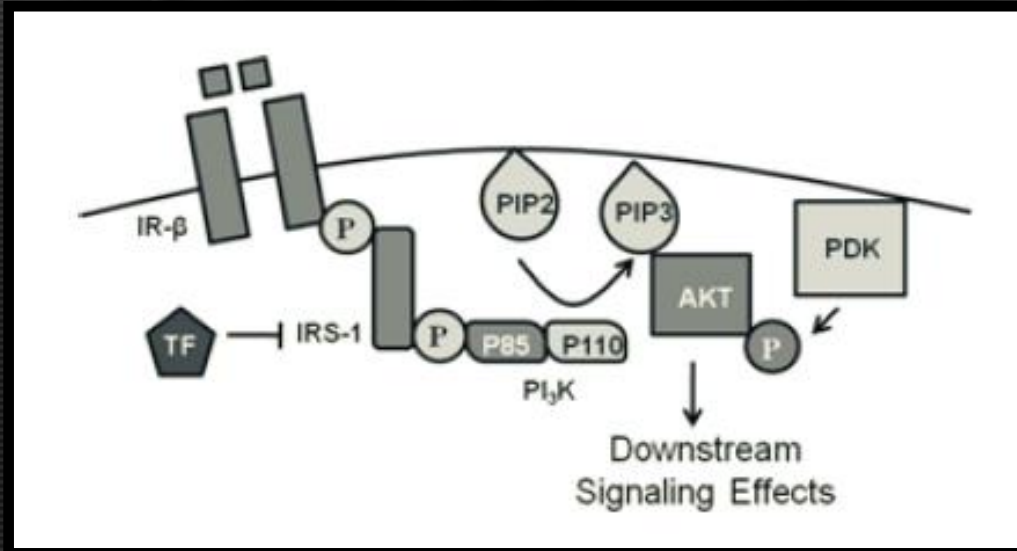
Air pollution/PM2.5 (Laing et al., 2010)

DDE (Howell & Magnum, 2011)

Increased MCP-1

PCB-77 (Arsenescu et al., 2008)

