

# CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

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**Année 2018-2019:**

“Épigénétique, Environnement et Biodiversité”

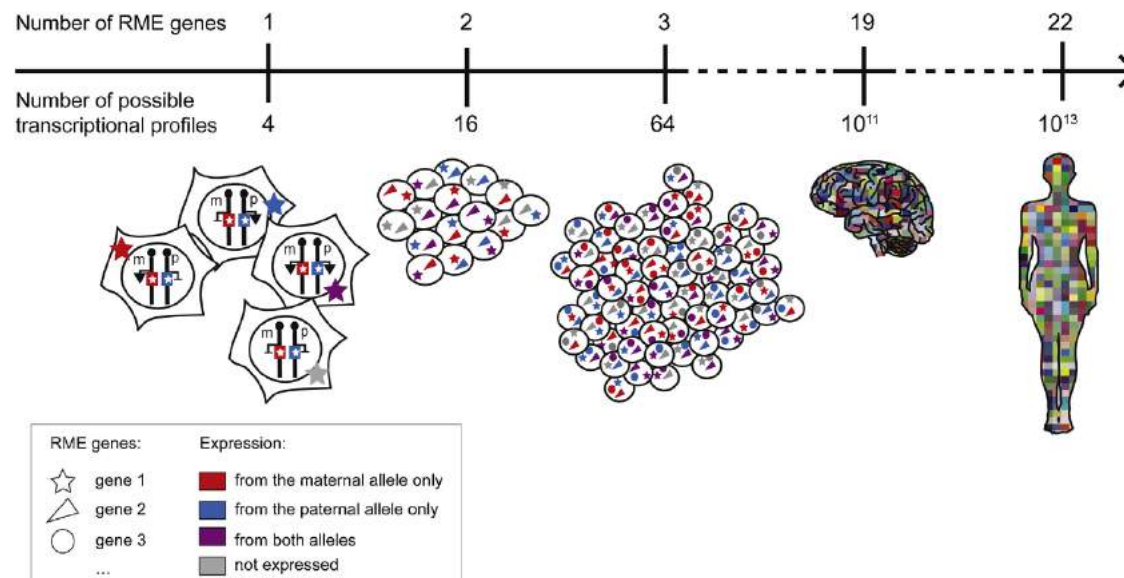
4 Décembre 2018

Quelle est l'influence de l'environnement sur les modifications épigénétiques et leur transmission?

# SUMMARY COURS I AND II :

## Epigenetics in life phase transitions and Epigenetics underlying biodiversity within individuals and species

- **Biodiversity within species** (phenotypic variation): one genotype multiple phenotypes - seemingly contrary to « genetic determinism » – but past studies often ignored environmental & stochastic changes
- **Cell-level stochasticity** can generate diversity in gene expression patterns:
  - It can give differences in cell physiological phenotypes
  - It can be non-clonal, stably propagated, or metastable
  - It can lead to different phenotypes within and between individuals
- **Cellular diversity** can provide a greater range of functional abilities for the organism eg cell determination
  - It can help monocellular organisms perform and survive better during extreme stress
  - It can be advantageous for the cell but deleterious for the organism (eg cancer)



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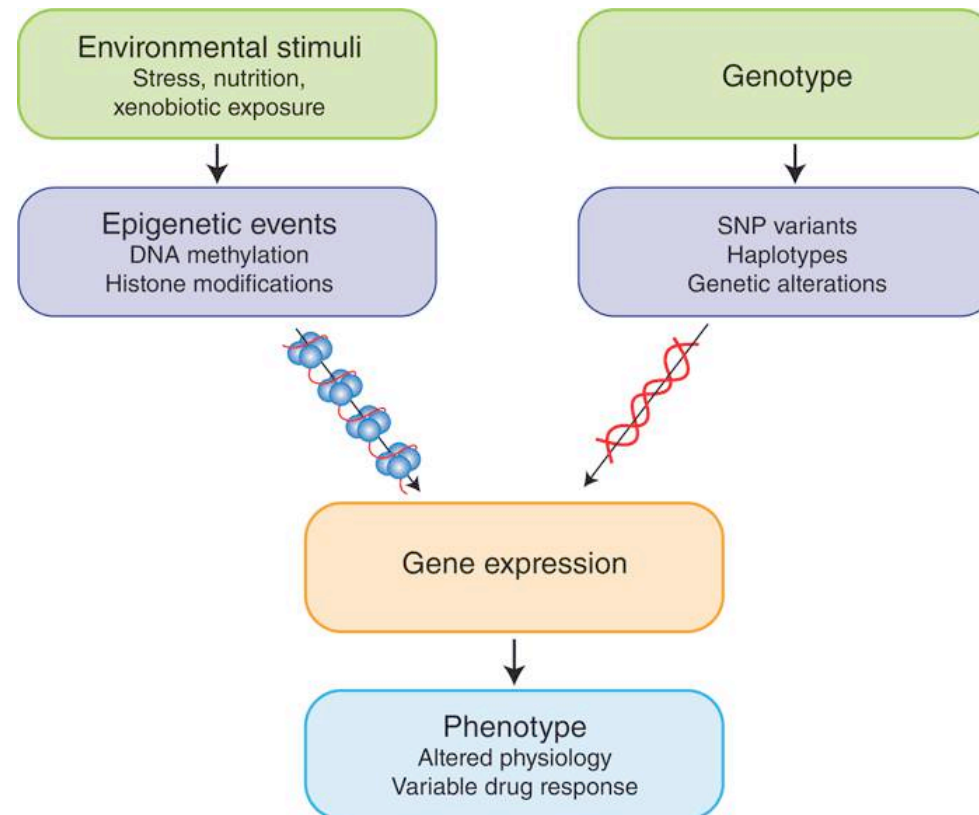
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  - It can be advantageous for the cell but deleterious for the organism (eg cancer)
- Most species display **cellular diversity** within individuals and **phenotypic plasticity** (stable or transient)
- It can be functional (and potentially adaptive), it can be neutral, or it can be deleterious
- How one genotype can give rise to different phenotypes through environmental effects is clearly an **EPIGENETICS** question (Waddington's original definition)
- Understanding this level of biodiversity will be key to understand life on our planet, and how it can (or cannot) adapt to the rapid, man-made changes we are imposing.
- The more diverse an ecosystem is, the more resources it has to help it recover from extremes conditions

# Epigenetics and the Environment

How much influence does the environment exert on epigenetic processes?

What is the impact on phenotypic variation via epigenetic processes of :  
temperature, climate, nutrition,  
toxins, stress, aging, culture...

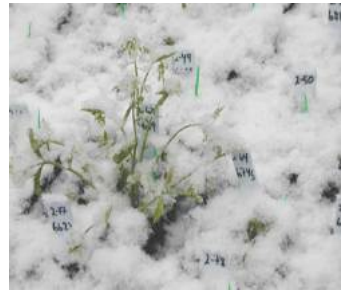


Gustav Klimt  
*The three ages of a woman*  
(1905)

# Environmentally programmed epigenetic changes

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1. Social insects represent a unique model for how the same genome can give rise to entirely different phenotypes — soldiers, common labourers, and queens.
2. Plants provide remarkable examples of climate-controlled programming - eg cold-induced flowering time (vernalisation)

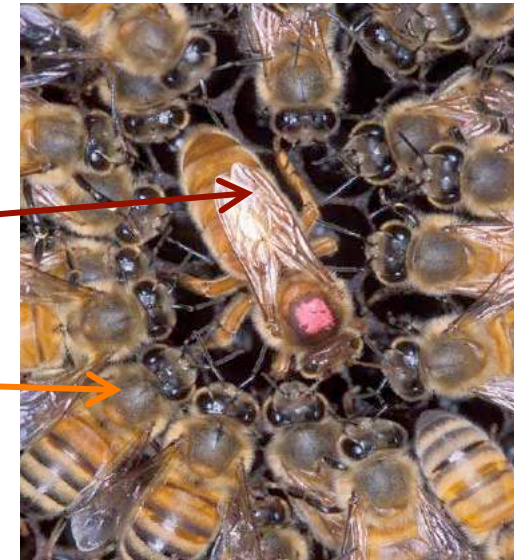




# Nutrition, Phenotype and Epigenotype in the Honeybee

## One genome – two destinies...

- A female bee's place in the social order—whether she becomes a *worker* or a *queen*—depends not just on her genes, but on whether she eats **royal jelly** and on **social context** (culture)
- Nutrition and juvenile hormone (JH) signaling determine the caste fate of the individual bee.
- Larval nutrition on royal jelly results in queen formation – sister larvae, fed briefly on royal jelly and then on pollen and nectar, become workers – despite SAME genetic constitution.



