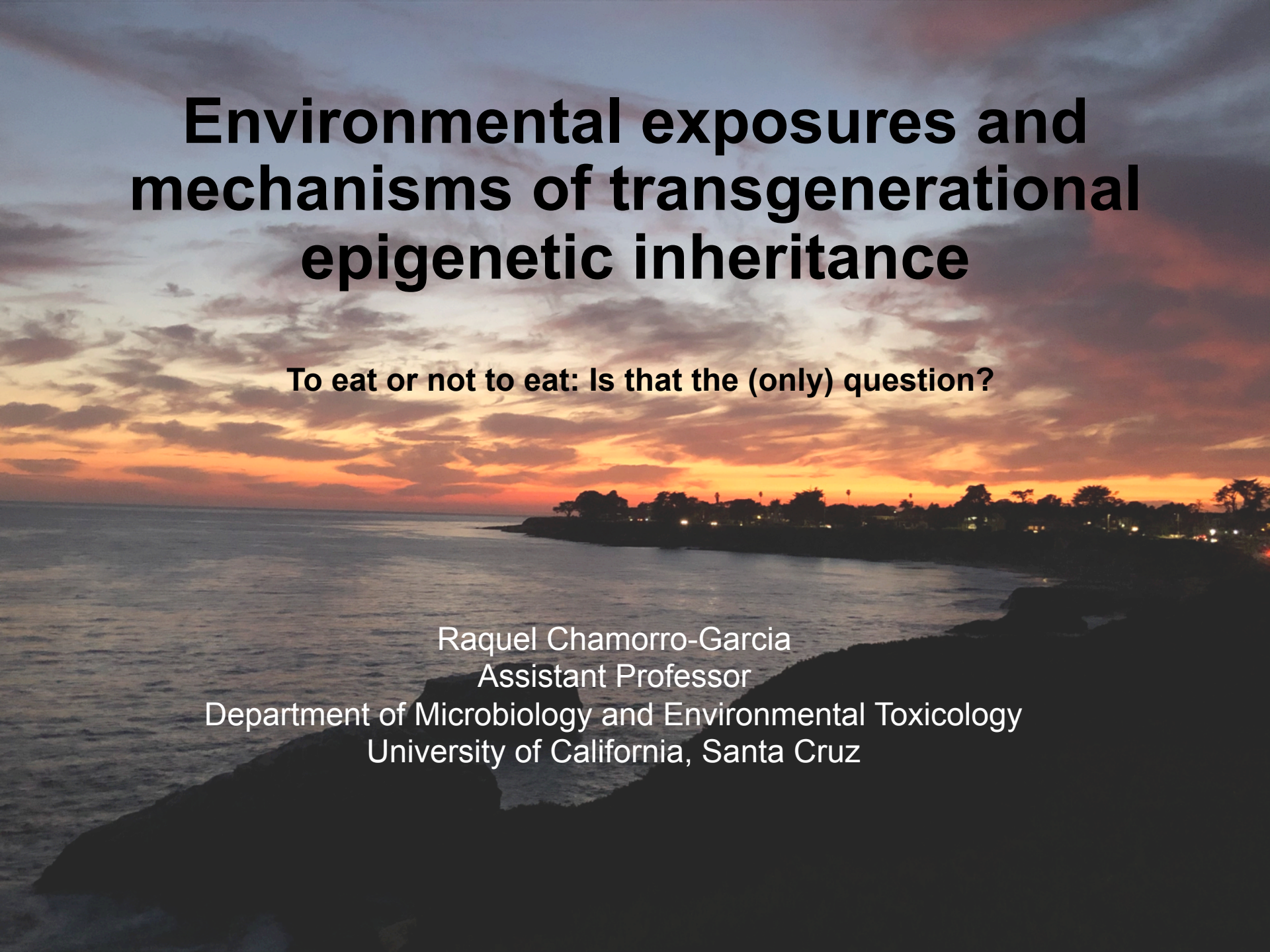


Environmental exposures and mechanisms of transgenerational epigenetic inheritance

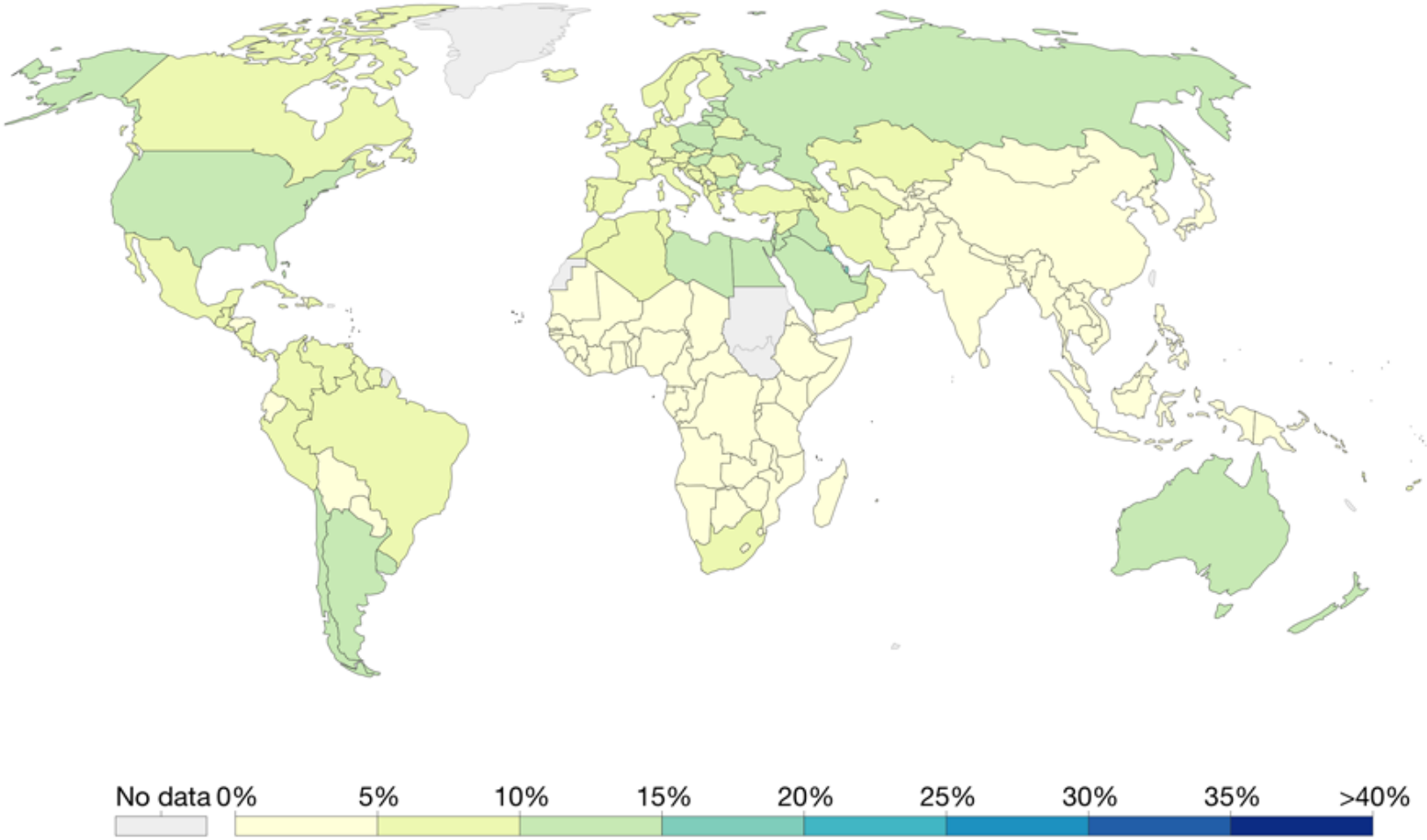
To eat or not to eat: Is that the (only) question?

