



EMSG49: Reprogramming of DNA methylation during mammalian development and environmental impact of Endocrine Disruptors

13th Annual Workshop 2011

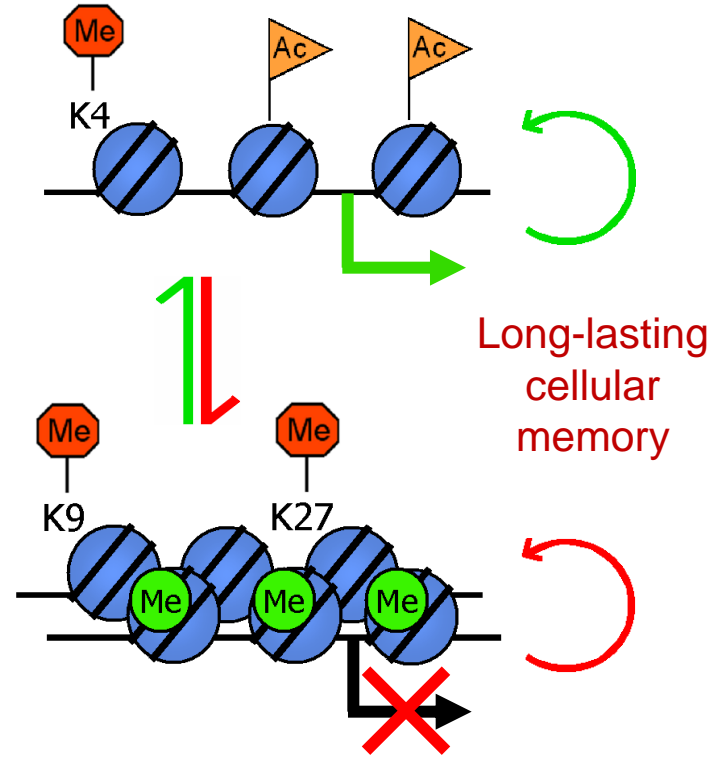


Dr. Michaël WEBER

UMR 7242 *“Biotechnology and Cell Signalling”*
CNRS/University of Strasbourg

DNA+Histones=Chromatin