Queen

Life-span: 3/4 years  
Roles: reproduction, social structure of the hive



Worker

Life-span: 40 days to 6 months  
Functions: Nursing, cleaning, building, foraging



# What are the epigenetic determinants in Royal Jelly?

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- Proteins in royal jelly (such as royalactin) are responsible for many of the physical differences that distinguish queens from workers – and can even induce queen bee-like traits in fruit flies (Malezka et al, 2008)
- >20% of honeybee genes are differentially expressed between queens and workers (Weinstock et al, 2006; Grozinger et al, 2007)
- Royal jelly contains HDAC inhibitors phenyl butyrate (Lyko et al, 2010) and (E)-10-hydroxy-2-decenoic acid (10-HDA) - comprises up to 5% of royal jelly - and can reactivate the expression of epigenetically silenced genes in mammalian cells (Spannhoff et al. 2011).
- Silencing of DNMT3 in newly hatched larvae mimics effects of royal jelly – ie larvae destined to become workers develop into queens with fully developed ovaries (Kucharski et al, 2008)

# Honey Bee Epigenomics from 2006 onwards



## The Honey Bee Epigenomes: Differential Methylation of Brain DNA in Queens and Workers

Frank Lyko<sup>1,3</sup>, Sylvain Foret<sup>2,3</sup>, Robert Kucharski<sup>3</sup>, Stephan Wolf<sup>4</sup>, Cassandra Falckenhayn<sup>1</sup>, Ryszard Maleszka<sup>3\*</sup>

## DNA methylation dynamics, metabolic fluxes, gene splicing, and alternative phenotypes in honey bees

Sylvain Foret<sup>a,b</sup>, Robert Kucharski<sup>b</sup>, Matteo Pellegrini<sup>c</sup>, Suhua Feng<sup>c</sup>, Steven E. Jacobsen<sup>c,d,e,1</sup>, Gene E. Robinson<sup>f</sup>, and Ryszard Maleszka<sup>b,1</sup>

## Open Questions

- which genes are critical in queen / worker distinction (via royal jelly)?
- does DNA methylation impact on their expression profiles?
- What do changes in DNA methylation tell us about Queen/Worker differential behaviour



# Epigenetic and gene expression differences between Queens & Workers?

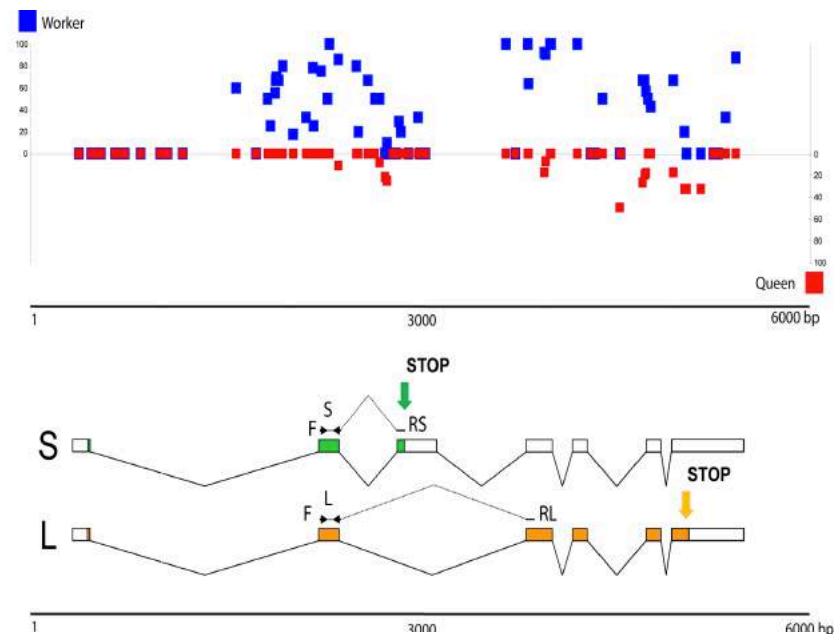
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PLoS Biology, 8, e1000506 (2010)

### CpG DNA methylation differences :-

- in Brains of Workers and Queens at >550 regions
- Mainly at conserved genes – involved in brain development or activity
- Not at CpG islands and promoters, but in *bodies* of expressed genes – and correlating with splice variants that are differentially expressed in queens & workers.
- Genes encoding **hormone receptors**, and/or implicated in **responses to juvenile hormone (JH)** (eg TOR signaling) are differentially methylated



### Conclusions:

- DNA me differences don't correlate with gene repression but differential mRNA splicing?
- Changes in expression of multiple genes – particularly involved in JH signalling

Which DNA methylation differences underlie Queens/Worker divide:  
Still unclear!

# Epigenetic and gene expression differences between Queens & Workers?



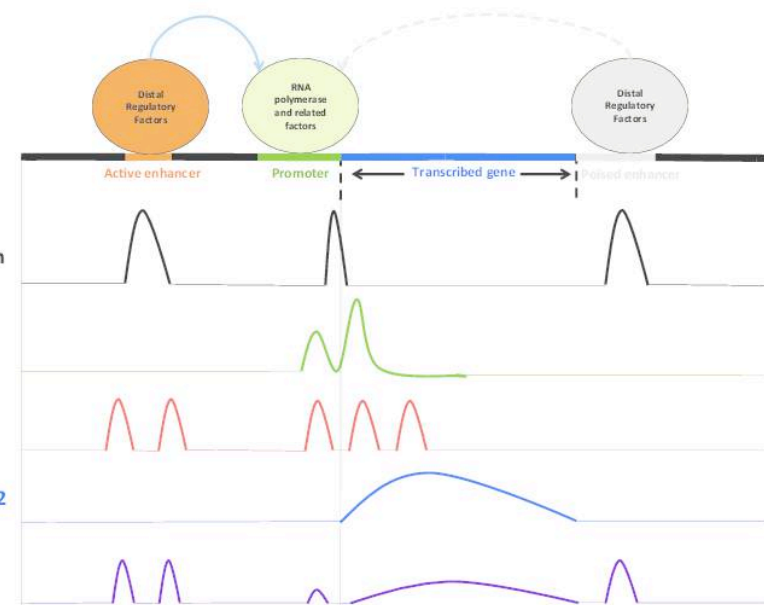
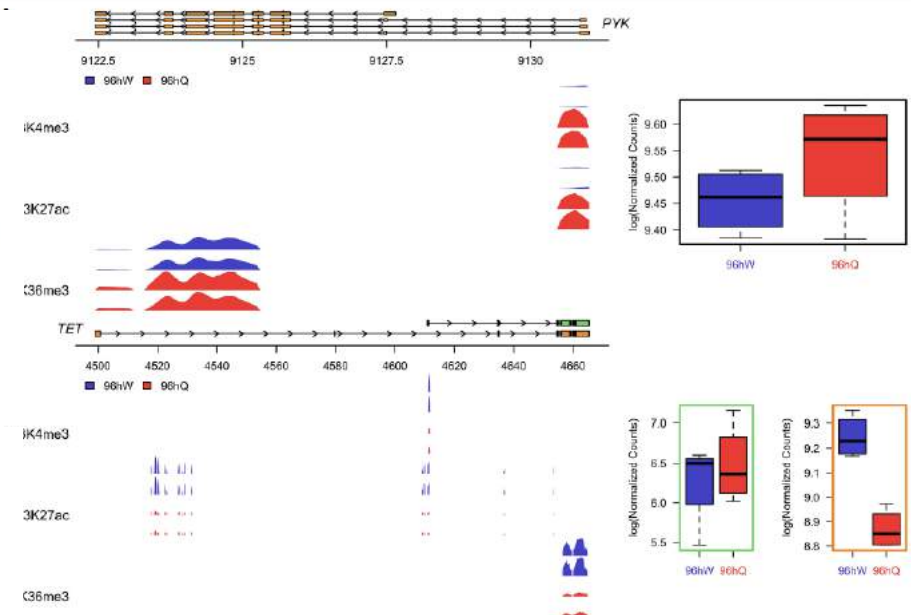
## Phenotypically distinct female castes in honey bees are defined by alternative chromatin states during larval development

Marek Wojciechowski, Robert Lowe, Joanna Maleszka, et al.

*Genome Res.* 2018 28: 1532-1542 originally published online August 22, 2018

Chromatin modifications play a crucial role in defining worker and queen honey bee castes by establishing and orchestrating caste-specific transcriptional networks

It is the **Worker** developmental pathway that is actively switched on from a default Queen developmental program!



# Becoming a Queen or a Worker is not just about Royal Jelly

OPEN **MicroRNAs in Honey Bee Caste Determination**

Regan Ashby<sup>1,2</sup>, Sylvain Forêt<sup>1</sup>, Iain Searle<sup>1,3,4,5</sup> & Ryszard Maleszka<sup>1</sup>

- Significant differences in microRNA and transcriptional profiles of diploid females relative to drone males as well as between queens and workers.
- Queens and drones show gene enrichment in physio-metabolic pathways, whereas workers show enrichment in processes associated with neuronal development, cell signalling and caste biased structural differences.
- Predicted miRNA targets are primarily associated with neuronal targets, while DNA methylation regulates physio-metabolic processes
- Plant RNAs, particularly miRNAs, are more enriched in beebread than in royal jelly, delay development and decrease body and ovary size in honeybees, thereby preventing larval differentiation into queens and inducing development into worker bees.
- amTOR, a stimulatory gene in caste differentiation, is the direct target of miR162a.