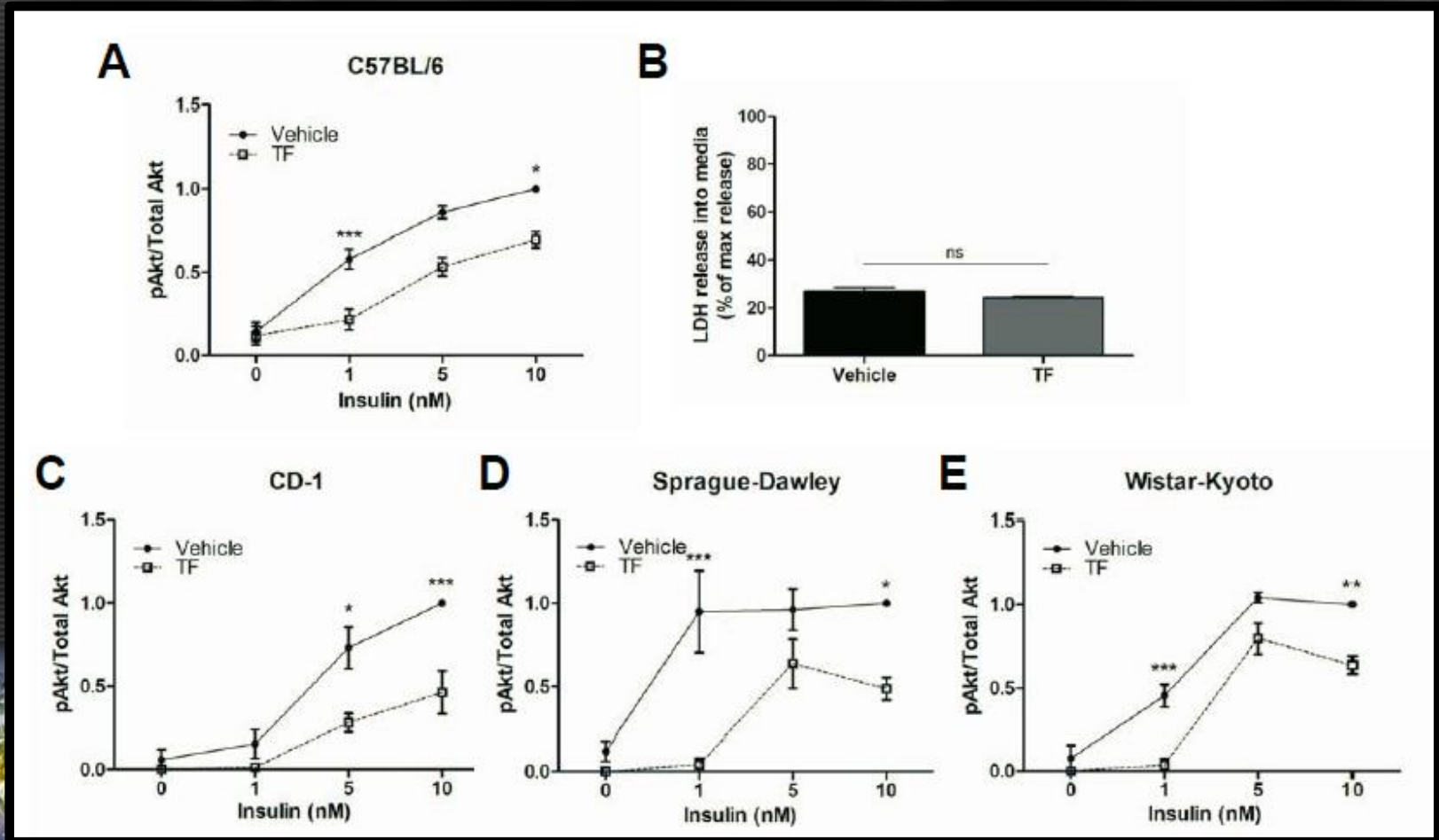
Disruption of Insulin Signaling



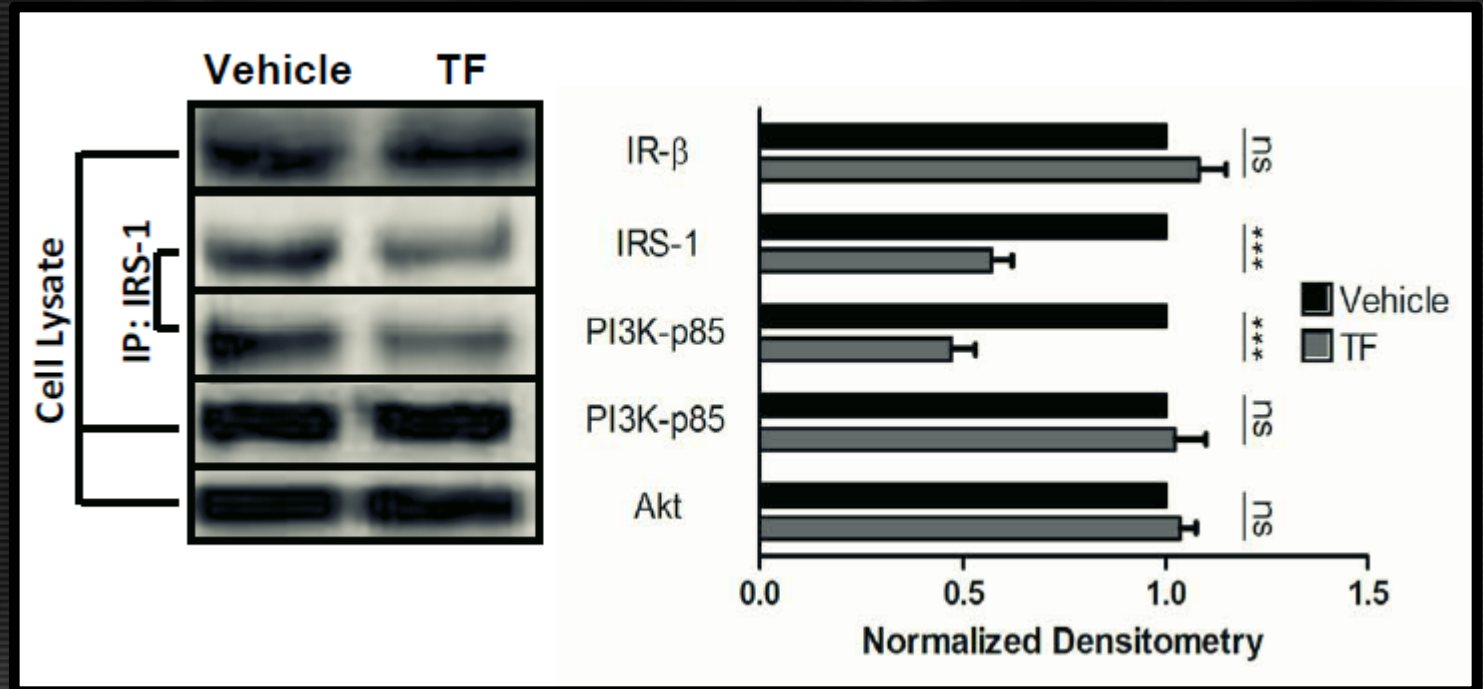
- Initiated by insulin binding to its surface receptor
- Cascade of intracellular events
- Phosphorylation of Akt
 - Readout of insulin action
- Culminate in downstream effects
 - Glucose uptake
 - Lipid synthesis