Raquel Chamorro-Garcia
Assistant Professor
Department of Microbiology and Environmental Toxicology
University of California, Santa Cruz

Share of adults that are obese, 1975

Obesity is defined as having a body-mass index (BMI) equal to or greater than 30. BMI is a person's weight in kilograms divided by his or her height in metres squared.

Our World in Data



Source: WHO, Global Health Observatory

OurWorldInData.org/obesity • CC BY

Share of adults that are obese, 2016

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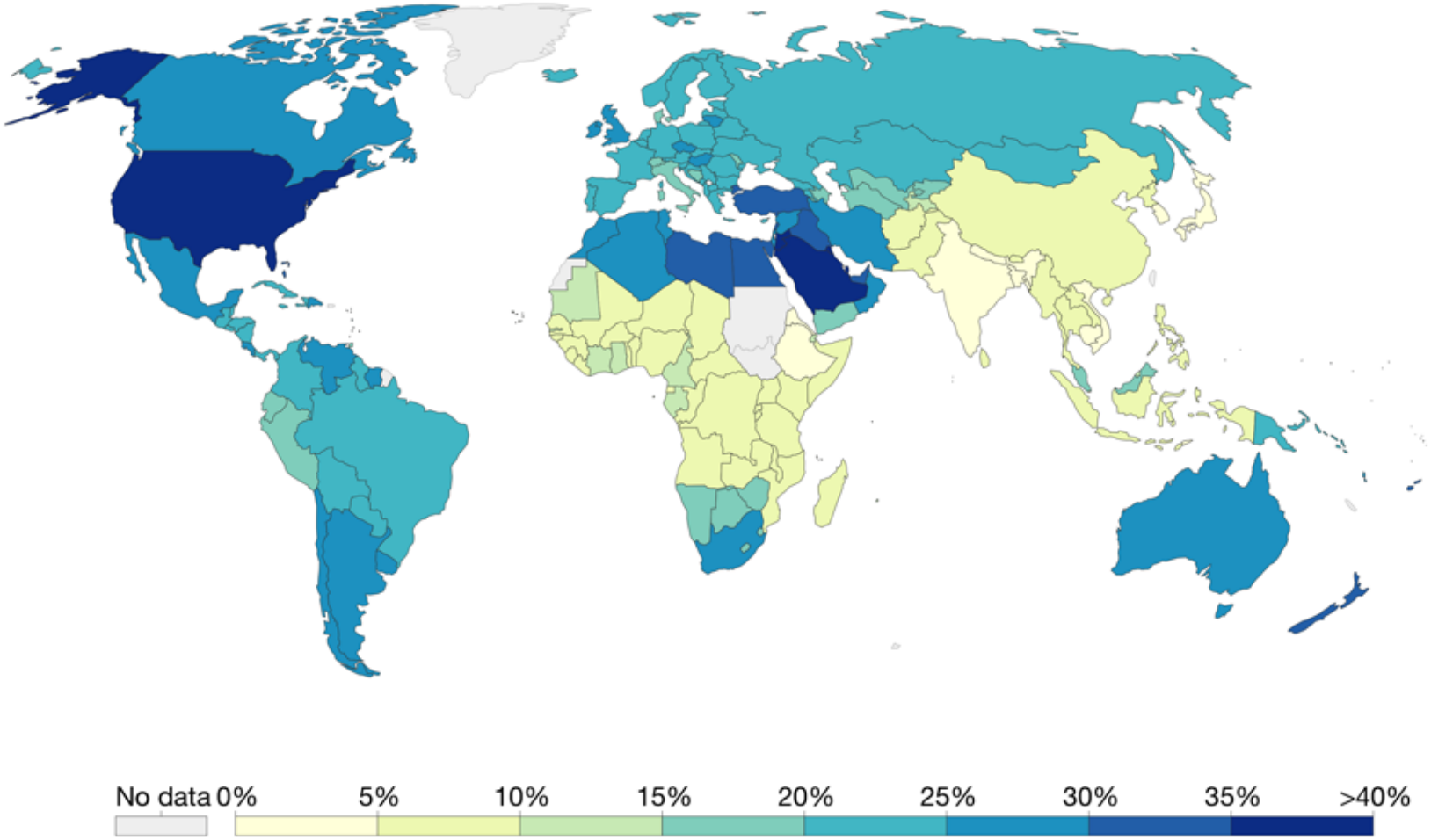