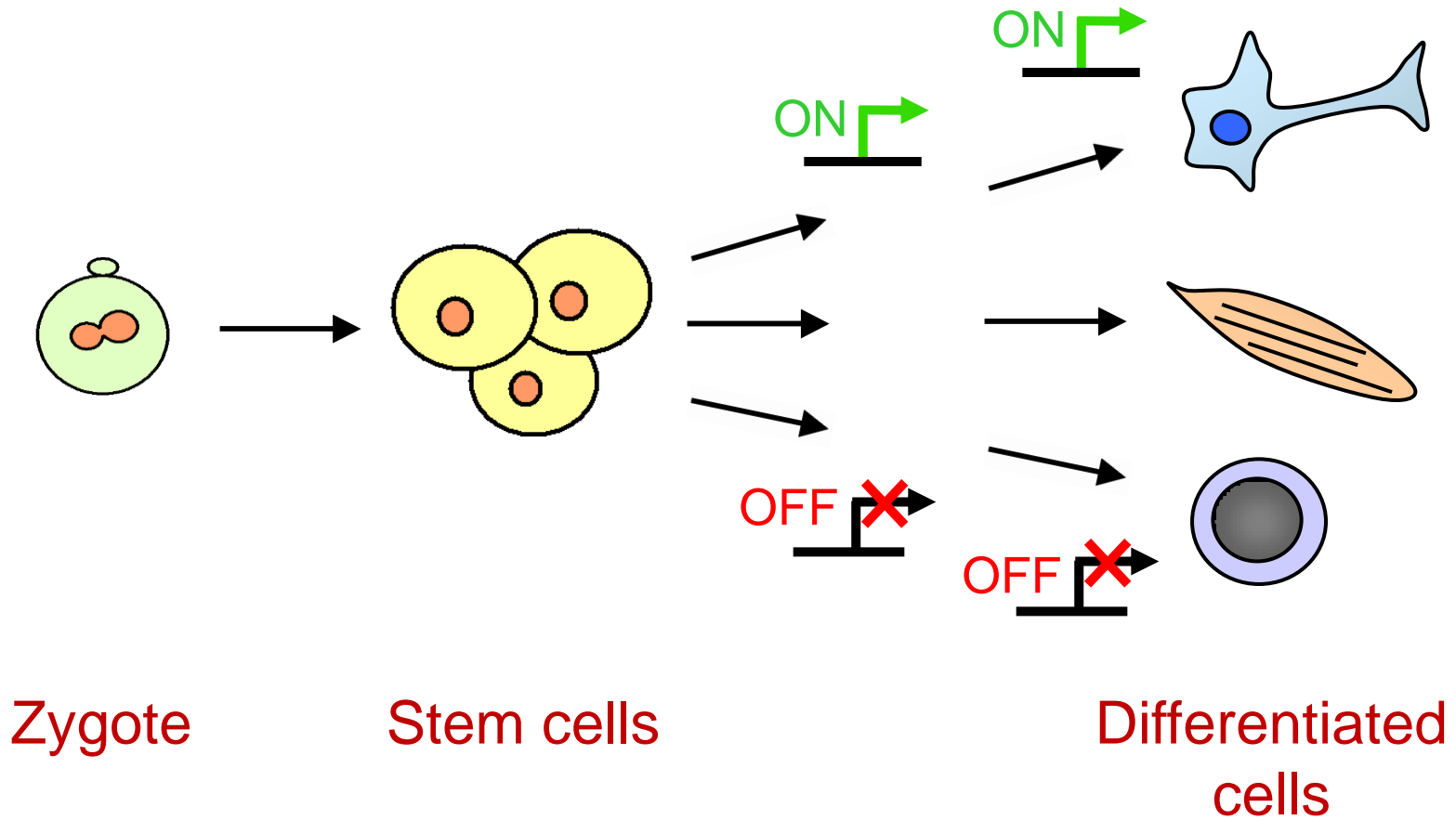
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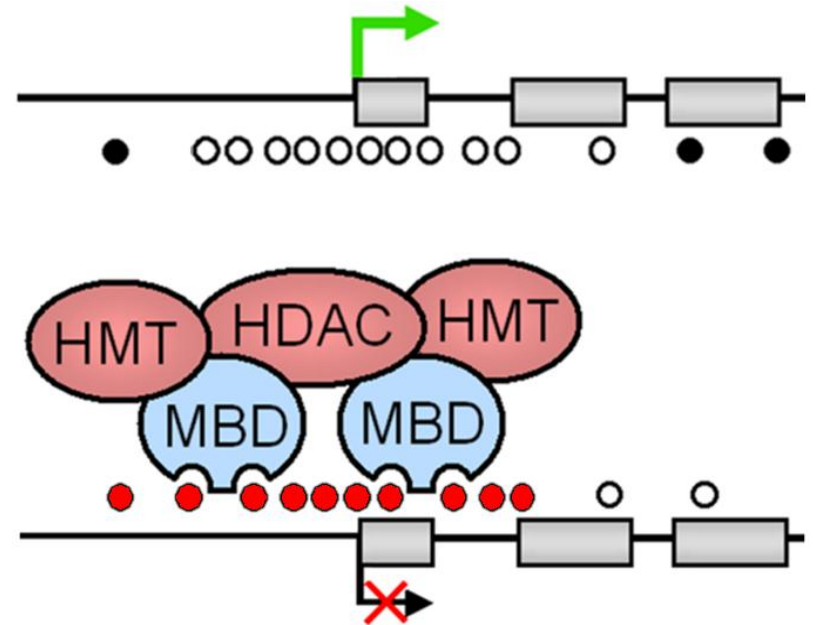
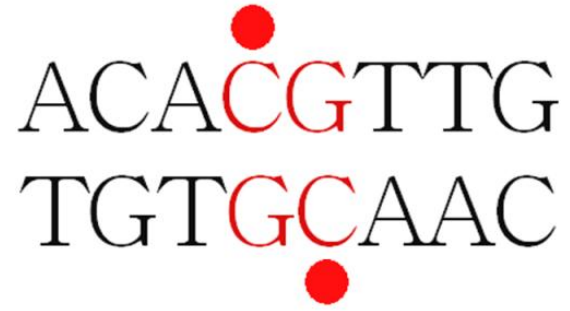
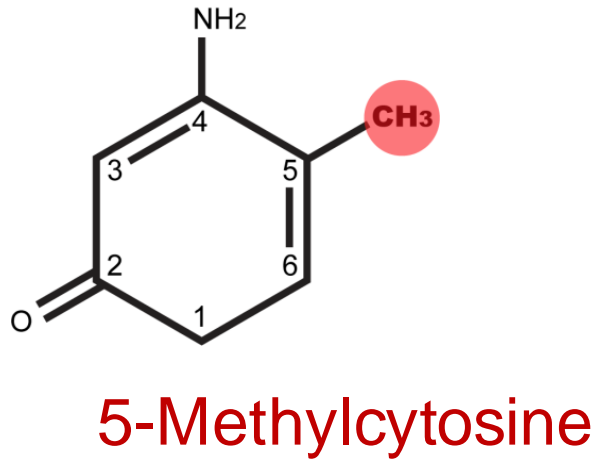
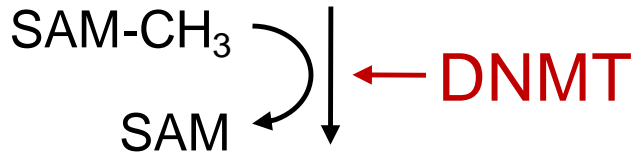
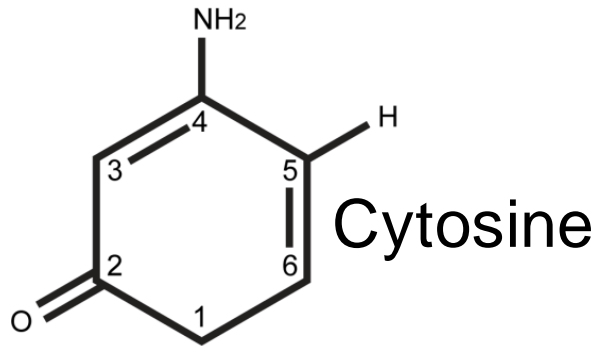
Genome