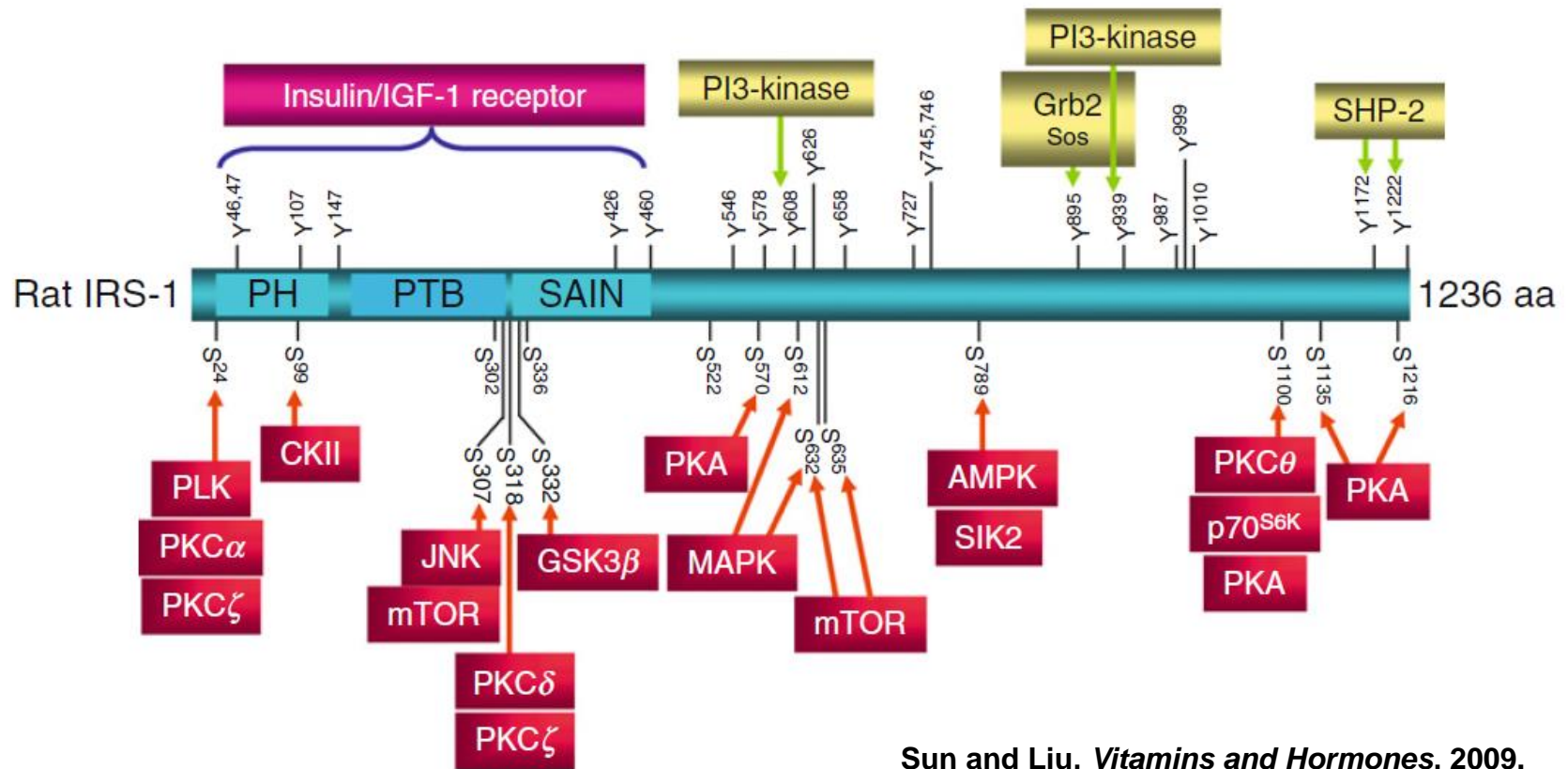
Tolyfluanid Impairs Insulin Action...



...through a Specific Reduction in IRS-1



IRS-1 as Integrator of Toxicity



Sun and Liu, *Vitamins and Hormones*, 2009.