RESEARCH ARTICLE

## Plant microRNAs in larval food regulate honeybee caste development

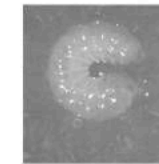
Kegan Zhu<sup>1\*</sup>, Minghui Liu<sup>1\*</sup>, Zheng Fu<sup>1\*</sup>, Zhen Zhou<sup>1</sup>, Yan Kong<sup>1</sup>, Hongwei Liang<sup>1</sup>, Zheguang Lin<sup>2</sup>, Jun Luo<sup>3</sup>, Huoqing Zheng<sup>2</sup>, Ping Wan<sup>2</sup>, Junfeng Zhang<sup>1</sup>, Ke Zen<sup>1</sup>, Jiong Chen<sup>1,3\*</sup>, Fulliang Hu<sup>2\*</sup>, Chen-Yu Zhang<sup>1\*</sup>, Jie Ren<sup>1\*</sup>, Xi Chen<sup>1\*</sup>

### Pollen and honey

Rich plant miRNA



Beebread



Delay development

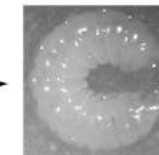


Poor plant miRNA

Rich nutrition



Royal Jelly



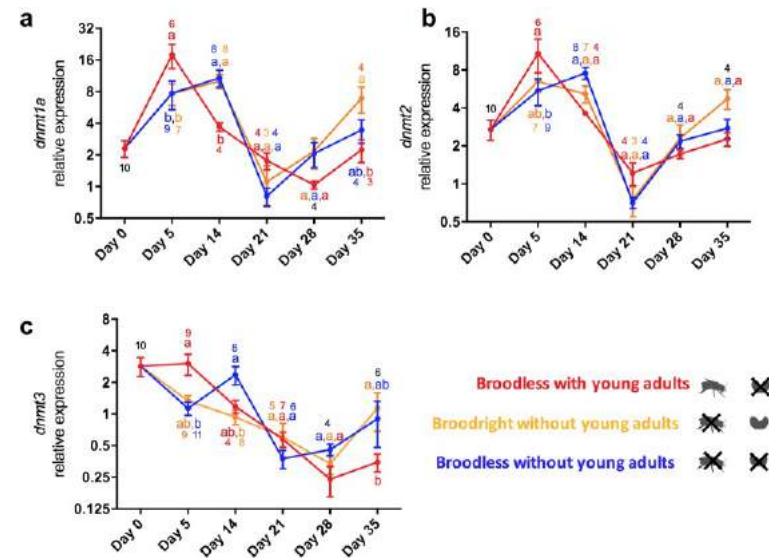
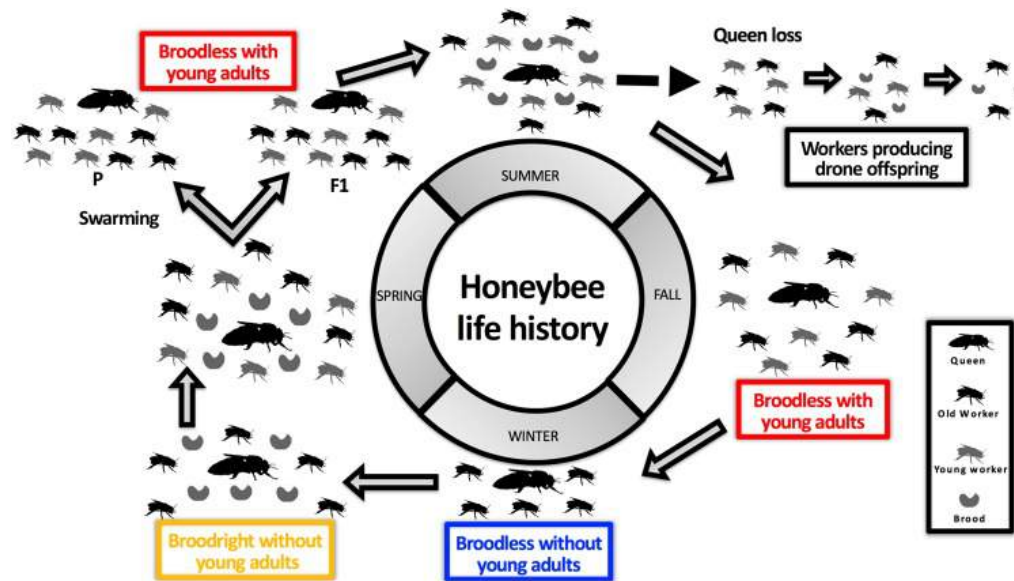
Promote development



### Glandular secretion

**Plant miRNAs in worker bee's food postpone larval development, thereby inducing sterile worker bees.**

# Social context affects the expression of DNMT genes



- Social context affects the expression of DNMT genes in Honey Bees
- Different brood pheromones trigger DNMT expression differences
- Pheromones spread within the colony and signal the presence of the queen and influence worker behavior for example.
- All three DNMT genes show altered expression, indicating that distinct molecular processes are affected by social interactions.
- Social insects may make use of DNA methylation epigenetic machinery to modulate behavioral responses according to social context

Le Conte et al . Primer effects of a brood pheromone on honeybee behavioural development. *Proc. Biol. Sci.* **268**, 163–168 (2001).

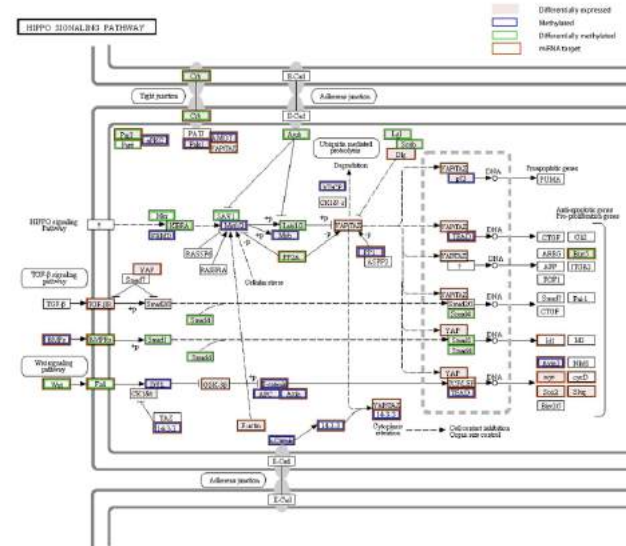
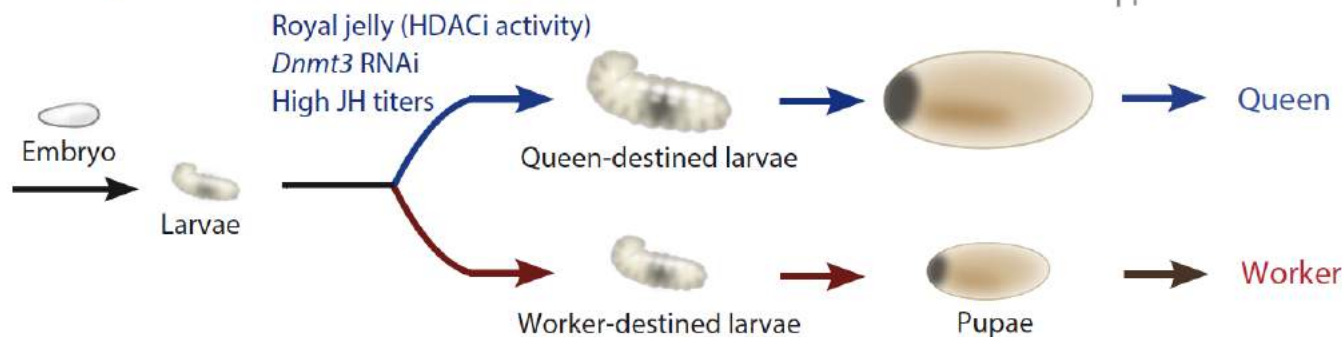
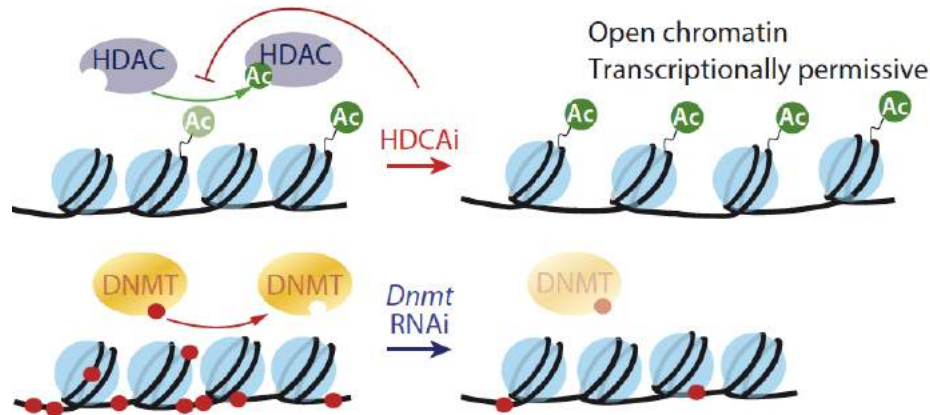
Holman, L. et al Queen pheromones modulate DNA methyltransferase activity in bee and ant workers. *Biol. Lett.* **12**, 20151038 (2016).

Pankiw, T., Winston, J. Variation in worker response to honey bee (*Apis mellifera* L.) queen mandibular pheromone. *J. Insect Behav.* **7**, 1–15 (1994).