Epigenome

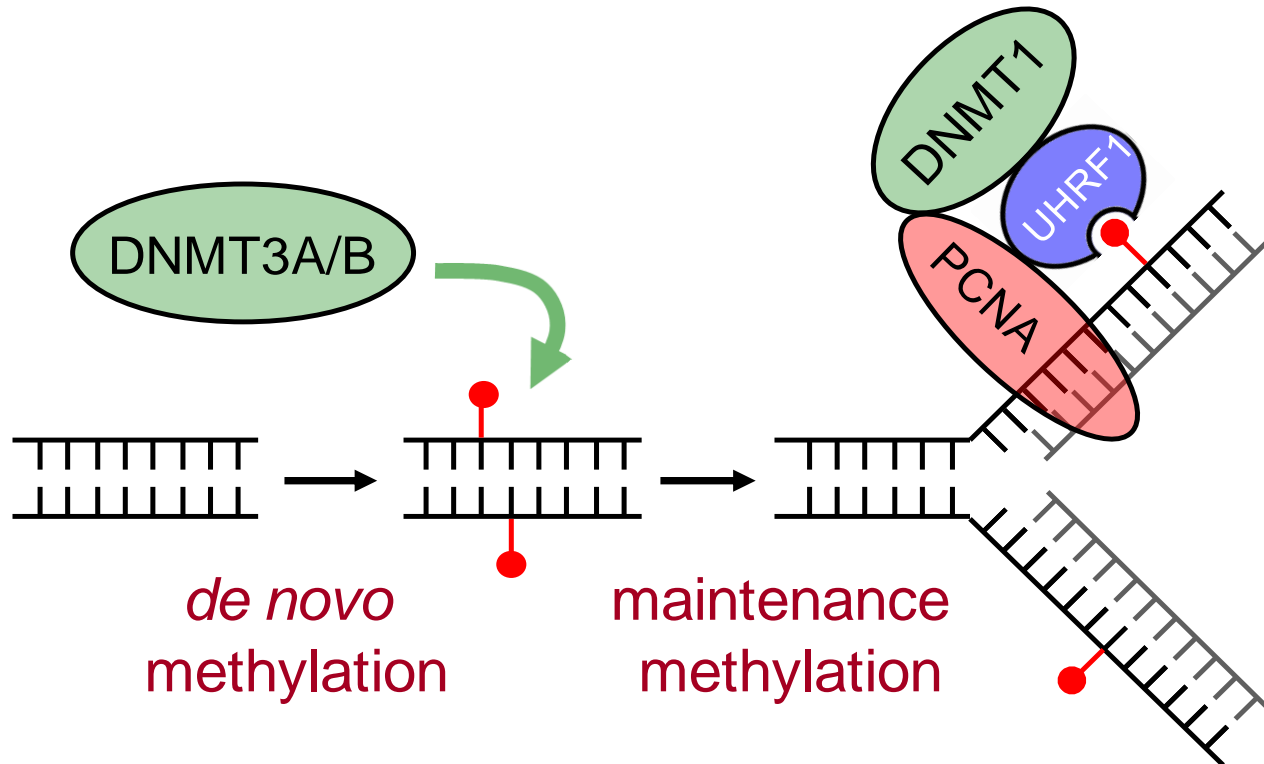
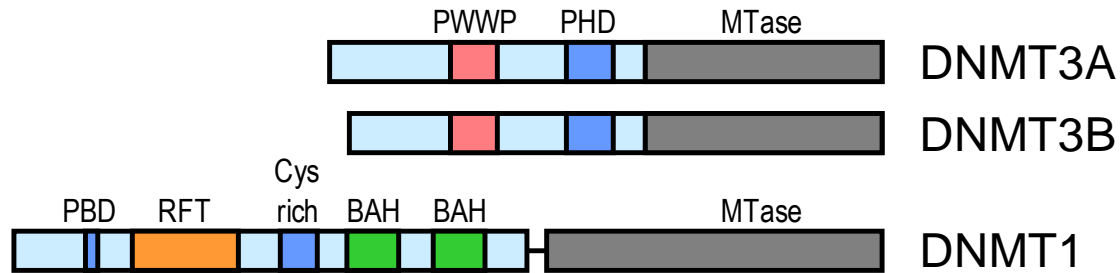
Heritable chromatin states maintain cellular identity



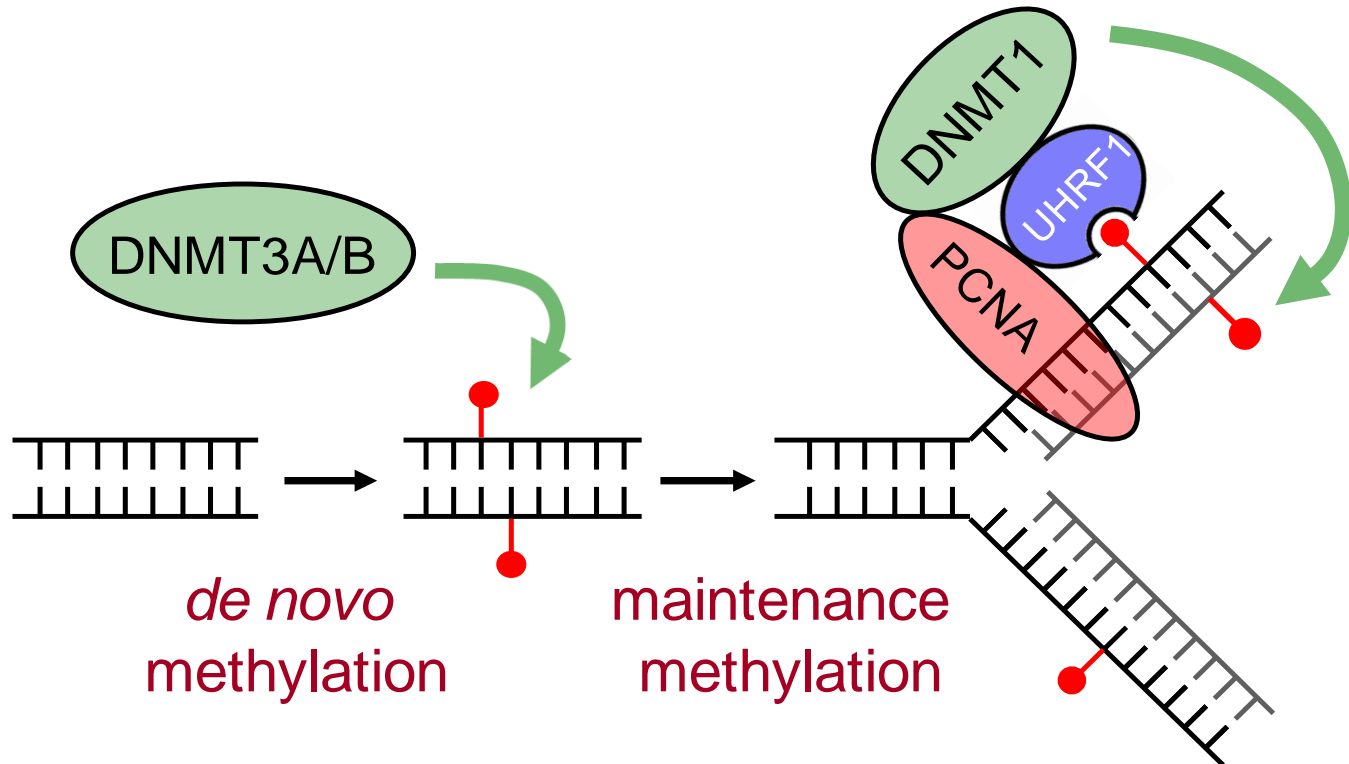
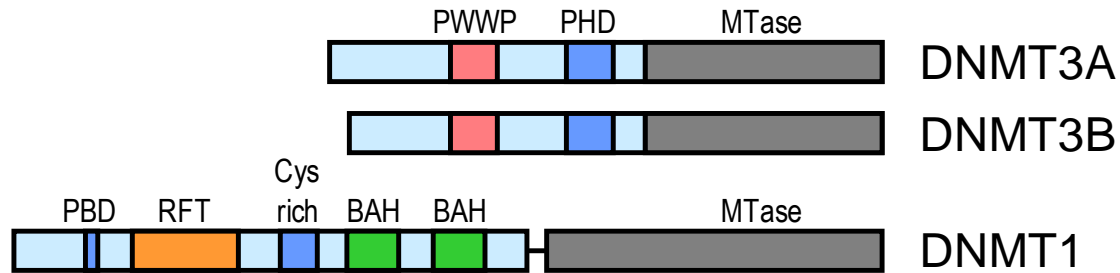
Cytosine methylation in Eukaryote genomes