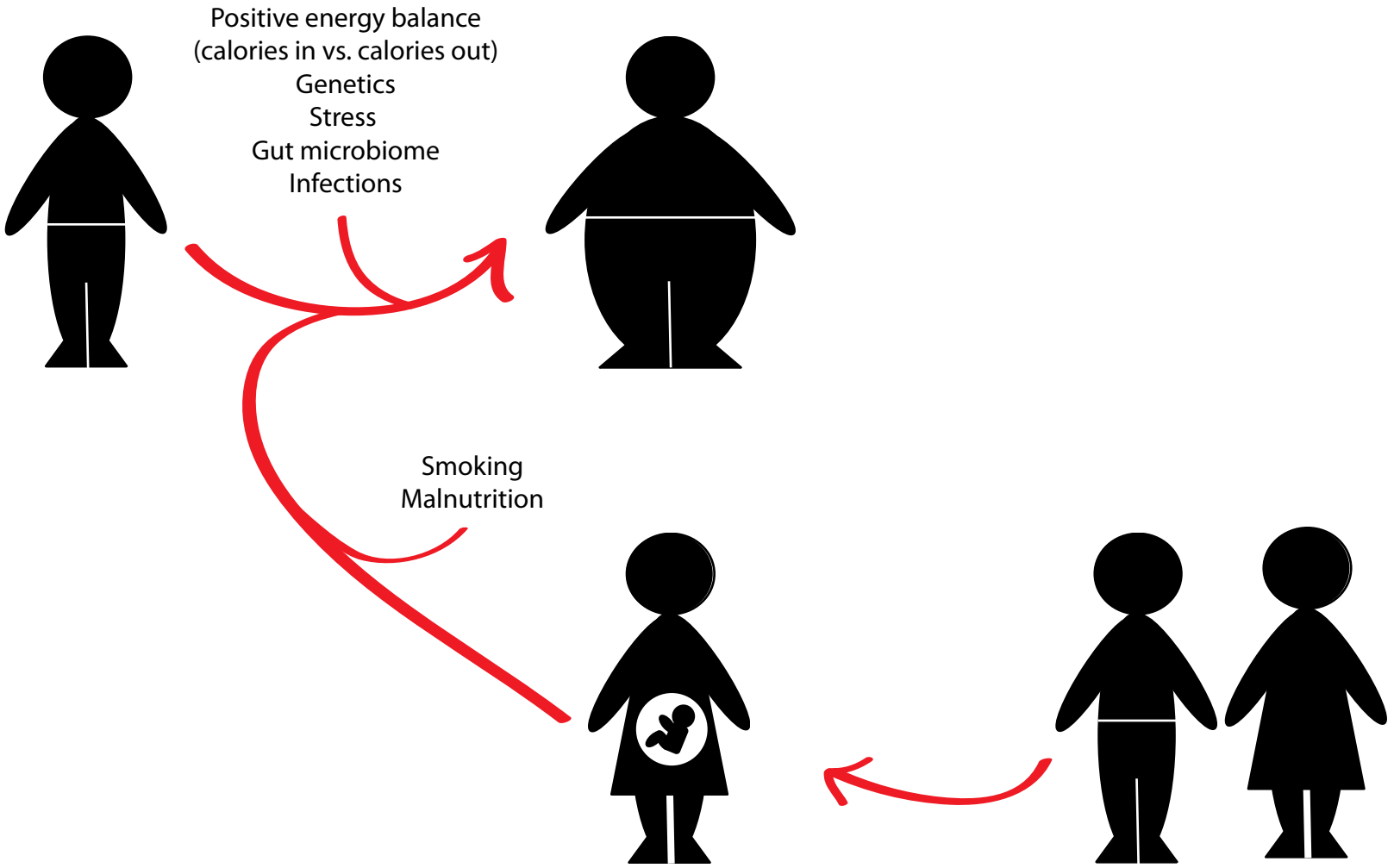
Source: WHO, Global Health Observatory

OurWorldInData.org/obesity • CC BY

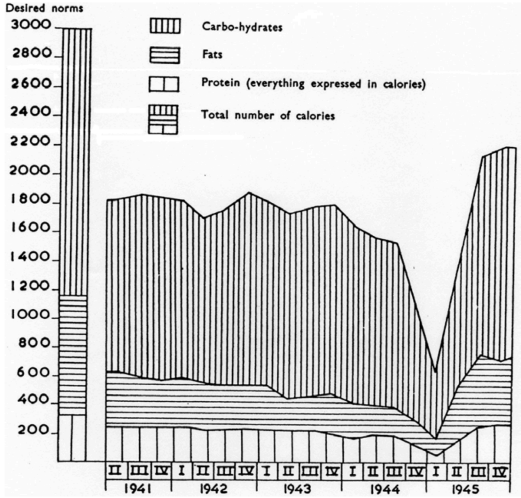
Global impact of obesity

Global Burden of Obesity		
Health	**Economy**	**Social**
• Cardiovascular disease • Diabetes • Musculoskeletal disorders • Cancer	• $2.0 trillion worldwide • Direct costs • Indirect costs	• Developing countries cannot afford the costs • Stigma

Contributing factors to obesity



Multigenerational studies in humans
Dutch famine



Lumey & Poppel, 2013

Preconception & in utero exposure to famine

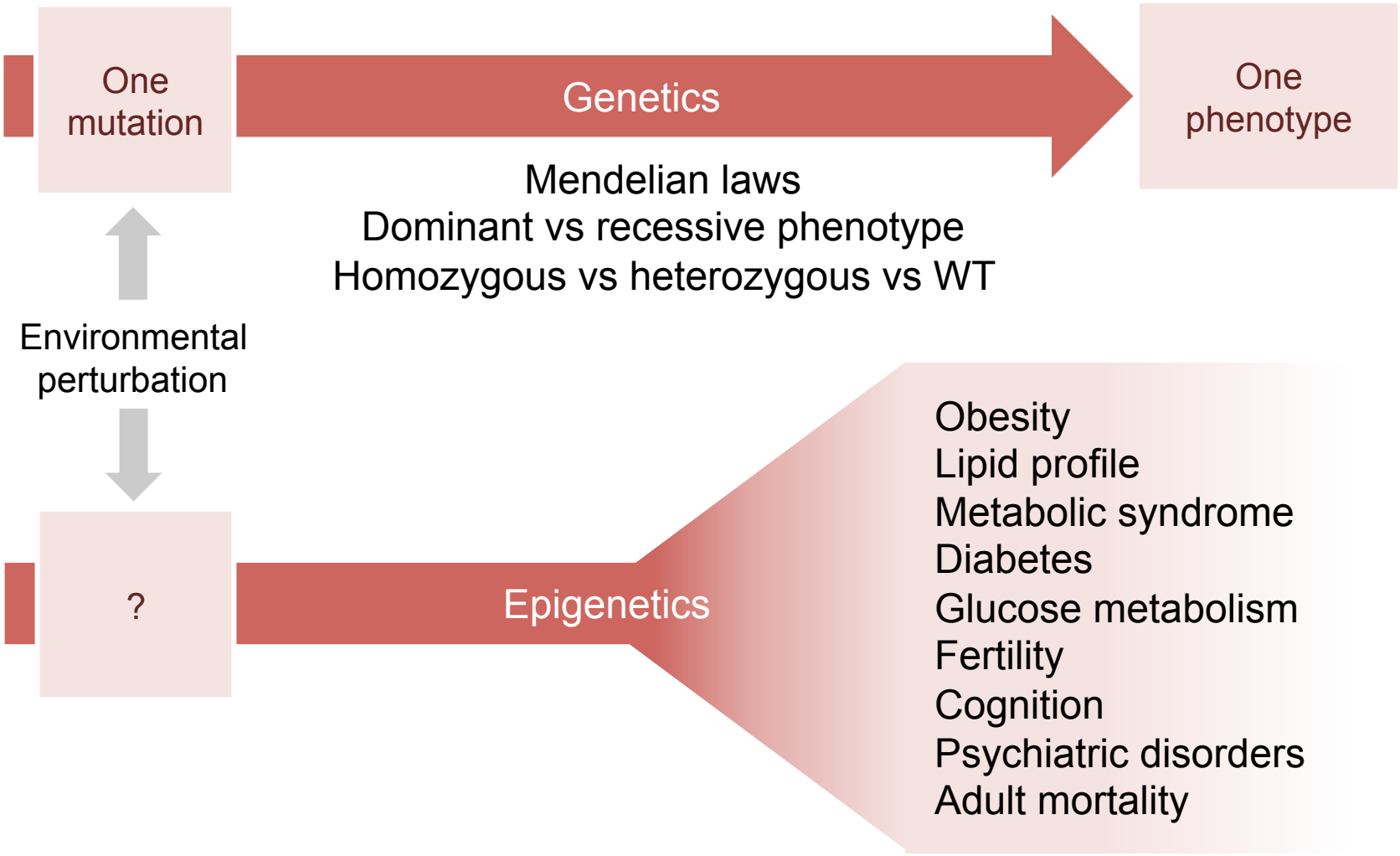
Health Outcomes in offspring

F2 offspring from F1 women

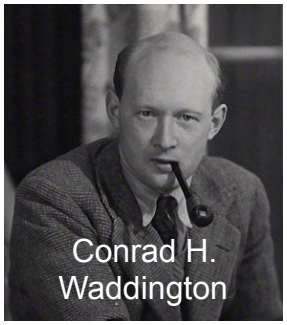
Obesity, lipid profile, metabolic syndrome
Diabetes, glucose metabolism
Fertility
Cognition, psychiatric disorders
Adult mortality