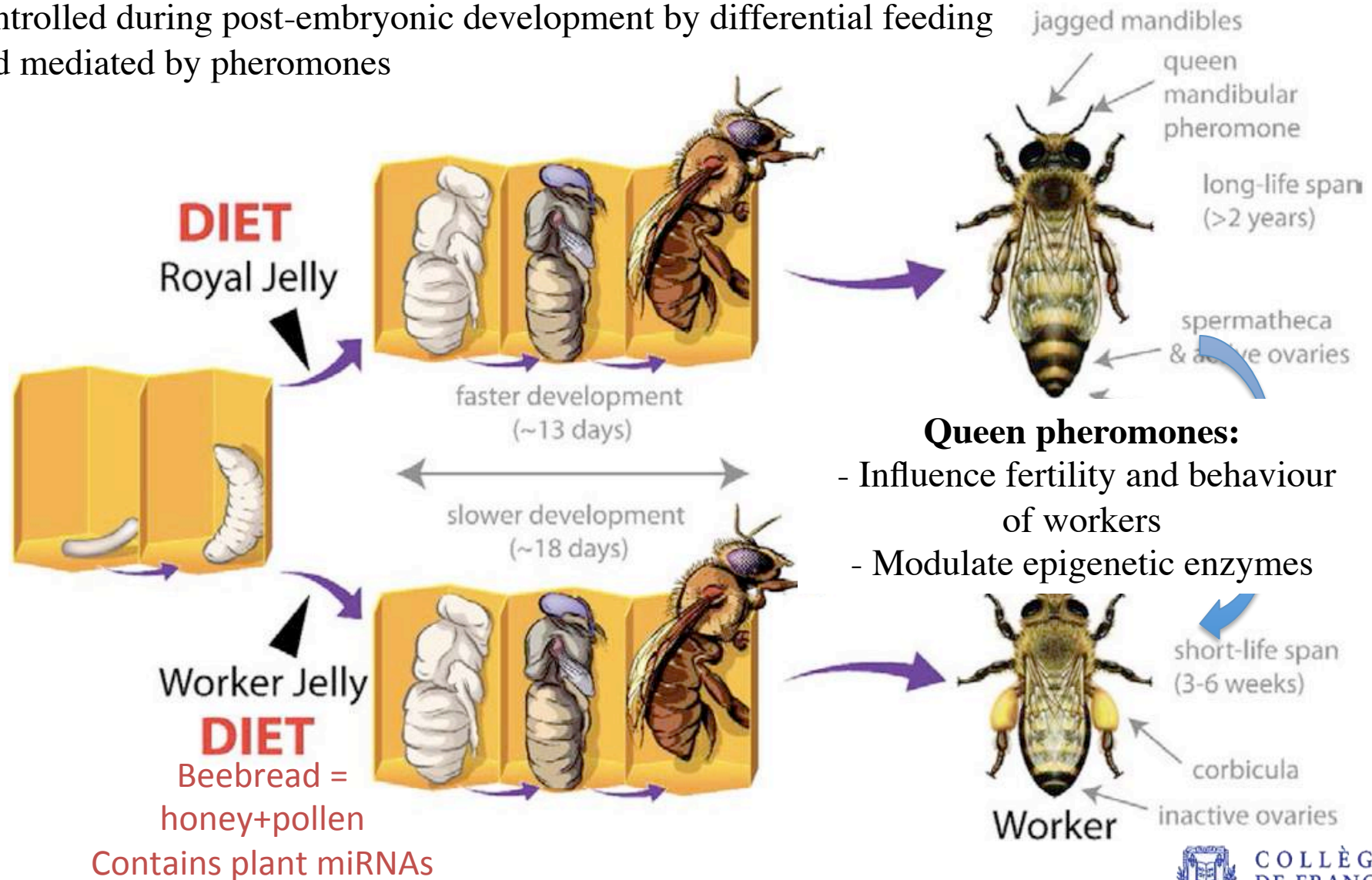
# Working out the epigenetic control of signalling pathways and genes enabling Queen or Worker phenotypes...

## Honeybee caste development



# The Queen-worker morphological and reproductive divide relies on multiple cues – not « just » Royal Jelly!

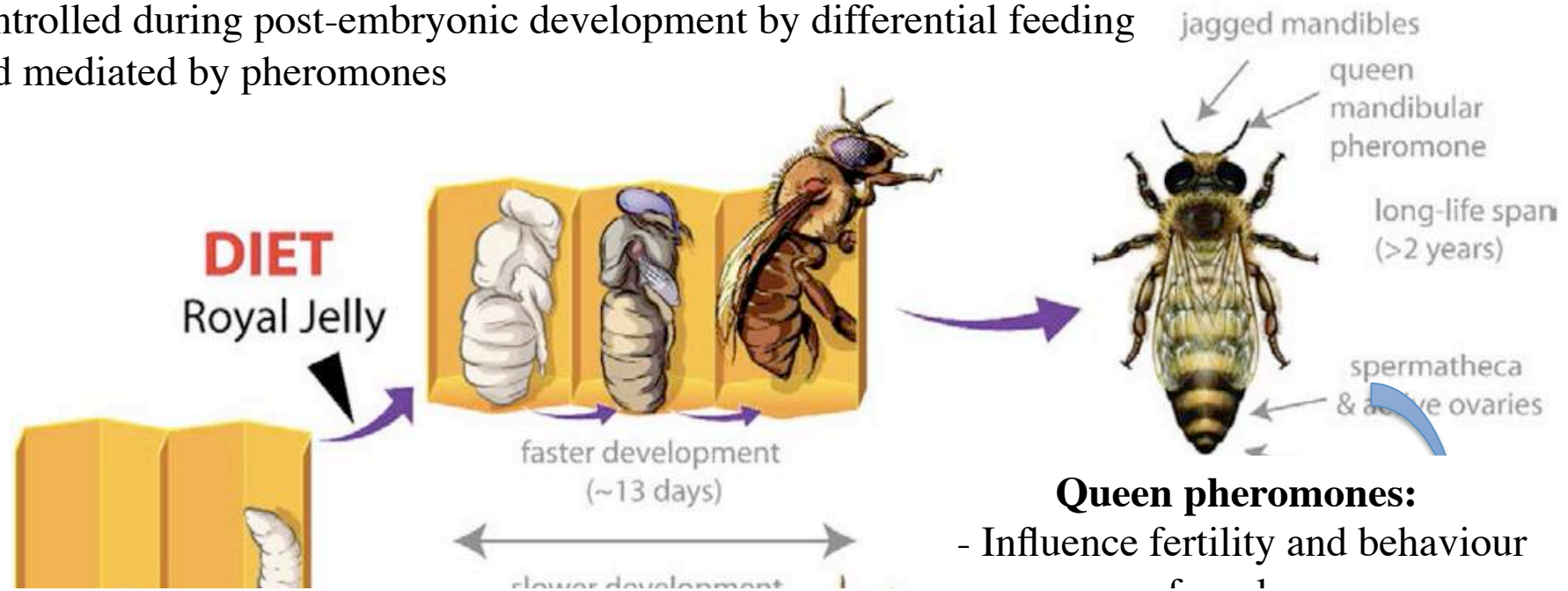
Queen-worker morphological and reproductive divide is environmentally controlled during post-embryonic development by differential feeding and mediated by pheromones



- Queen pheromones:**
- Influence fertility and behaviour of workers
  - Modulate epigenetic enzymes

# The Queen-worker morphological and reproductive divide relies on multiple cues – not « just » Royal Jelly!

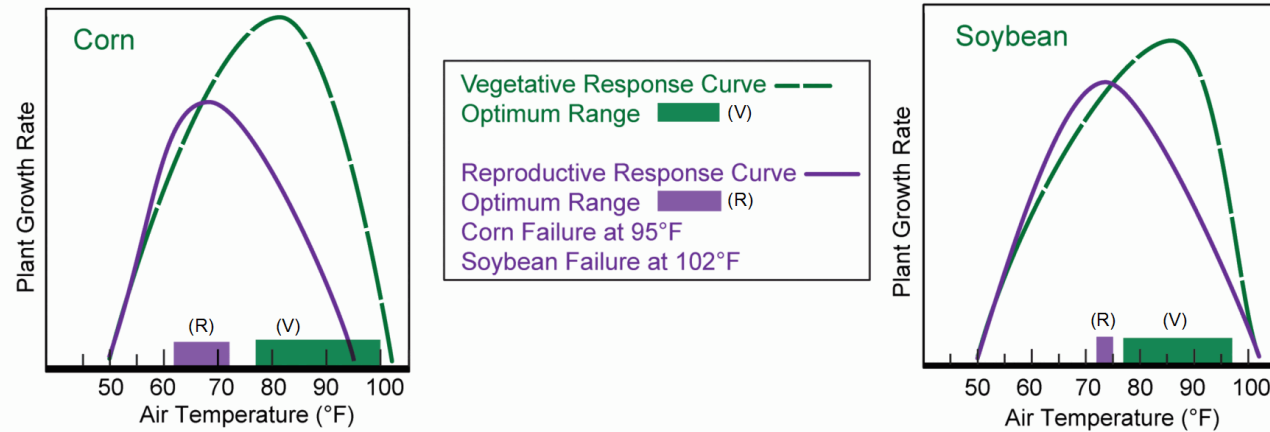
Queen–worker morphological and reproductive divide is environmentally controlled during post-embryonic development by differential feeding and mediated by pheromones



Techniques to rear Queens for commercial purposes:

- Queens raised from Worker larvae differ from queens raised from eggs in the expression of genes involved in the immune system, caste differentiation, body development and longevity.
- DNA methylation levels are higher than normal in queen larvae raised from worker larvae
- Many of the genes downregulated are involved in metabolism, body development, reproductive ability, and longevity (Yin et al, 2018)
- Environmental (nutrition and space) changes induced by commercial rearing practices result in a *sub-optimal queen phenotype* which may be due to epigenetic processes, and can potentially contribute to the evolution of queen-worker dimorphism.
- This has probably contributed to the global increase in honeybee colony failure rates.