DNA methyltransferases (DNMTs)

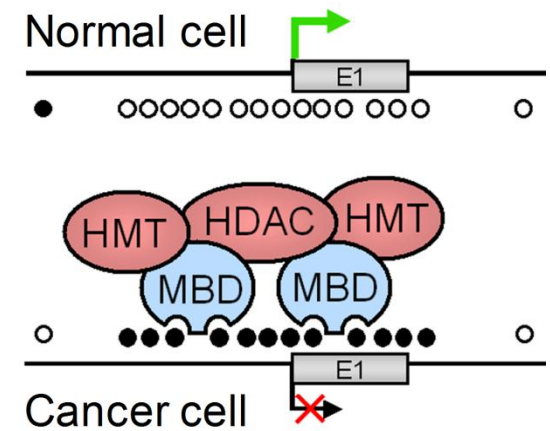


DNA methyltransferases (DNMTs)



Abnormal DNA methylation in a variety of pathologies

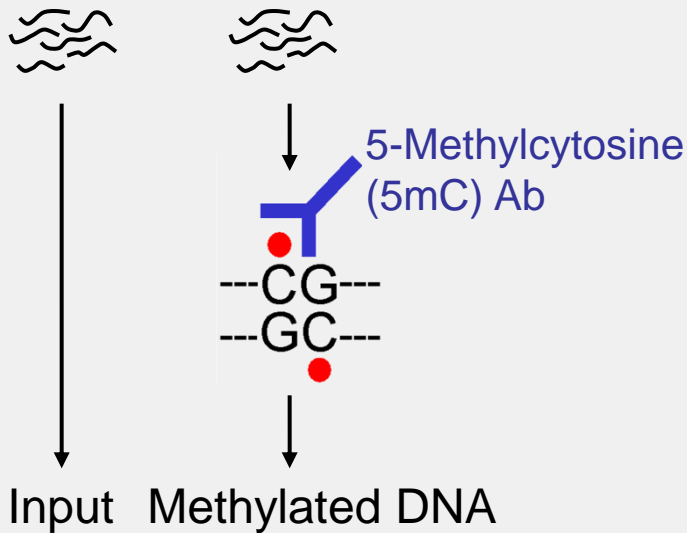
- Growth and neuro-developmental syndromes
 - ICF syndrome
 - Beckwith-Wiedemann syndrome
 - Prader-Willi syndrome
 - Angelman's syndrome
- Auto-immune and metabolic diseases
- All types of cancer



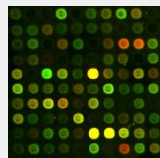
- Important to study targets and mechanisms of abnormal DNA methylation
 - Diagnostic markers
 - Therapeutic targets

Methods for genome-wide profiling of DNA methylation

MeDIP (Methylated DNA Immunoprecipitation)

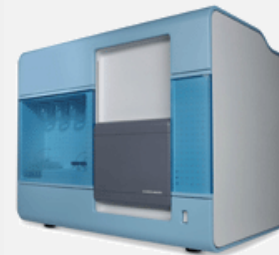


MeDIP-ChiP



- = methylated
- = medium
- = unmethylated

MeDIP-Seq



Bisulfite conversion

ACTCGGTACGC

Sodium Bisulfite

ATTCGGTATGT

BS-Seq



EMSG49: Investigation of normal variability and chemically induced epigenetic modifications