Poor health

Multigenerational inheritance

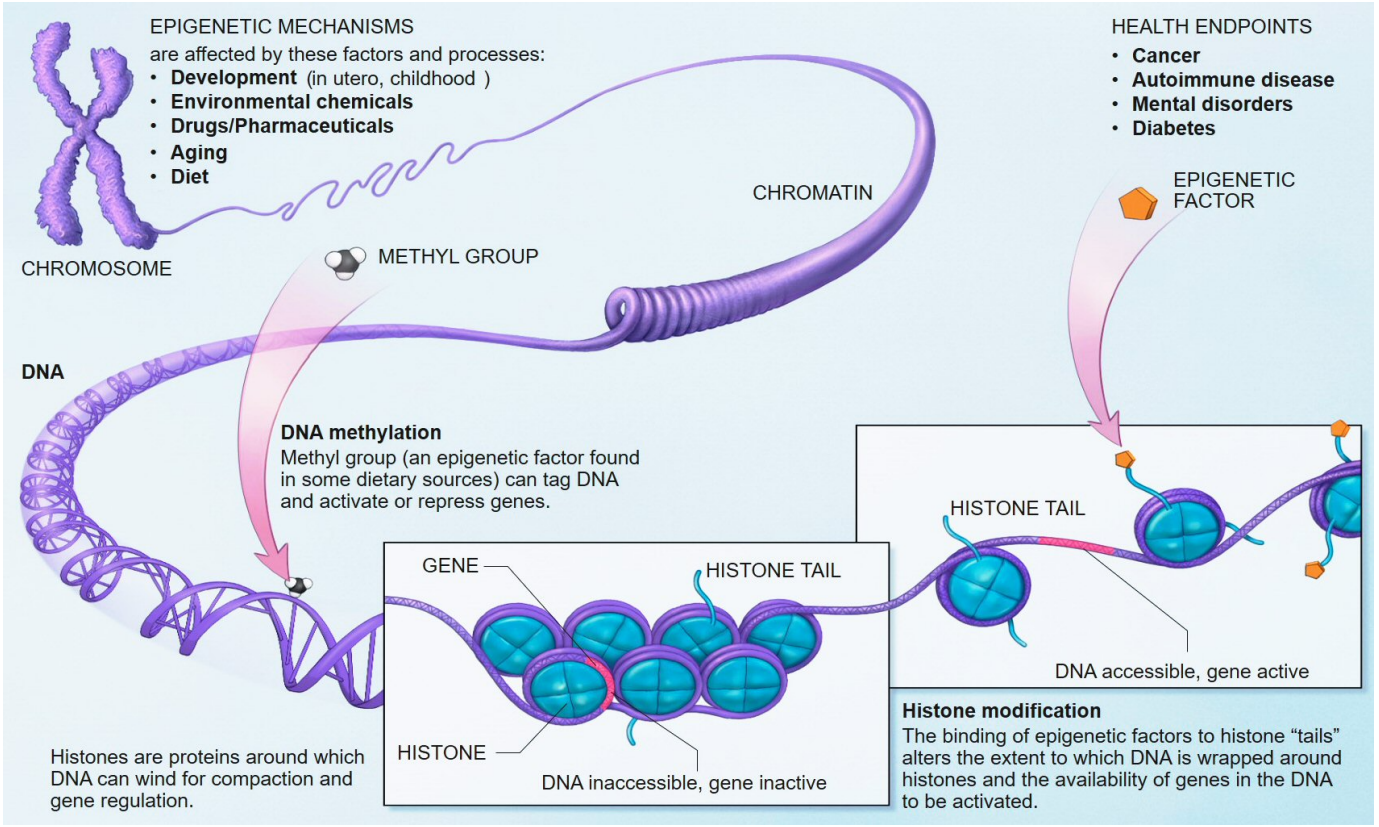


Epigenetics



Alterations that lead to a “stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence”

- Cold Spring Harbor Conference, 2008



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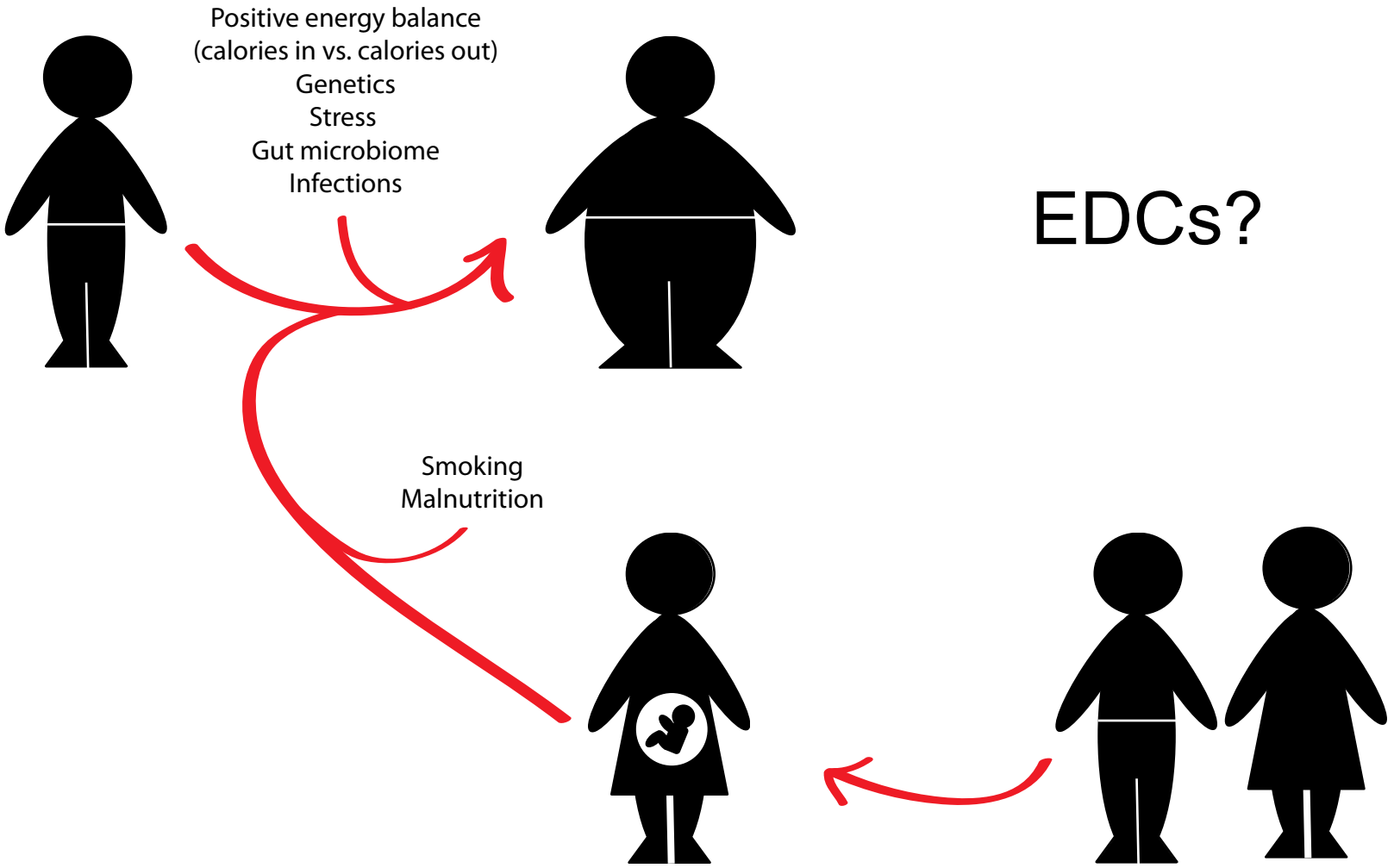
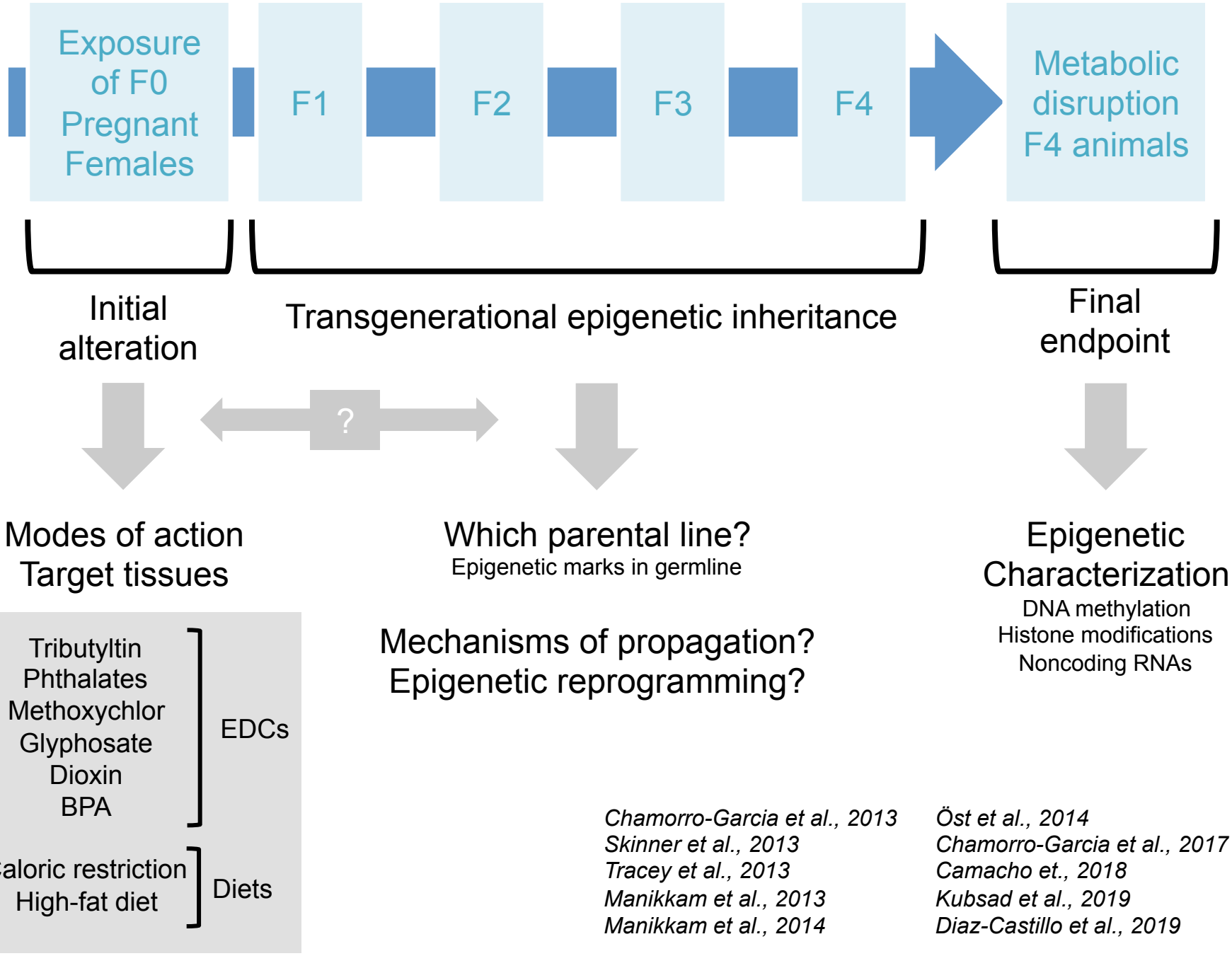