# Temperature and Epigenetic changes in Plants



ARS USDA

Every plant variety has an **optimal temperature for vegetative growth**, and a **specific range of temperatures at which a plant will produce seed**. Outside of this range, the plant will not reproduce. Eg corn will fail to reproduce at temperatures above 95 °F (35 °C) and soybean above 102 °F (38.8 °C).



Many plants are completely dependent on subtle aspects of the weather to survive Eg **Vernalization** – a period of cold required for appropriate flowering timing

Plants that need to be vernalised include important food species such as sugar beet and wheat, which feed millions and provide much-needed income globally.



# In nature, environment and timing are crucial...

- Correct timing of flowering is key to reproductive success
- Eg to ensure that reproductive development and seed production occurs in spring and summer, not autumn
- Multiple pathways have evolved to mediate different environmental and endogenous cues
- Eg. Longer days as well as cold temperatures are required for winter **wheat** plants to go from the vegetative to the reproductive state (*VRN1*, *VRN2*, and *FT* (*VRN3*) genes)

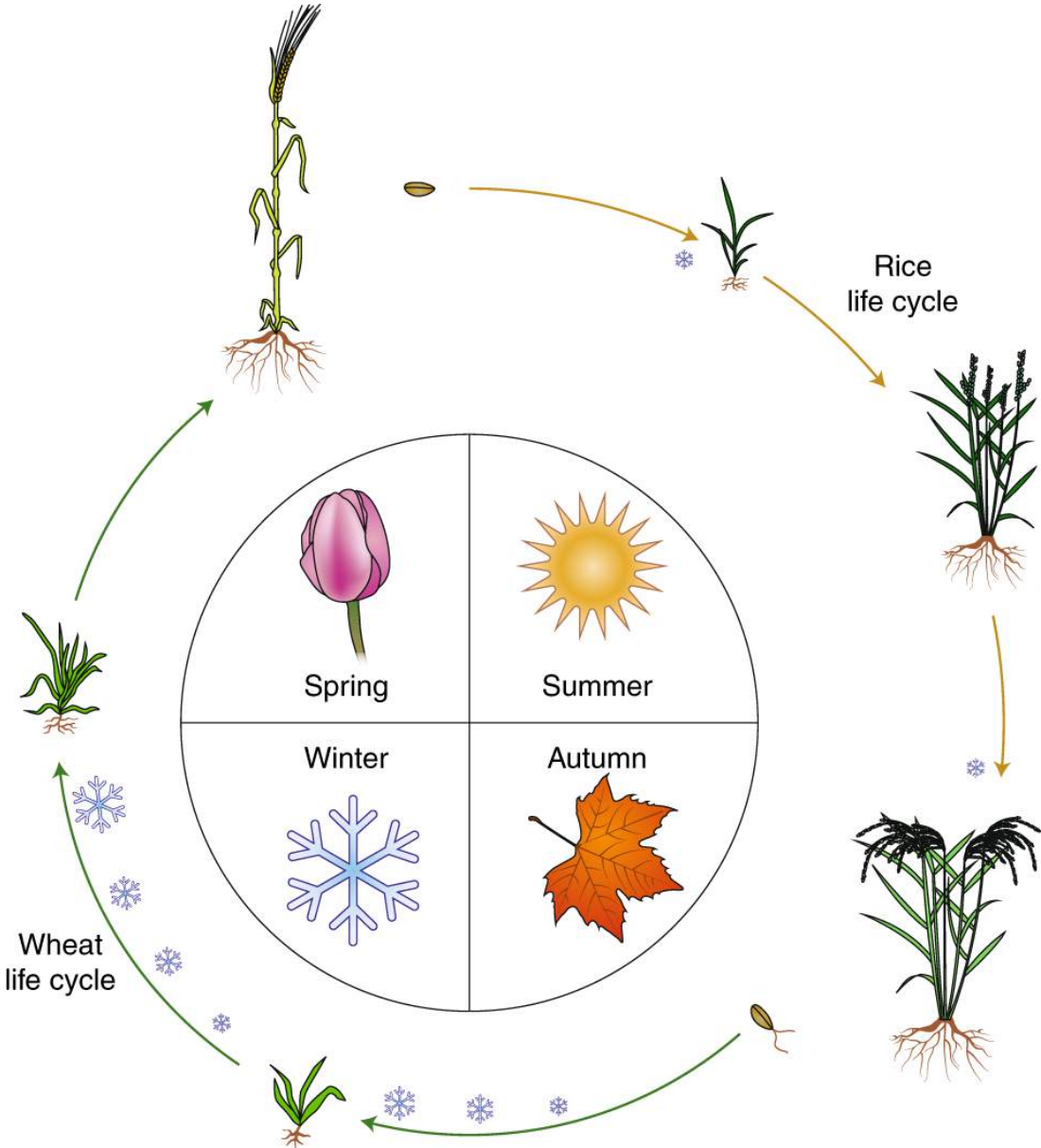


J. Stinchcombe



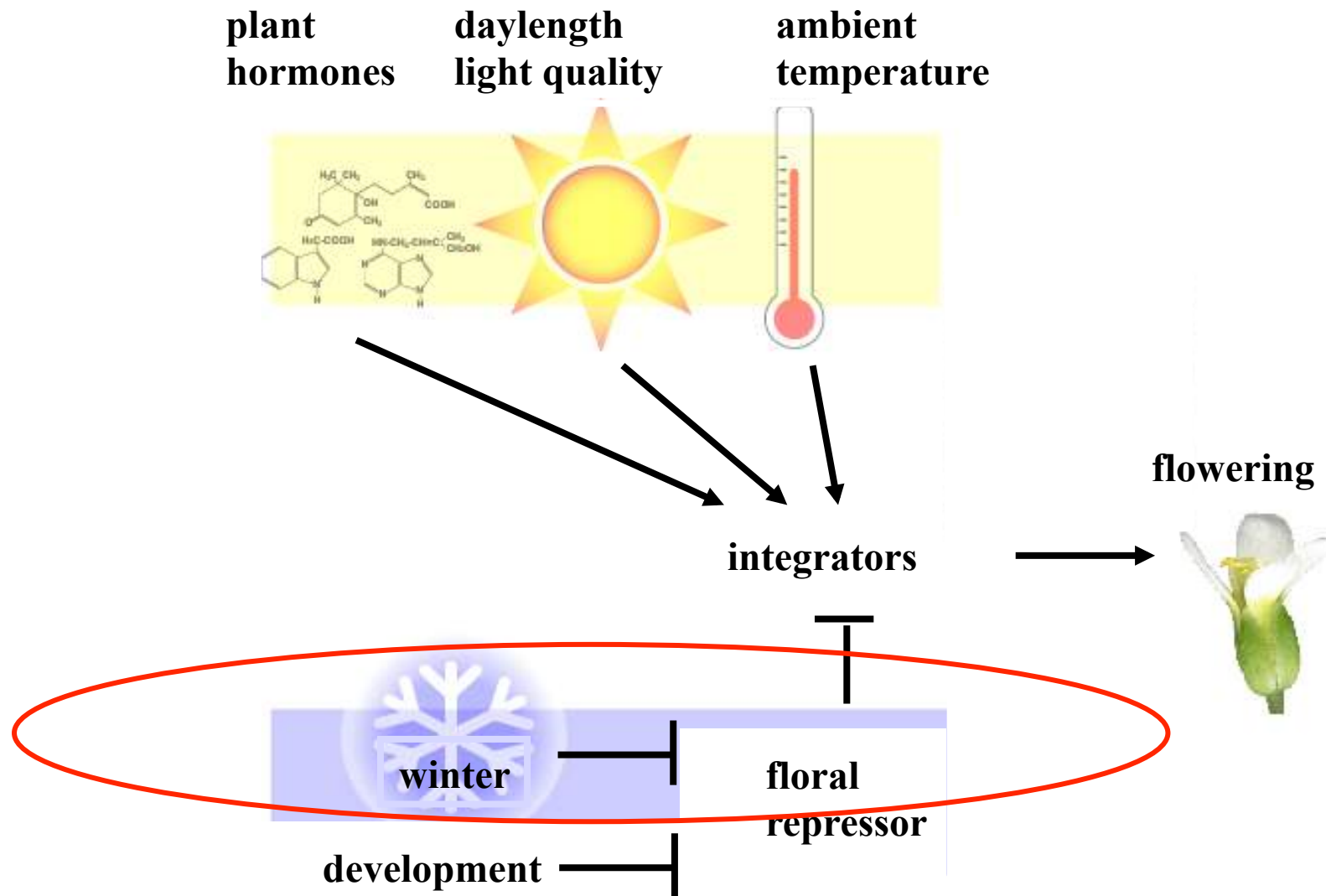
*Courtesy of C. Dean*

# In nature, environment and timing are crucial...



From Xu and Chong, *Nature Plants* **4**: 997–1009 (2018)