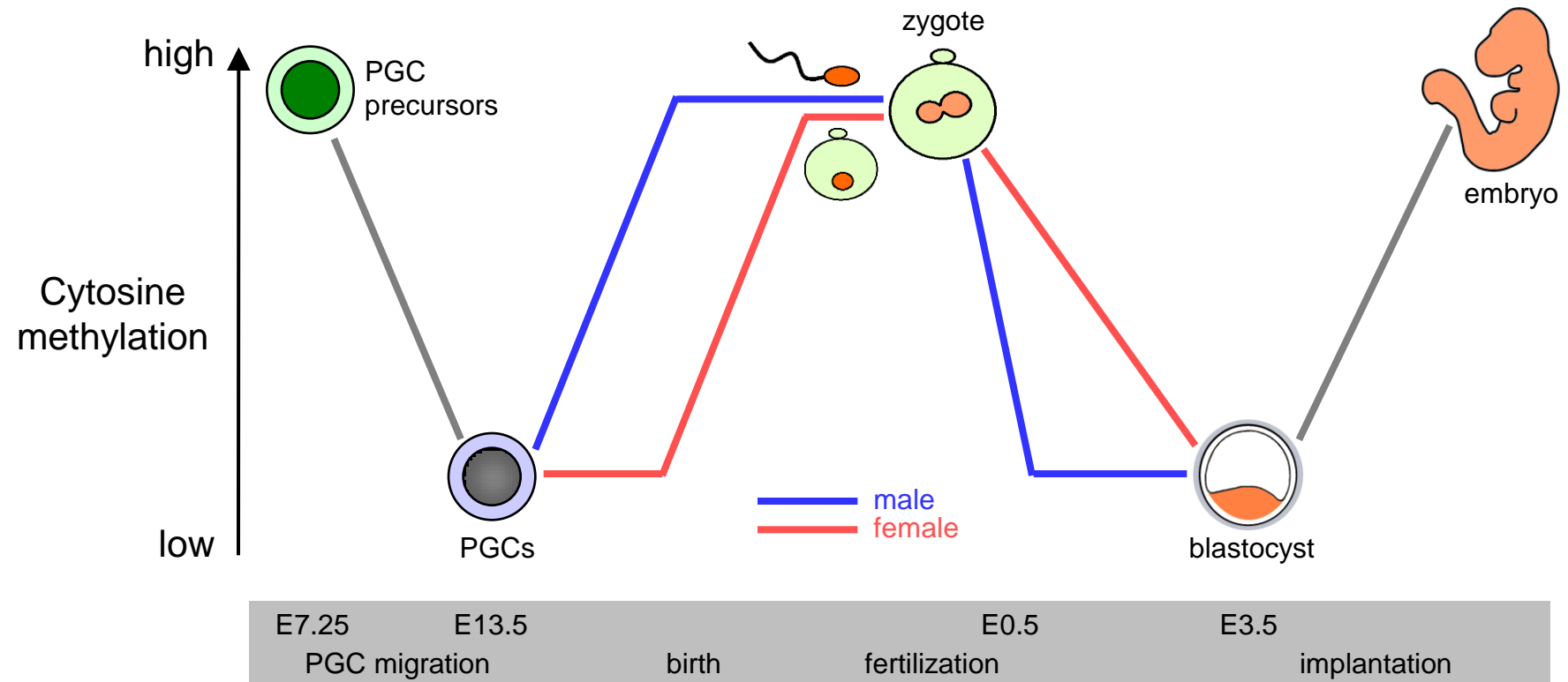
Scope:

There is little understanding of the normal state of the epigenome and what epigenetic changes might occur as a result of exposure to environmental stressors such as industrial chemicals. In recent years there has been growing concern that epigenetic events may play a role in chemically and/or nutritionally driven adverse health effects; with particular focus towards reproductive toxicity and non-genotoxic carcinogenesis. The evidence that epigenetic changes influence environmentally induced disease has been concomitant with recent improvements in sensitivity and throughput for analyzing DNA methylation.

Phase 1: Refine the landscape of "normal" DNA methylation patterns.

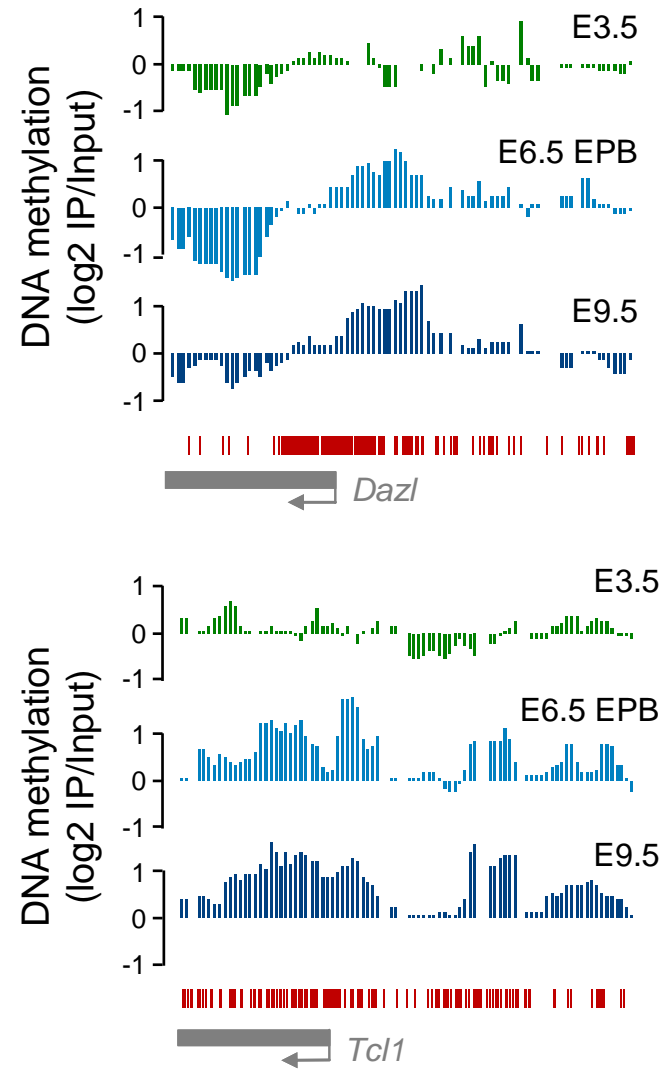
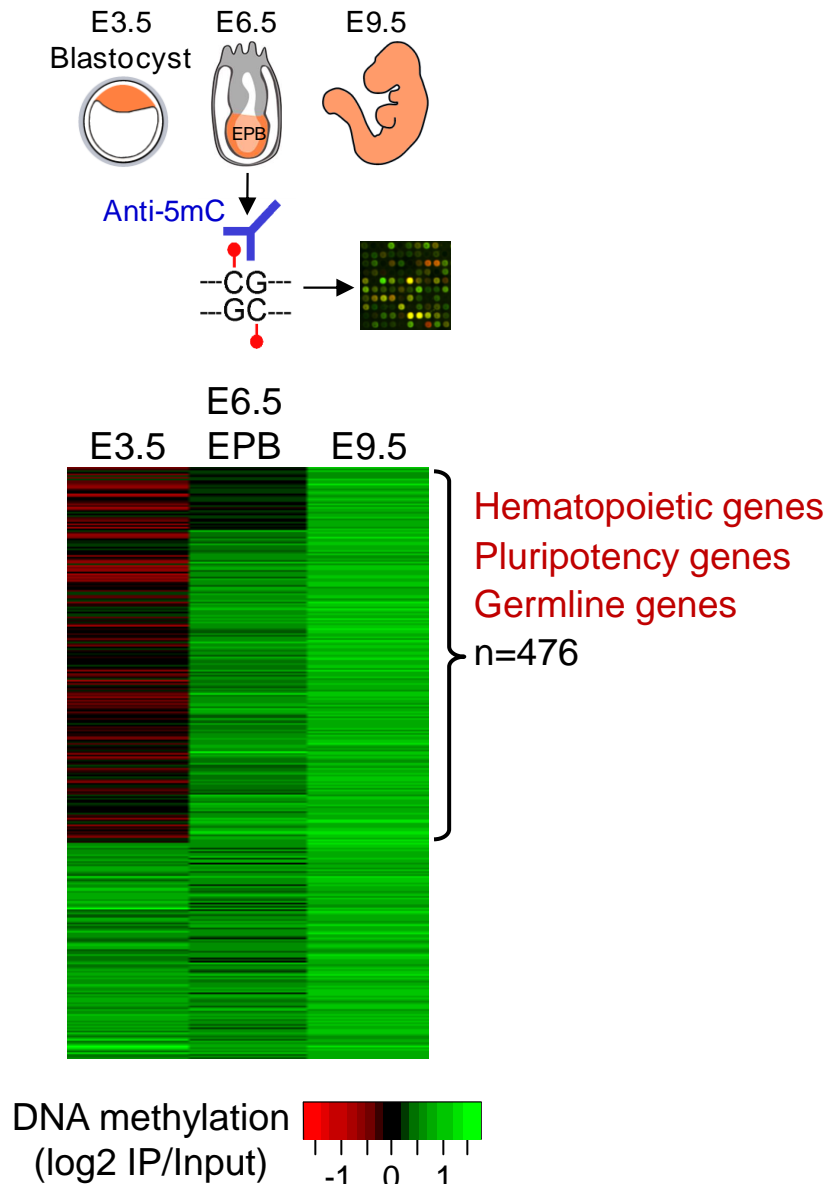
Phase 2: Apply data generated in Phase 1 to provide a framework for chemically-induced DNA methylation alterations.