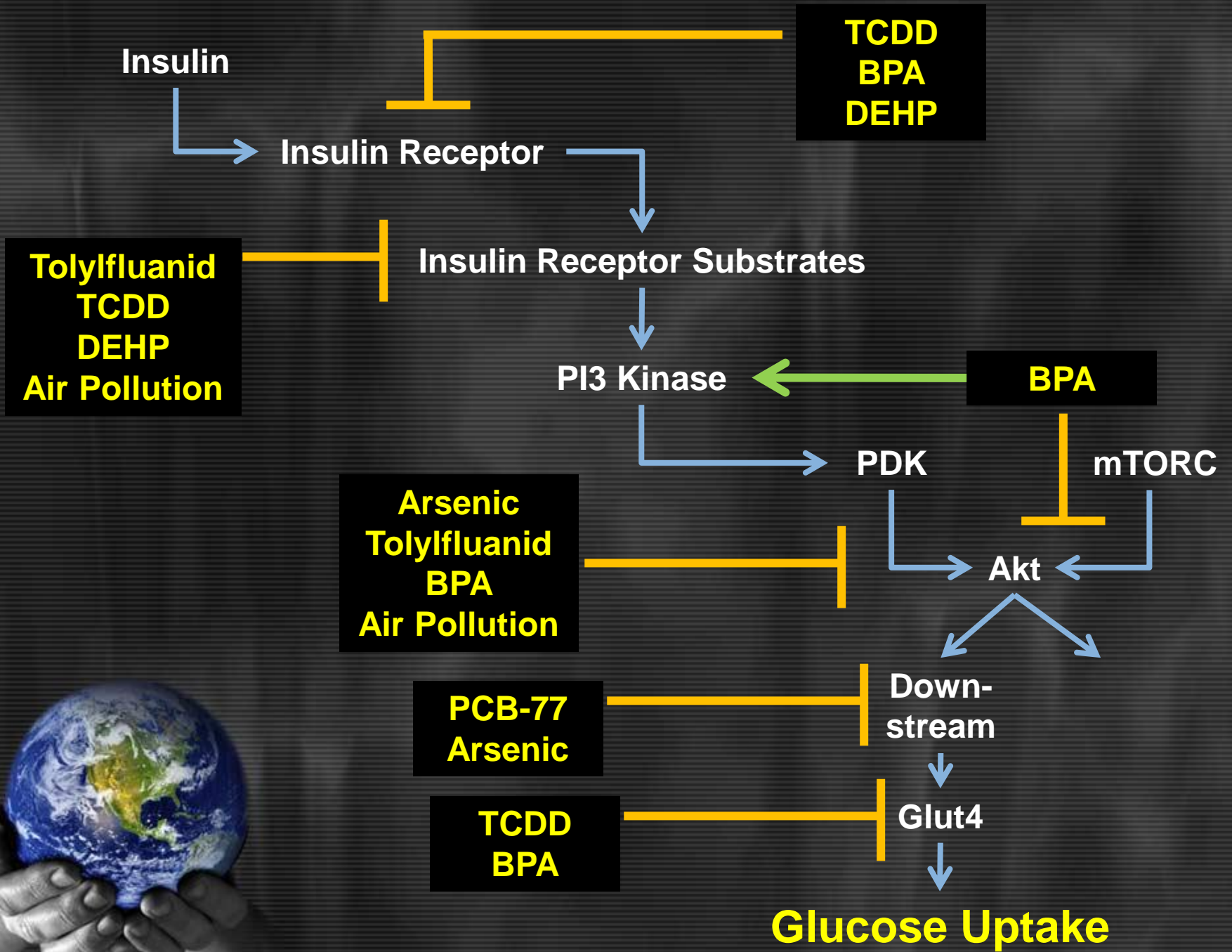
Air Pollution: \uparrow JNK (Zheng et al., 2013) and \uparrow PKC (Sun et al., 2009)

TCDD: \uparrow JNK and \uparrow MAPK (Nishiumi et al., 2010)