# Multiple environmental and endogenous cues regulate the switch to flowering

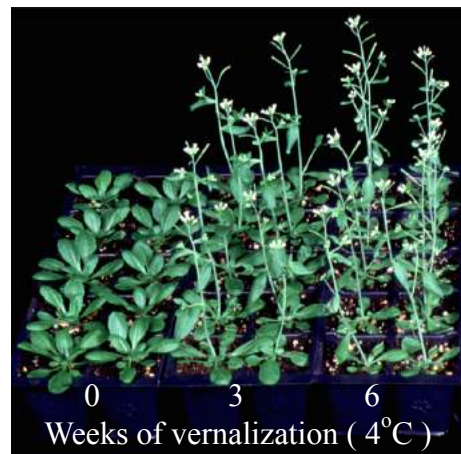


Courtesy of C. Dean

# Vernalization

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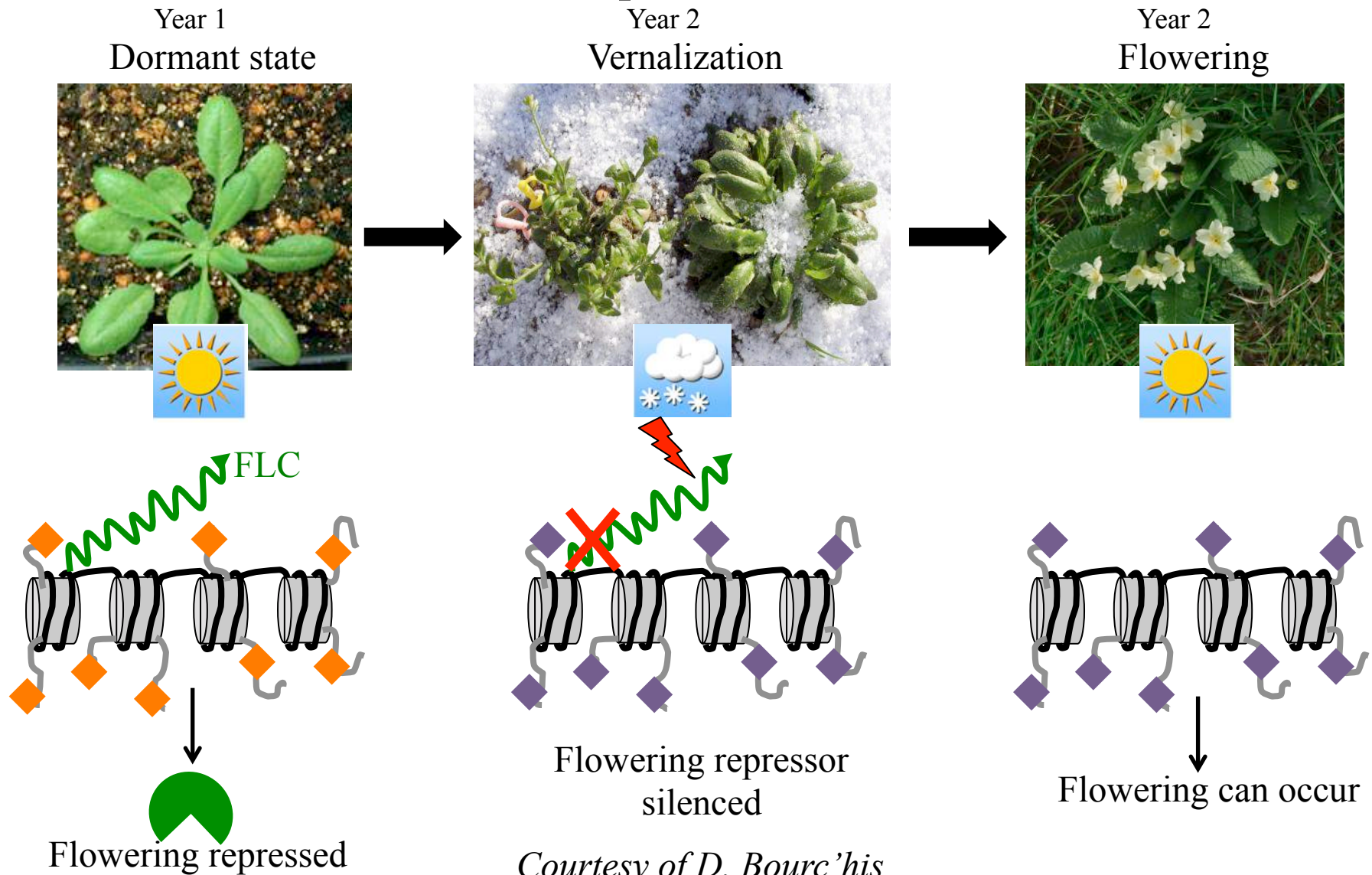
In plants such as *Arabidopsis thaliana*, prolonged exposure to cold temperatures (winter cold), triggers the mitotically stable epigenetic silencing of the potent floral repressor FLOWERING LOCUS C (FLC), and renders plants competent to flower in the spring





# Vernalization

Vernalization causes a gradual reduction in expression of a floral repressor *FLC*



*Courtesy of D. Bourc'his*

# Vernalization

Vernalization causes a gradual reduction in expression of a floral repressor *FLC*



Caroline Dean (1957)  
British plant scientist

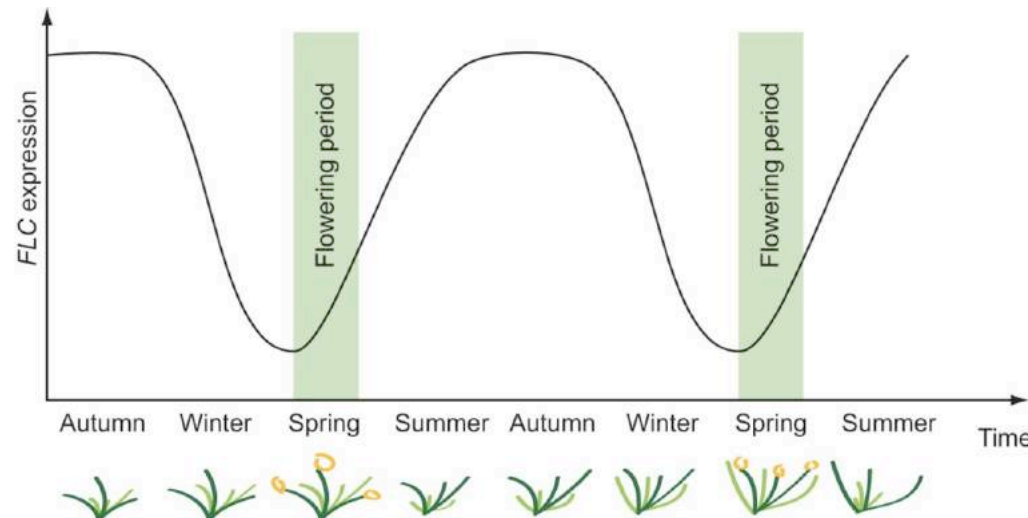
vernalization



*FLC*  
(*Flowering Locus C* =  
a Transcription Factor  
that represses the flowering program )



flowering



# Vernalization

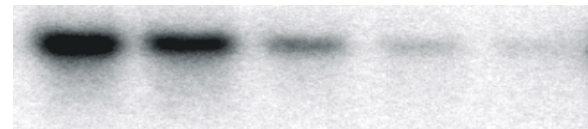
Vernalization causes a gradual reduction in expression of a floral repressor *FLC*  
*FLC* expression then remains off throughout the rest of development

Cold temperature (weeks)