Phase 1: DNA methylation reprogramming in development

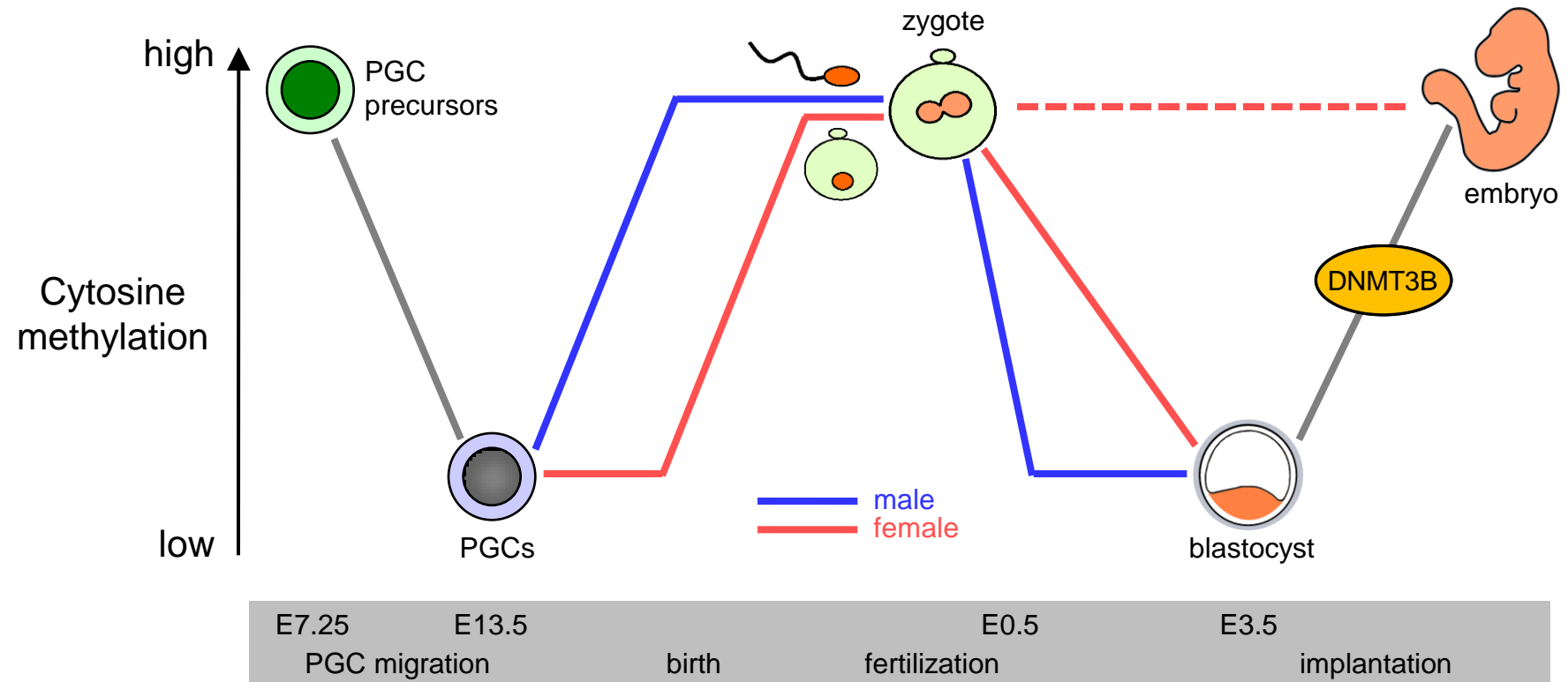


Phase 1: DNA methylation reprogramming in development

Borgel J *et al*, *Nat Genet* (2010)