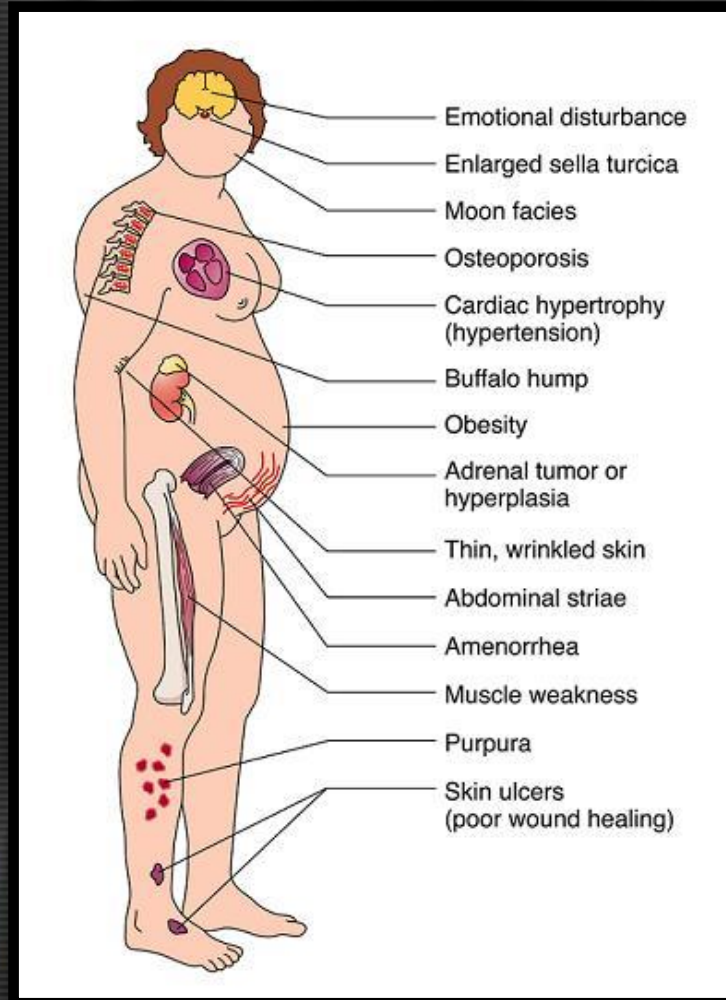
BPA: \uparrow PI3-kinase (Masuno et al., 2005)

Arsenic: \downarrow p70-S6-kinase (Yen et al., 2010)

PCBs: \uparrow CKII and \uparrow MAPK (Fischer et al., 1999)