Chamorro-Garcia et al., 2013
Skinner et al., 2013
Tracey et al., 2013
Manikkam et al., 2013
Manikkam et al., 2014
Öst et al., 2014
Chamorro-Garcia et al., 2017
Camacho et., 2018
Kubsad et al., 2019
Diaz-Castillo et al., 2019

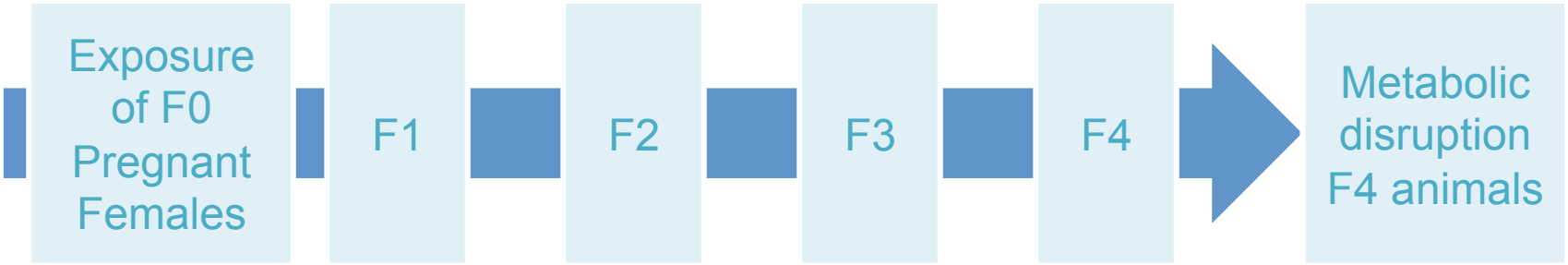
Exposure of F0 Pregnant Females → F1 → F2 → F3 → F4 → Metabolic disruption F4 animals

Tributyltin

Biocide

Seafood

Metabolic disruptor



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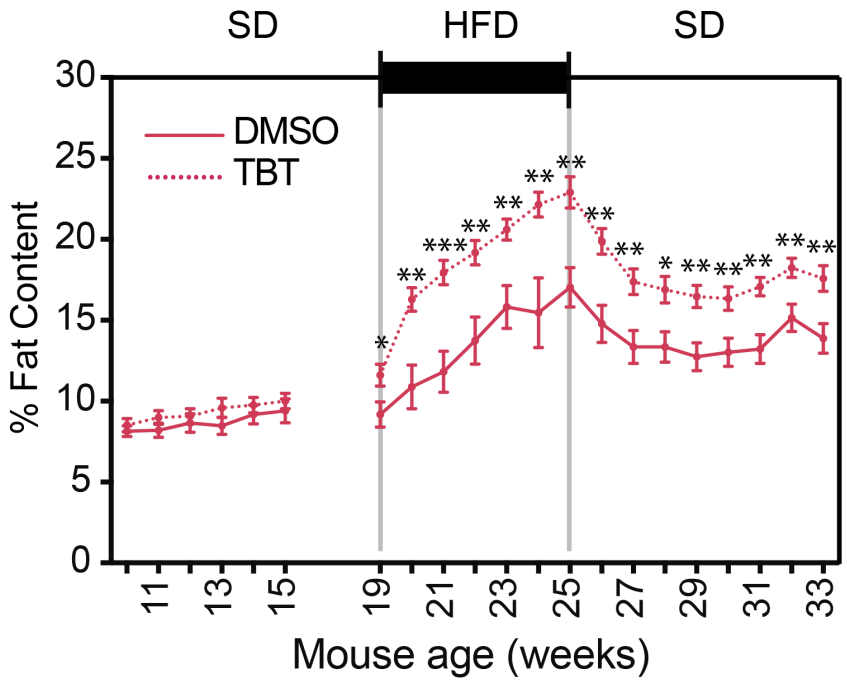
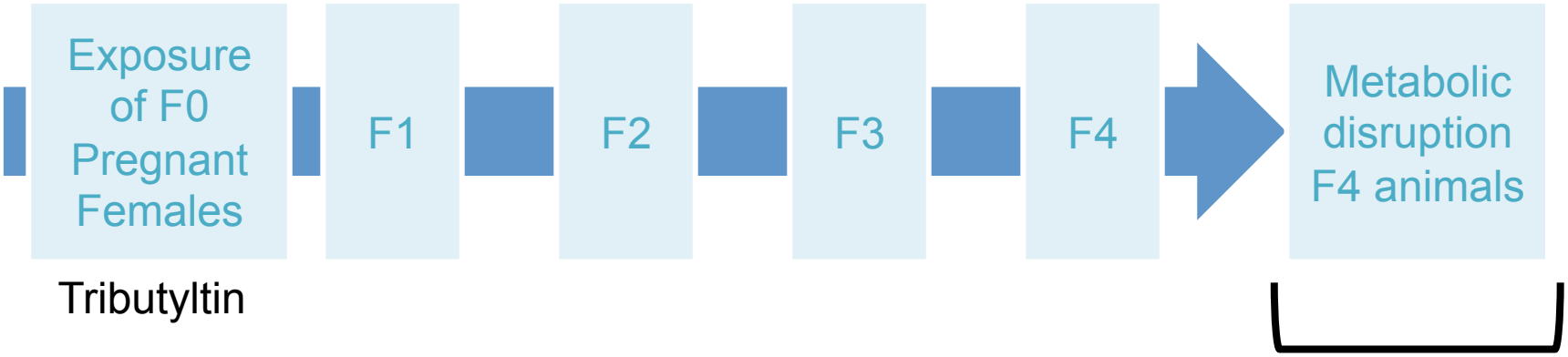