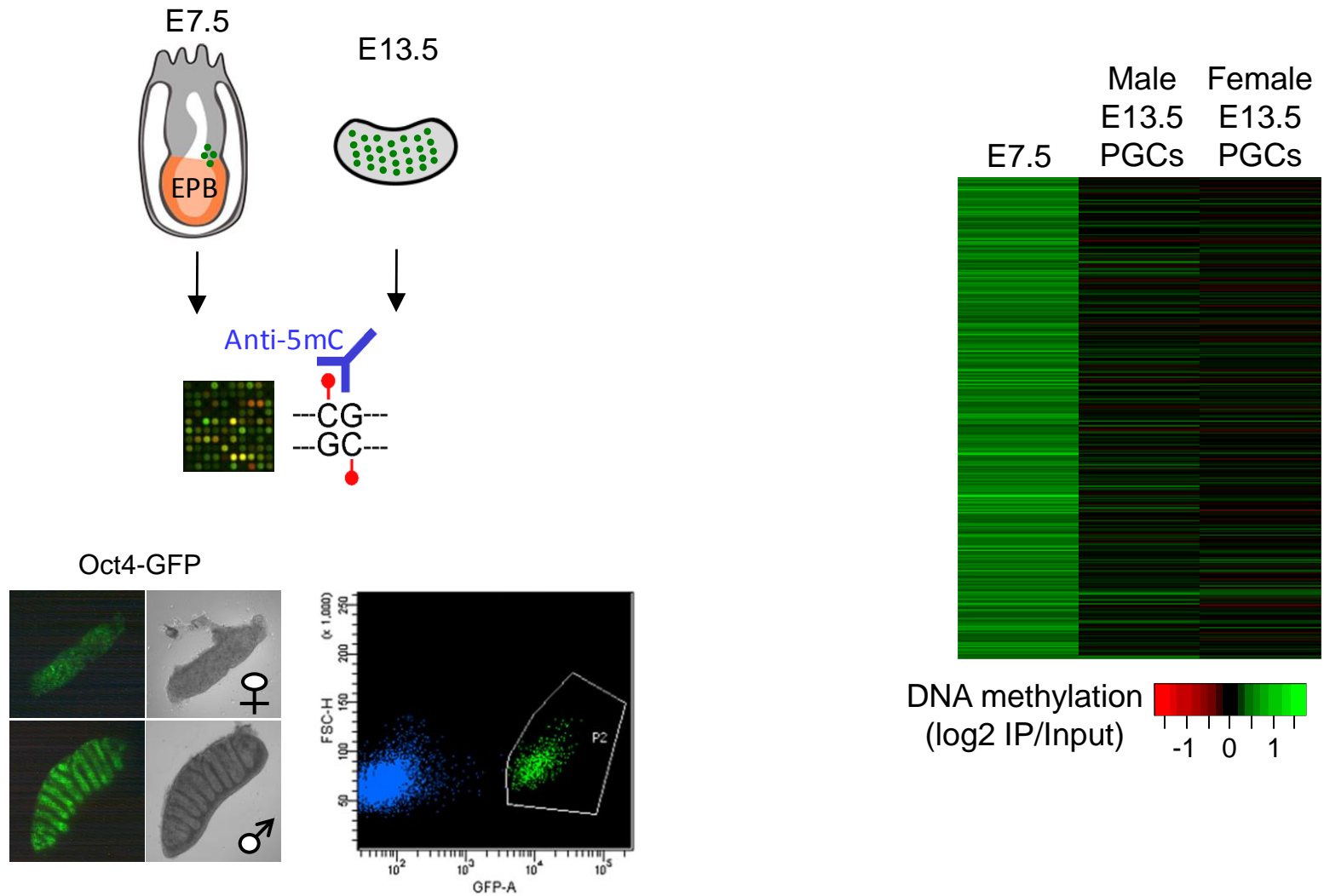


Phase 1: DNA methylation reprogramming in development



Phase 1: DNA methylation reprogramming in development

Guibert S *et al.*, in revision



Phase 2: Alteration of DNA methylation in germ cells by EDs

- Divergent DNA methylation in monozygotic twins discordant for diseases

Fraga MF et al., *PNAS* 2005
Mastroeni D et al., *PLoS ONE* 2009

Baranzini SE et al., *Nature* 2010
Javierre BM et al., *Genome Res* 2010

- DNA methylation is most susceptible to alterations during early life, which could lead to increased risks of disease in adults

- Changes in DNA methylation in rodents after *in utero* maternal exposure to chemicals, diet, alcohol