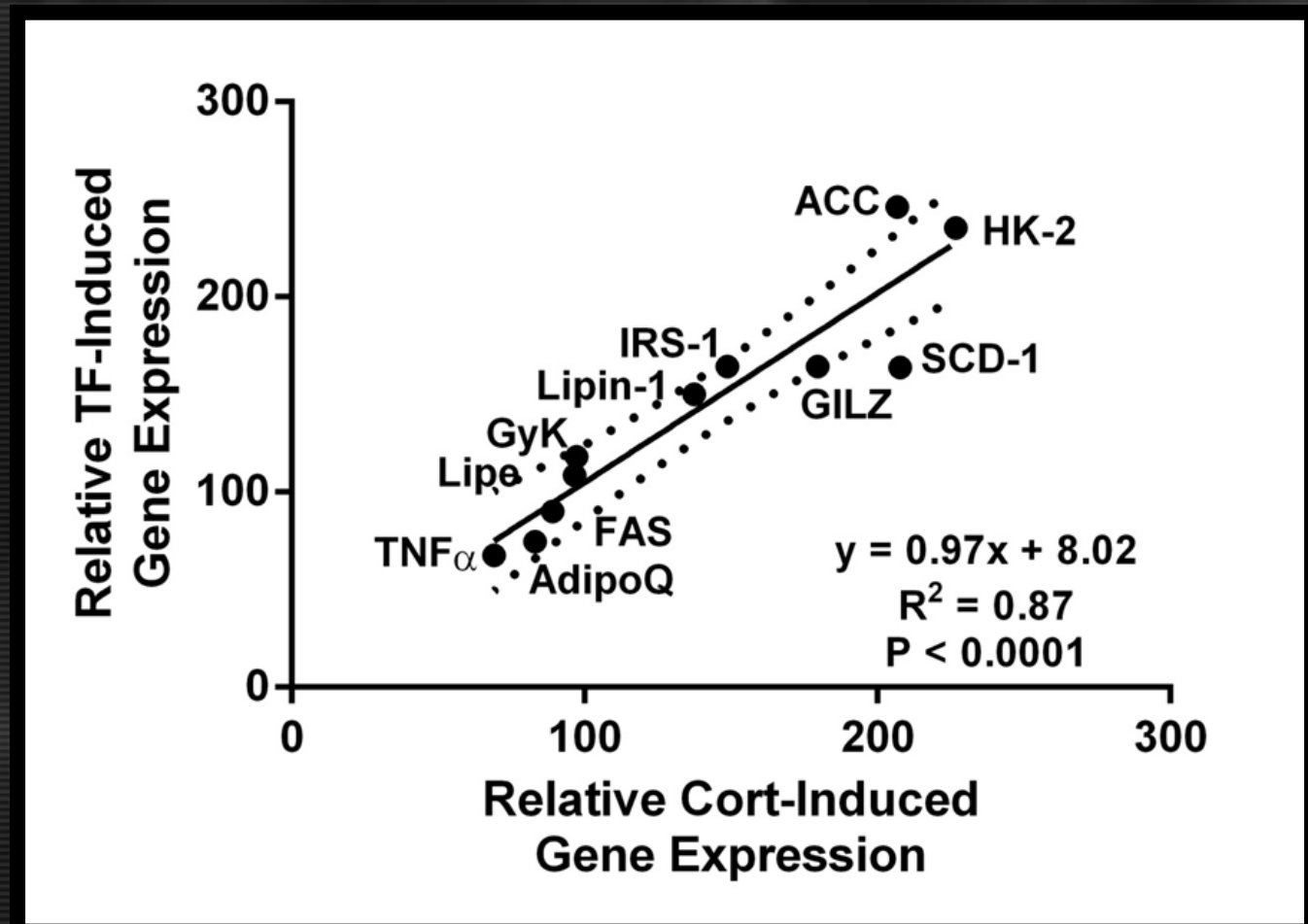
Glucocorticoid Disruption of Metabolism



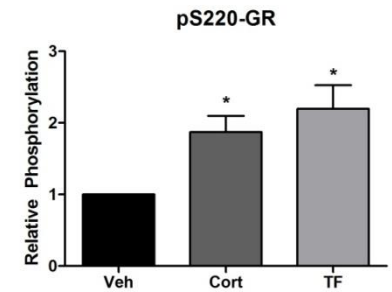
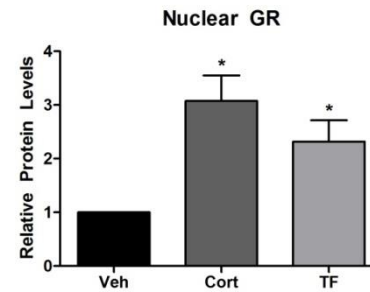
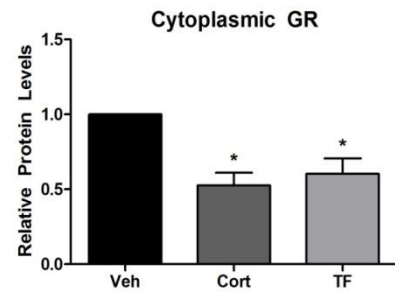
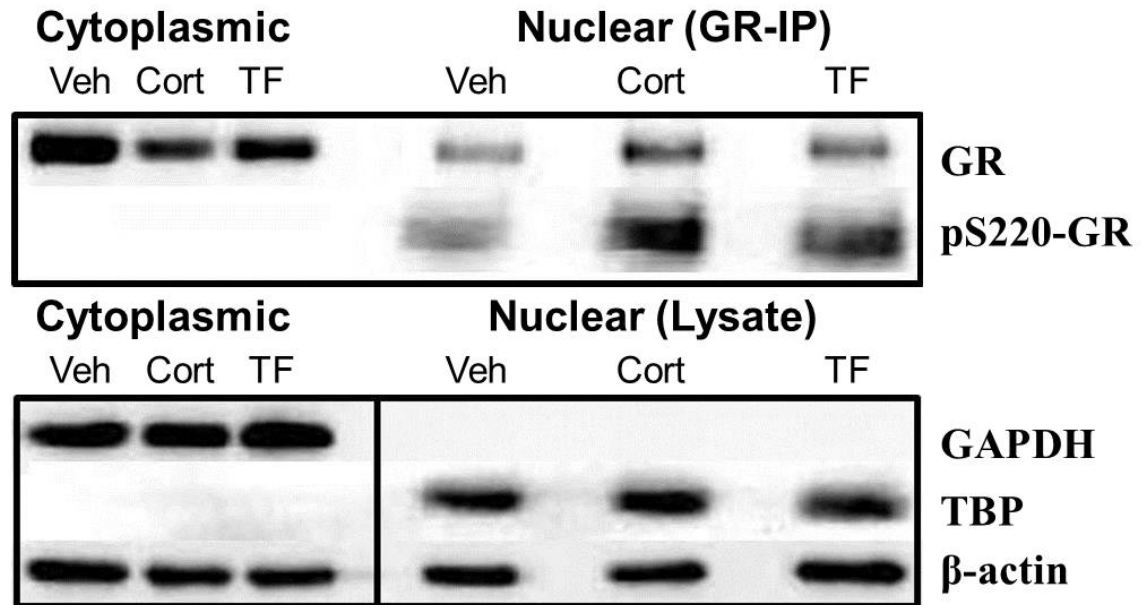
- **Cushing's Syndrome**
 - Visceral obesity
 - Insulin resistance
 - Diabetes
- **Attractive target for metabolic disruption**
- **Few studies have investigated disruption of glucocorticoid signaling.**
 - Generally restricted to modulation of 11β -HSD-1/2