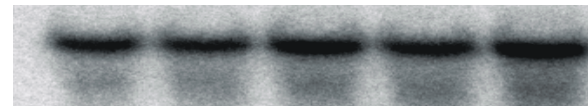
0 1 2 3 4

Northern blot

*FLC*



*b-TUBULIN*



Courtesy of C. Dean

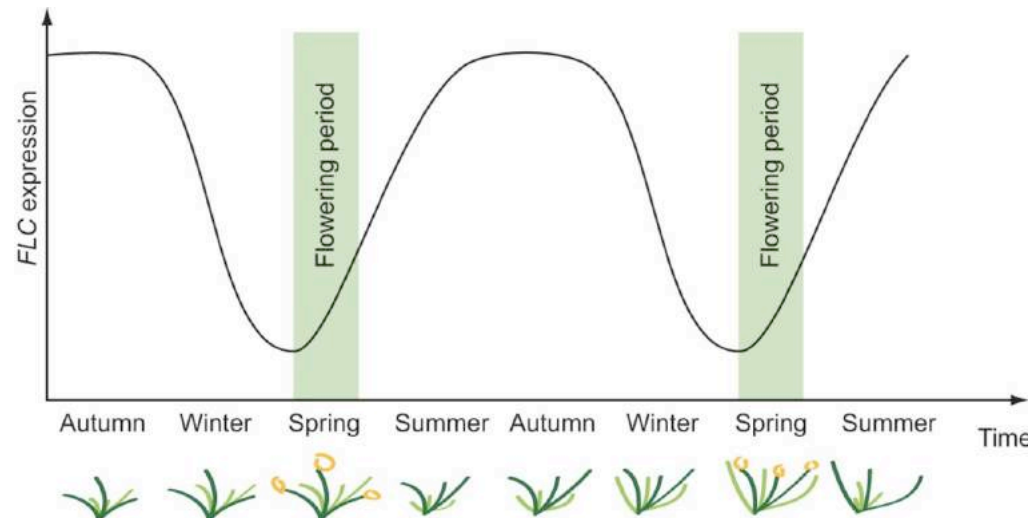
vernalization



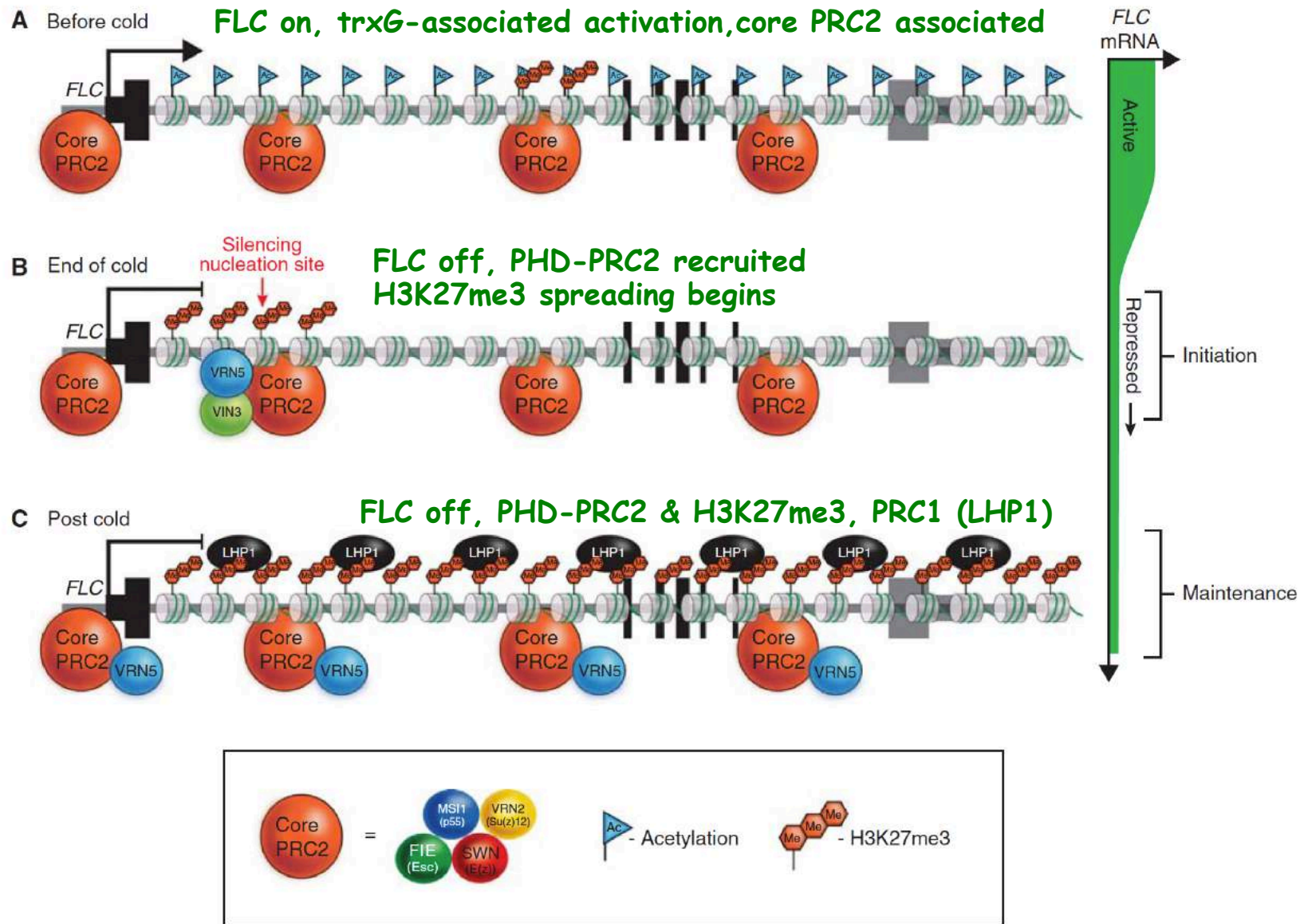
*FLC*  
(Flowering Locus C =  
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flowering



# Memory of Winter : Polycomb group protein repression at *FLC* locus



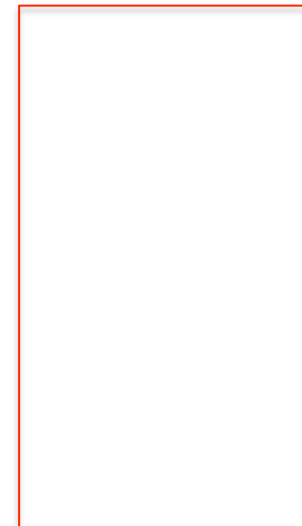
For review, see Dean and Baulcombe, *CSH Perspectives*, 2014

# Non-coding RNAs and chromatin repression enable memory of silent state at the *FLC* locus

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After cold, nucleated H3K27me3 causes some cells to switch to a silenced state with high levels of H3K27me3 blanketing the gene  
(NB requires cell division)

The greater the number of cells with H3K27me3, the more likely *FLC* will remain repressed & flowering will occur

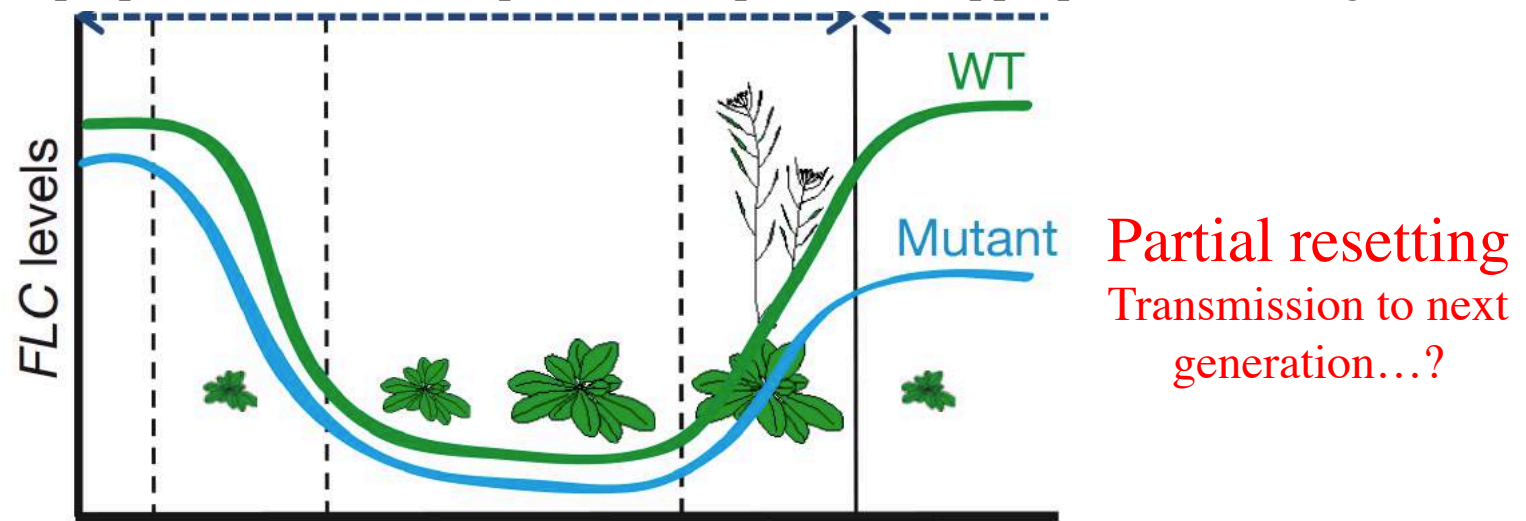




# Reprogramming following vernalisation

## Cold-induced Polycomb repression of the *FLC* locus (a repressor of flowering)

A strategy to allow proper coordination of plant development and appropriate flowering time



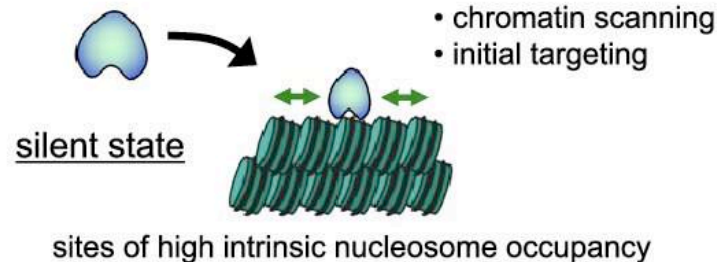
- ELF6 has H3K27me3 demethylase activity – a single nucleotide mutation at a highly conserved amino-acid reduced ELF6 enzymatic activity
- In next generation of mutant plants, H3K27me3 levels at the *FLC* locus stayed higher, & *FLC* expression remained lower, than in the wild type.
- Early flowering phenotype was stable for at least three generations following vernalisation but was not enhanced by a second vernalisation treatment in later generations.