Ho SM et al., *Cancer Res* 2006
Dolinoy DC et al., *PNAS* 2007

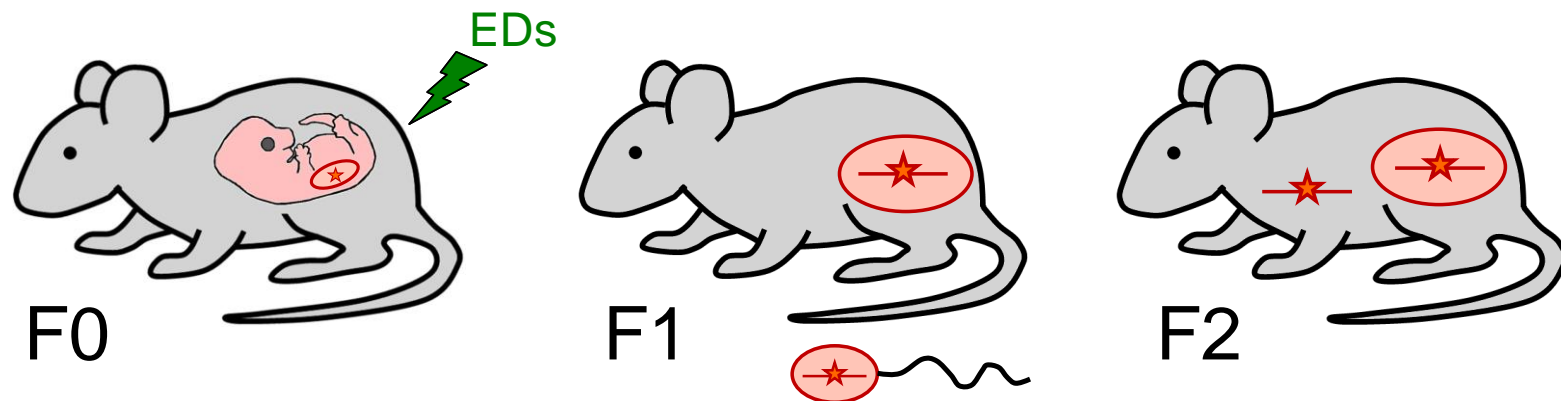
Zama AM et al., *Endocrinology* 2009
Bromer JG et al., *Endocrinology* 2009

Waterland R et al., *Mol Cell Biol* 2003
Kaminen-Ahola N et al., *PLoS Genet* 2010

- Multigenerational non-mendelian effects suggest possible transmission of altered DNA methylation through generations

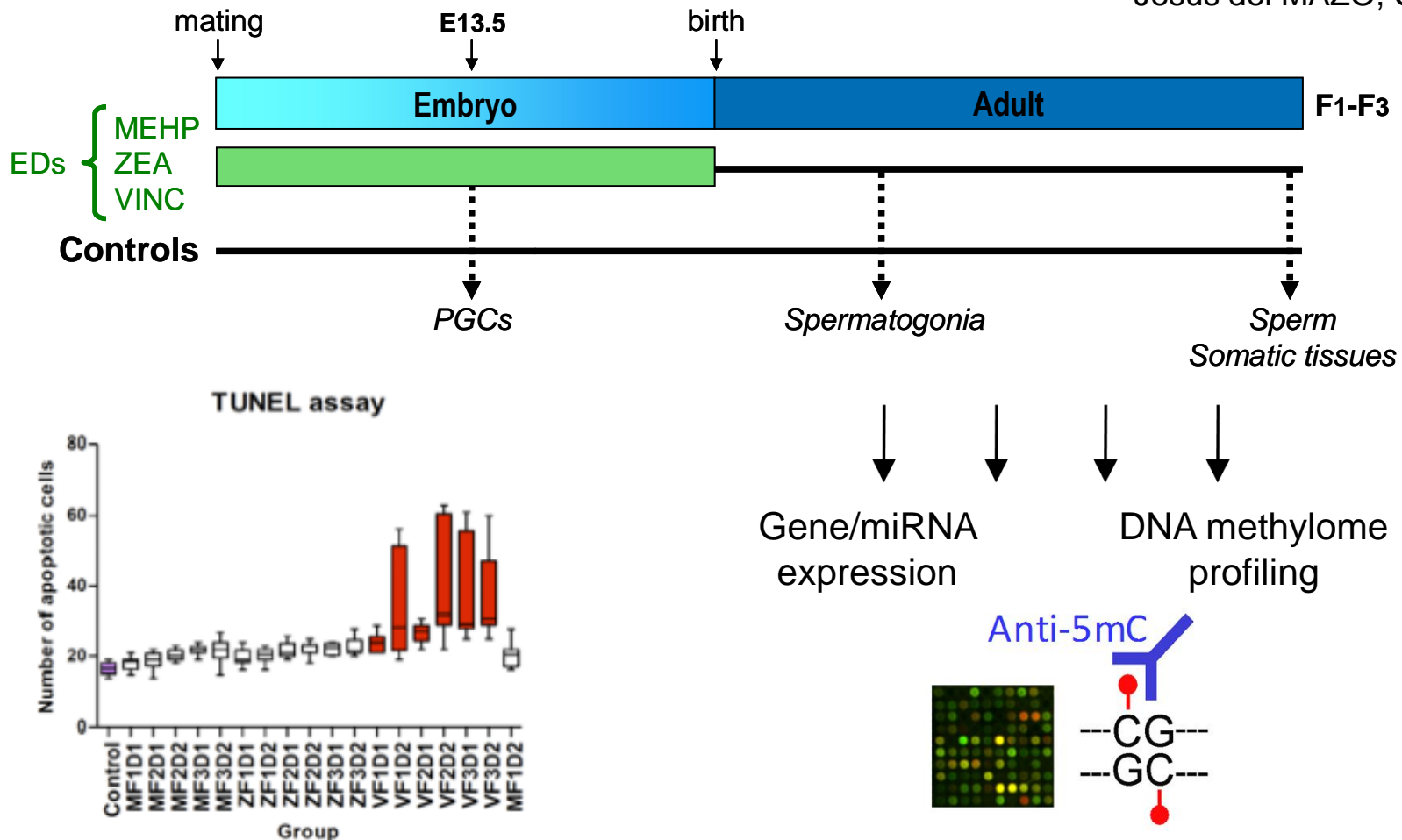
Anway MD et al., *Science* 2005
Cropley JE et al., *PNAS* 2006

Stouder C et al., *Reproduction* 2010



Phase 2: Alteration of DNA methylation in germ cells by EDs

Jesus del MAZO, CIB, Madrid



- Objectives:
- Understand epigenetic mechanisms of action of EDs
 - Identify DNA methylation biomarkers related to ED exposure

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UMR 7242 “*Biotechnology and
Cell Signalling*”
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