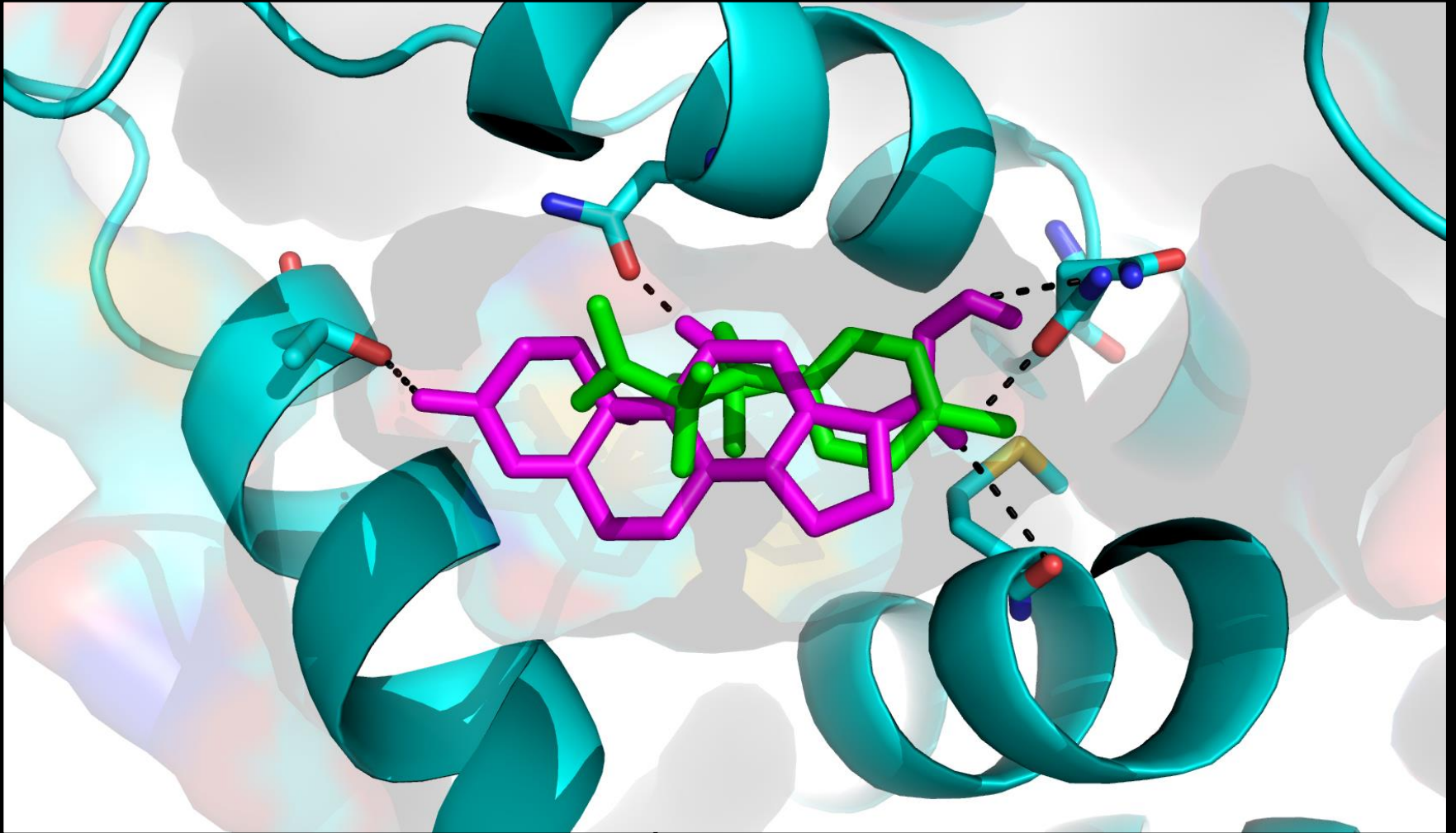
Transcriptional Synchrony



GR Nuclear Translocation

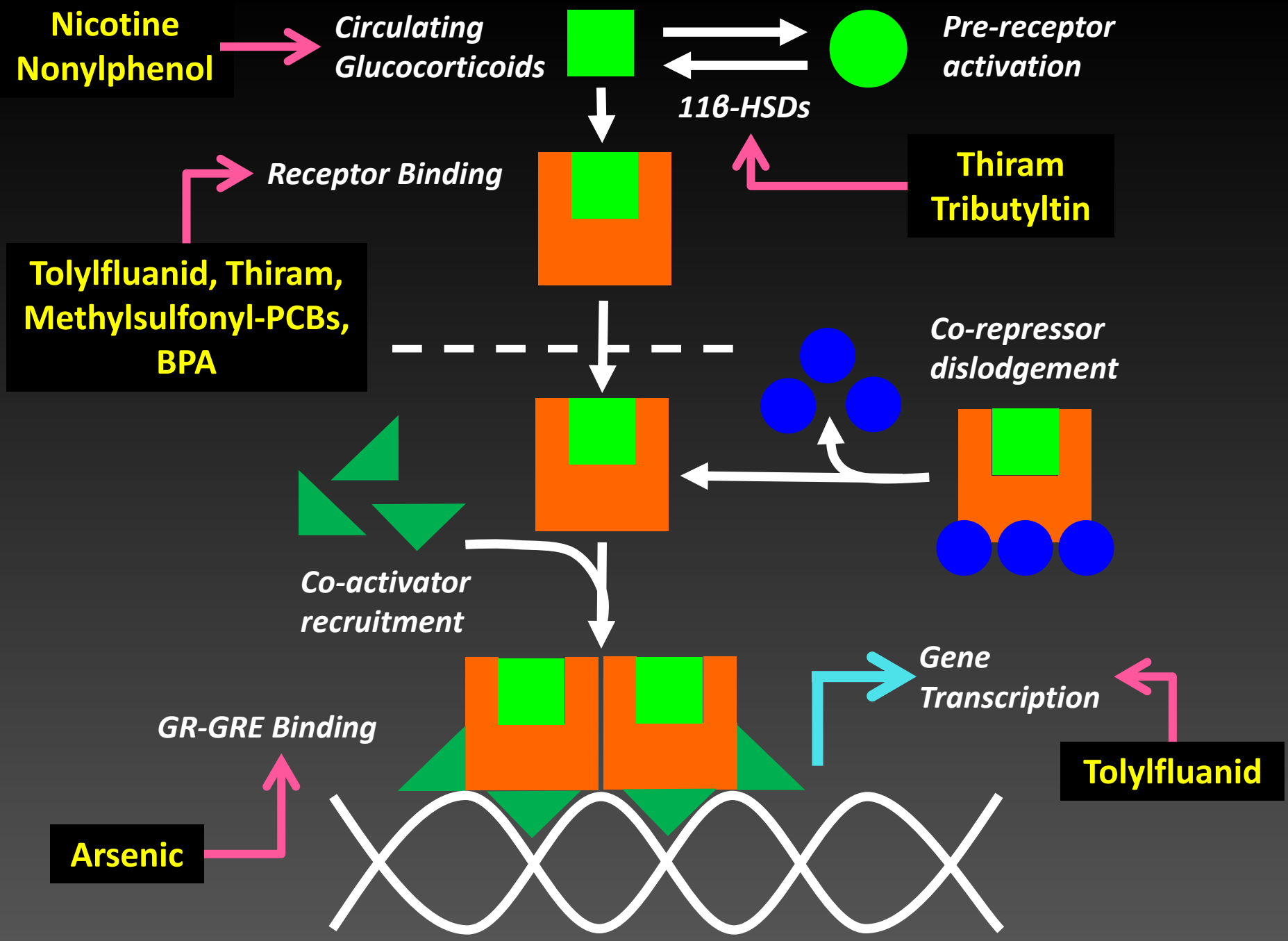


In Silico Binding to GR LBD



$\Delta G = -6.3$ kcal/mol vs. $\Delta G = -9.8$ kcal/mol

Neel et al., *Mol Endo*, 2013.



Environmental Challenges in a Growing Asia



Stevewebel.com



theguardian.com

Air Pollution

Hyperinsulinism/insulin resistance

↓ adiponectin; ↑ $\text{TNF}\alpha$; ↑ IL-6

↓ Insulin signaling

↑ JNK; ↑ PKC

↑ ER stress; ↑ mitochondrial stress; ↑ oxidative stress



Environmental Challenges in a Growing Asia

PNAS

Release of arsenic to deep groundwater in the Mekong Delta, Vietnam, linked to pumping-induced land subsidence

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Arsenic

Hyperinsulinism/insulin resistance

Glucose intolerance

↓ β -cell function

↓ Myoblast differentiation

↓ Adipocyte differentiation

↓ Glucose uptake

Altered glucocorticoid activity

↓ Insulin signaling

↑ JNK; ↑ PKC



Toxicology-Metabolism Synergy

Mechanism of Diabetes

Known

Unknown

Mechanism of Toxicity

Known

Unknown

Predictions of diabetogenic chemicals

- *A priori*
- Screens

Novel pathways leading to diabetes.

- New therapies

Novel pathways leading to toxicity.

- New therapies
- Screens

Potentially new areas of biology



Our Team

- Celeste Thomas, MD, MS
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- Andrew Kirkley
- Wakanene Kamau

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