SD: Standard Diet

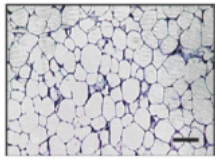
HFD: High Fat Diet

Chamorro-Garcia et al., Nat Comms, 2017



Hypothesis I: *TBT alters DNA methylation of promoters for metabolically-relevant genes*

Rejected



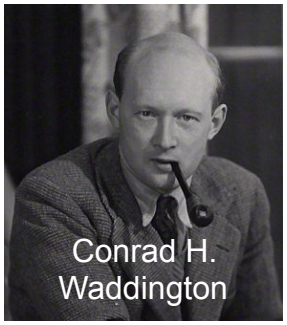
F4
Adipose tissue

Hypothesis II: *TBT alters nuclear genome organization*

Alterations in methylome & transcriptome

Chamorro-Garcia et al., Nat Comms, 2017

Epigenetics



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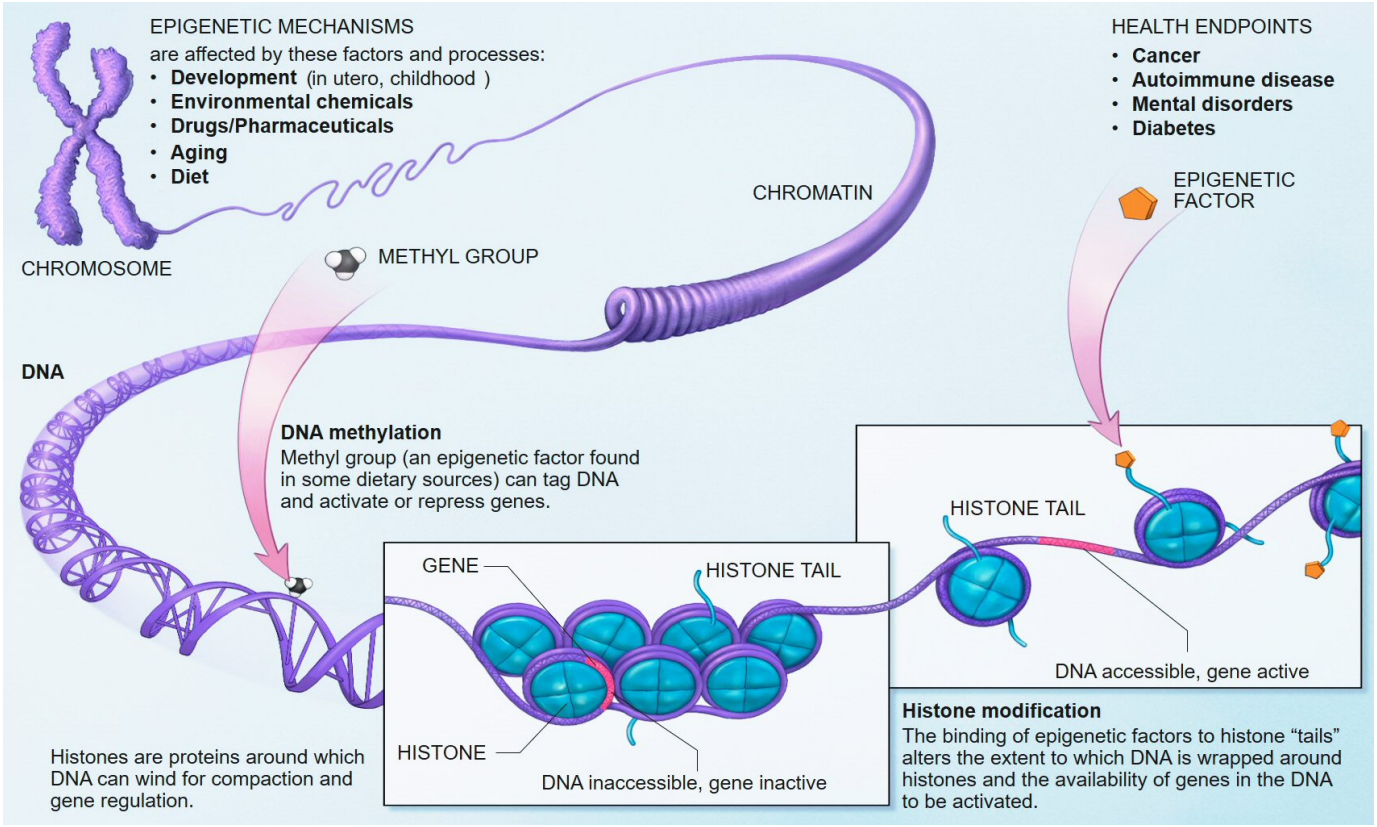
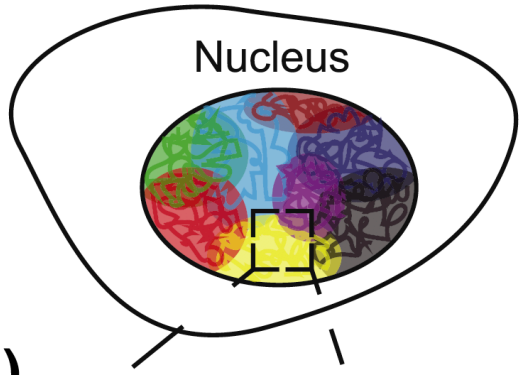


National Institutes of Health - http://commonfund.nih.gov/epigenomics/figure.aspx

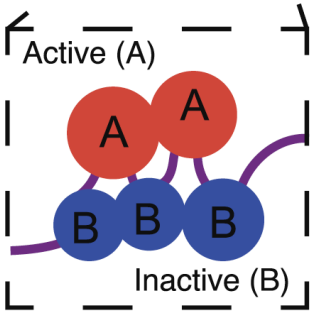
Nuclear genome organization

(A)

Eukaryotic cell

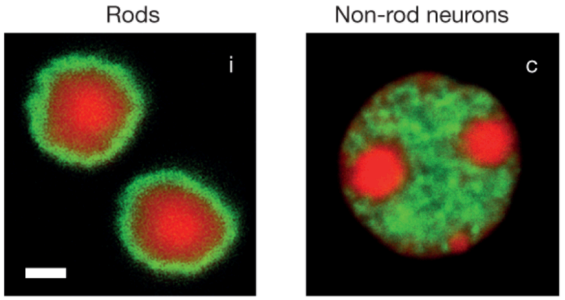


(B)



Chromosome compartments

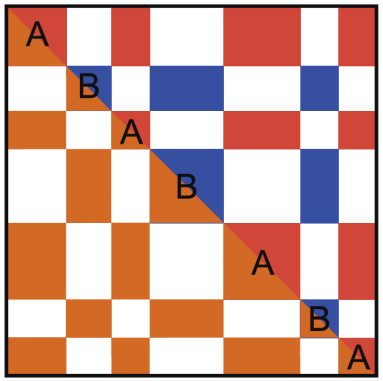
Immunofluorescence



Euchromatin
Heterochromatin

Hi-C

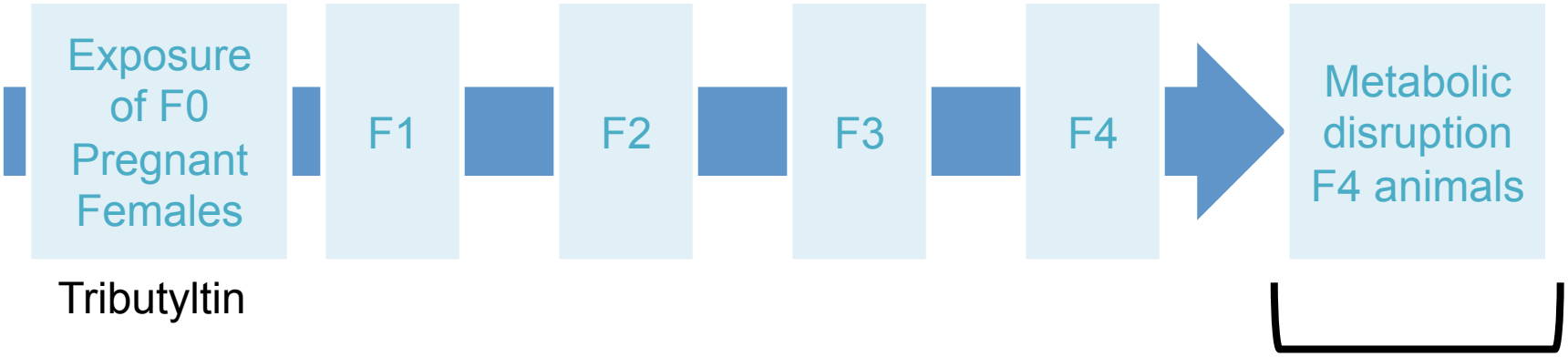
(D)



Schematic of compartment signal by Hi-C

Compartment A	**Compartment B**
Euchromatin	Heterochromatin
Active genes,	Transcriptionally inactive
Higher accessibility	Less accessible
High GC content	High AT content

Hildebrand & Dekker, 2020 – Trends Biochem Sci
Falk et al., 2019 - Nature



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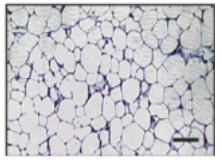

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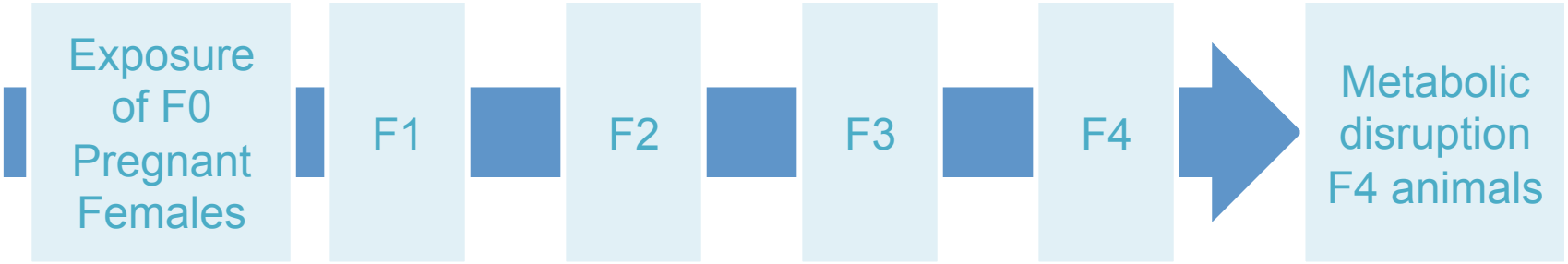
Alterations in methylome & transcriptome

Chamorro-Garcia et al., Nat Comms, 2017



Tributyltin

How?

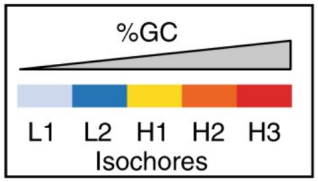
Isochores

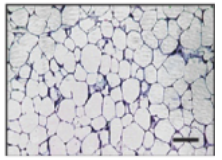
- Large regions of DNA (>300 Kb) with highly homogenous base composition (GC- vs. AT-content)
- Reflect multiple levels of organization (TADs, eu-/heterochromatin, compartment A/B)
- Are invariable across tissues, generations and sexes

- Analysis of genomic traits with regards isochores before and after randomly rearranging datasets 10,000 times

Compartment B
Heterochromatin
AT-enriched

Compartment A
Euchromatin
GC-enriched

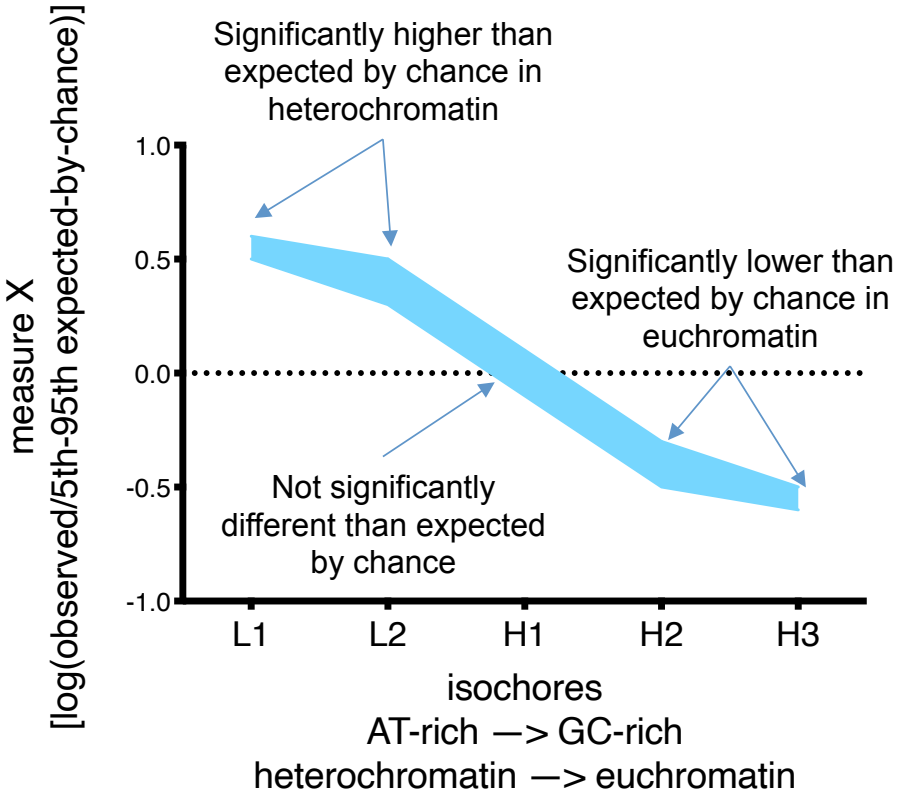


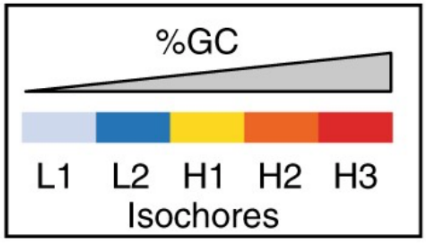


F4
Adipose tissue

Alterations in methylome & transcriptome

Heterochromatin-euchromatin organization disruption TBT vs Control





Exposure of F0 Pregnant Females

F1

F2

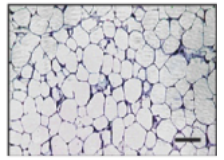
F3

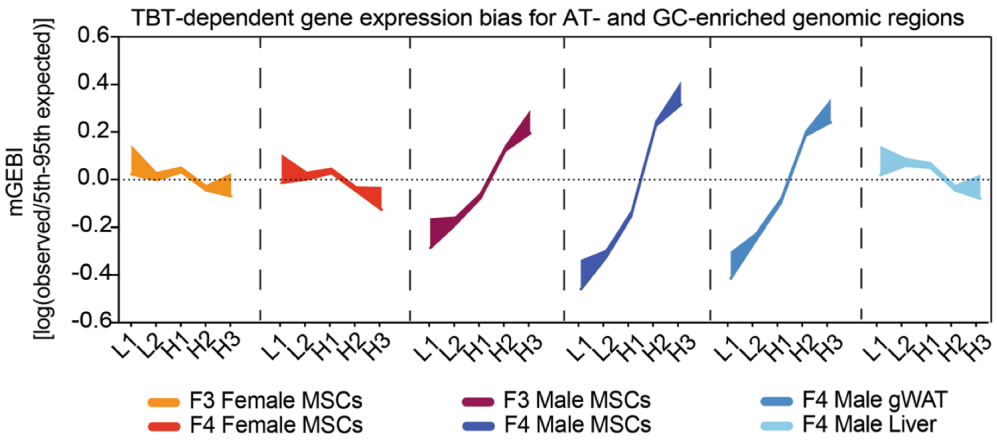
F4

Metabolic disruption F4 animals

Tributyltin

Molecular mechanism?





Fat tissue
Liver
MSCs

Males & Females

Transcriptome
&
Methylome

F4
Adipose tissue

Alterations in methylome & transcriptome

Nuclear genome organization

Chamorro-Garcia et al., Nat Comms, 2017

Diaz-Castillo et al., Sci Rep, 2019

Exposure of F0 Pregnant Females

F1

F2

F3

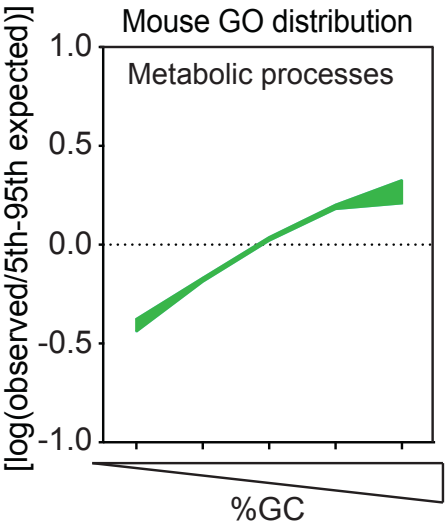
F4

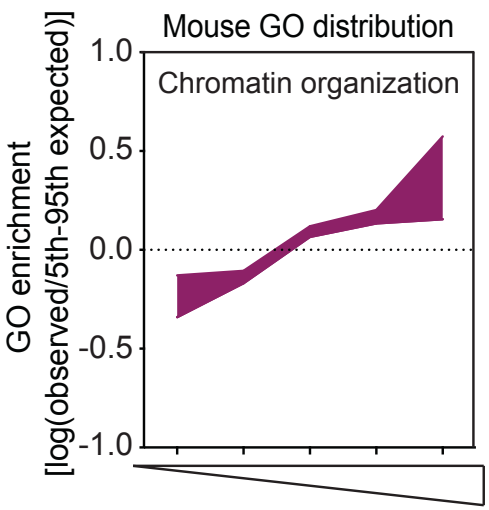
Metabolic disruption F4 animals

Tributyltin

Self reconstructive propagation

Molecular mechanism?





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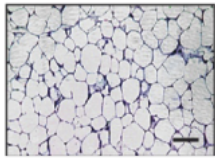

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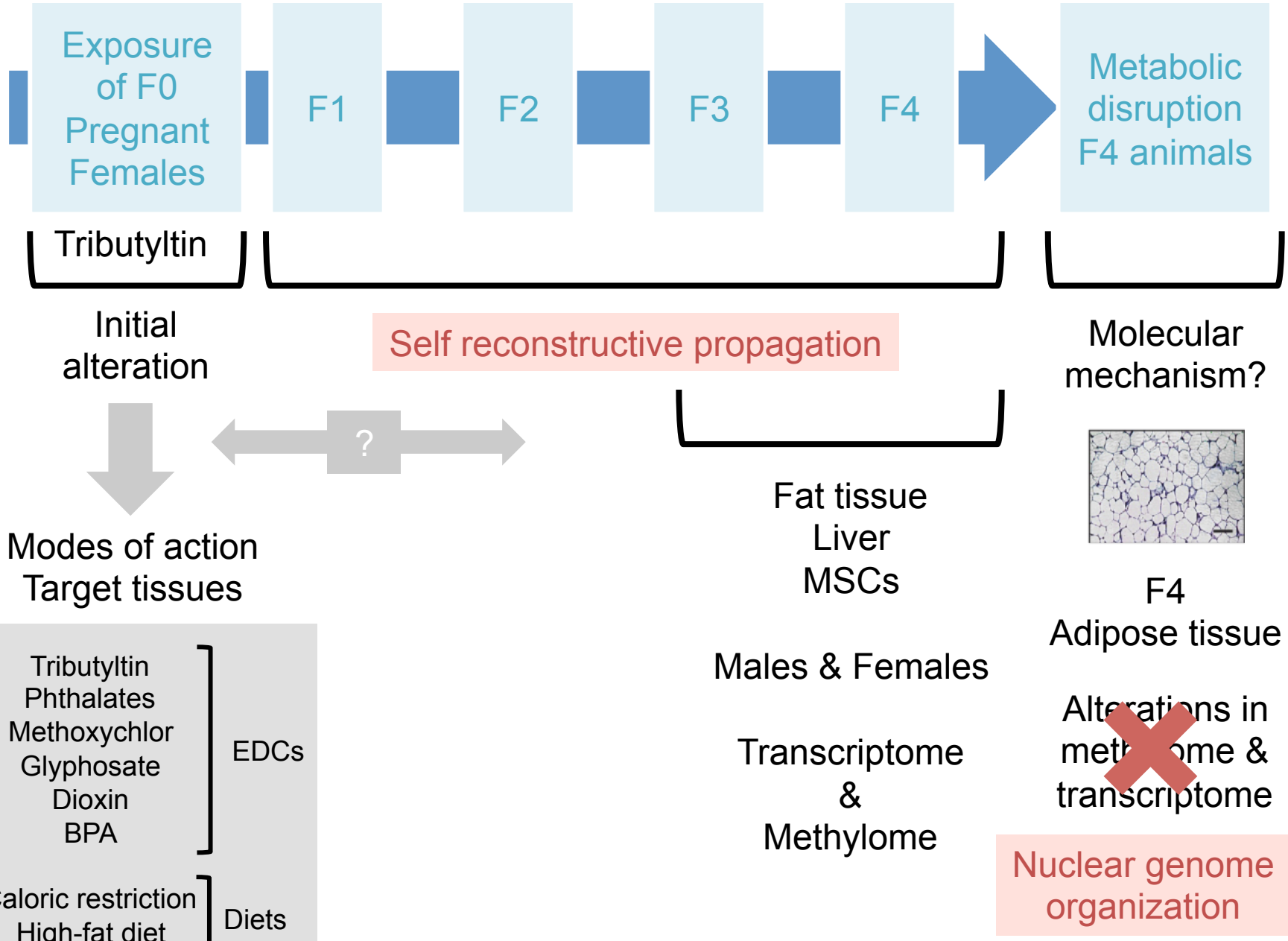

Chamorro-Garcia et al., Nat Comms, 2017

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Prithvi Singh

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Diana Laird, UCSF

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Institute for the Biology of Stem Cells

MICROBIOLOGY ENVIRONMENTAL TOXICOLOGY

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Riann Egusquiza
Bassem Shoucri
Heidi Kaech
Ron Leavitt

MGH-Harvard Med School
Toshi Shioda

INRA-Toxalim, Toulouse, France
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