**Role for H3K27 demethylation in the reprogramming of epigenetic states in embryos, to prevent transgenerational inheritance of “acquired traits”**

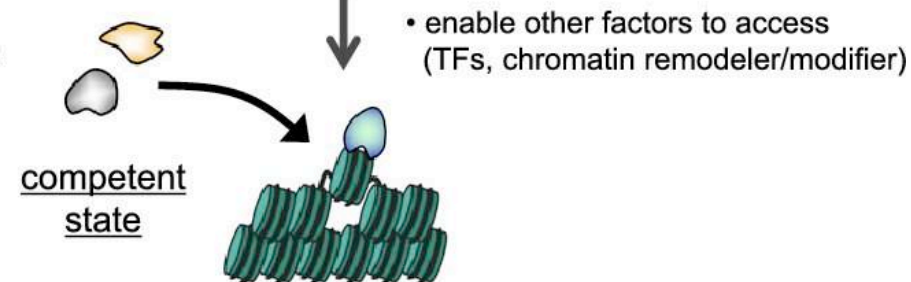
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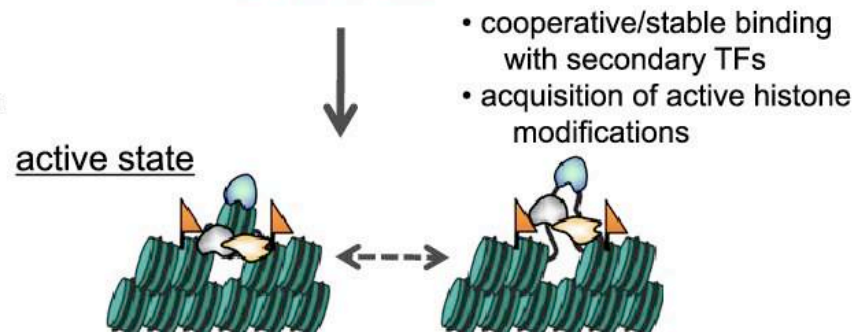
## A. Pioneer factor



## B



## C



## Resetting at every generation:

Through ELF6 (H3K27 demethylase) to erase silent chromatin state (Crevillen et al, Nature 2014)

And Pioneer transcription factor LEC1 that acts in early pro-embryo to open up *FLC* chromatin and activate it *de novo* (Tao et al, Nature 2017)

**NB Few environmentally induced traits are inherited across generations, even in plants!**

# Relation between periods of heat and epigenetic memory?

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ARTICLE

DOI: [10.1038/s41467-018-03065-7](https://doi.org/10.1038/s41467-018-03065-7)

OPEN

## Absence of warmth permits epigenetic memory of winter in *Arabidopsis*

Jo Hepworth<sup>1</sup>, Rea L. Antoniou-Kourounioti<sup>1</sup>, Rebecca H. Bloomer<sup>1</sup>, Catja Selga<sup>2</sup>, Kristina Berggren<sup>3</sup>, Deborah Cox<sup>1</sup>, Barley R. Collier Harris<sup>1</sup>, Judith A. Irwin<sup>1</sup>, Svante Holm<sup>3</sup>, Torbjörn Säll<sup>2</sup>, Martin Howard<sup>1</sup> & Caroline Dean<sup>1</sup>

- A *lack* of spikes of high temperature, not just prolonged cold, is thus the major driver for vernalisation

## Heat can erase epigenetic marks of vernalization in *Arabidopsis*

---

Frédéric Bouché, Nathalie Detry, and Claire Périlleux\*

University of Liège; Laboratory of Plant Physiology; PhytoSYSTEMS; Liège, Belgium

- High temperature leads to devernalization and FLC reactivation
- Repressive epigenetic H3K27me3 decreases at the FLC locus when vernalized seedlings are grown at 30°C, unless they were first exposed to a stabilizing period at 20°C.
- Ambient temperature thus controls the epigenetic memory of winter.

# Relation between periods of heat and epigenetic memory?

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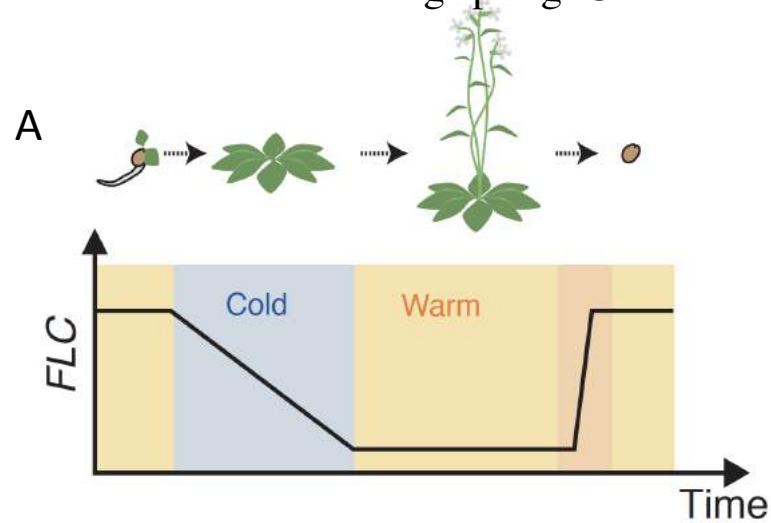
Frédéric Bouché, Nathalie Detry, and Claire Périlleux\*

**« The erasing effect of heat highlights a risk for winter plants if we think of the extreme and erratic weather events that are becoming more common as the climate changes ».**



# Alternative strategies ?

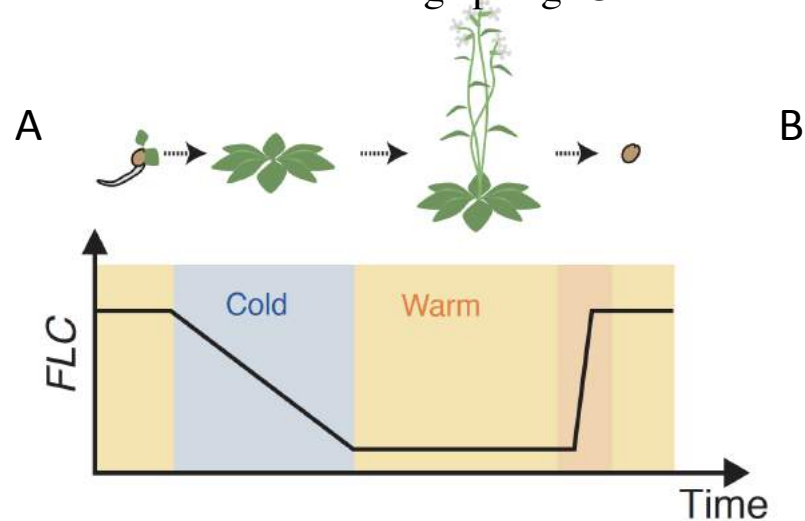
Plants use continuous monitoring of long-term temperature signals to infer seasonal progression in order to align development with external conditions. **Vernalization** ensures that plants over-winter vegetatively and flower in the following spring. Central to this is regulation of the FLOWERING LOCUS C (*FLC*)



FLC is transcriptionally repressed during exposure to cold temperatures (i.e vernalization)

# Alternative strategies ? Transposons again!

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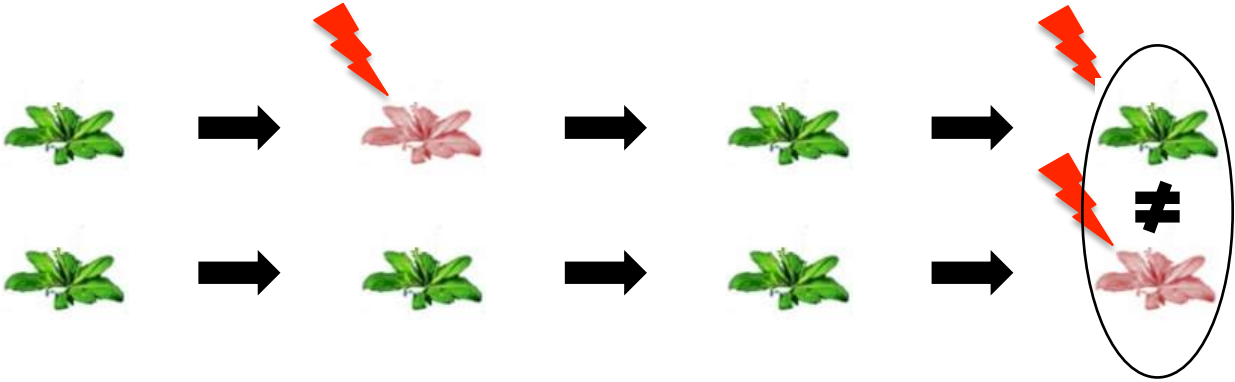
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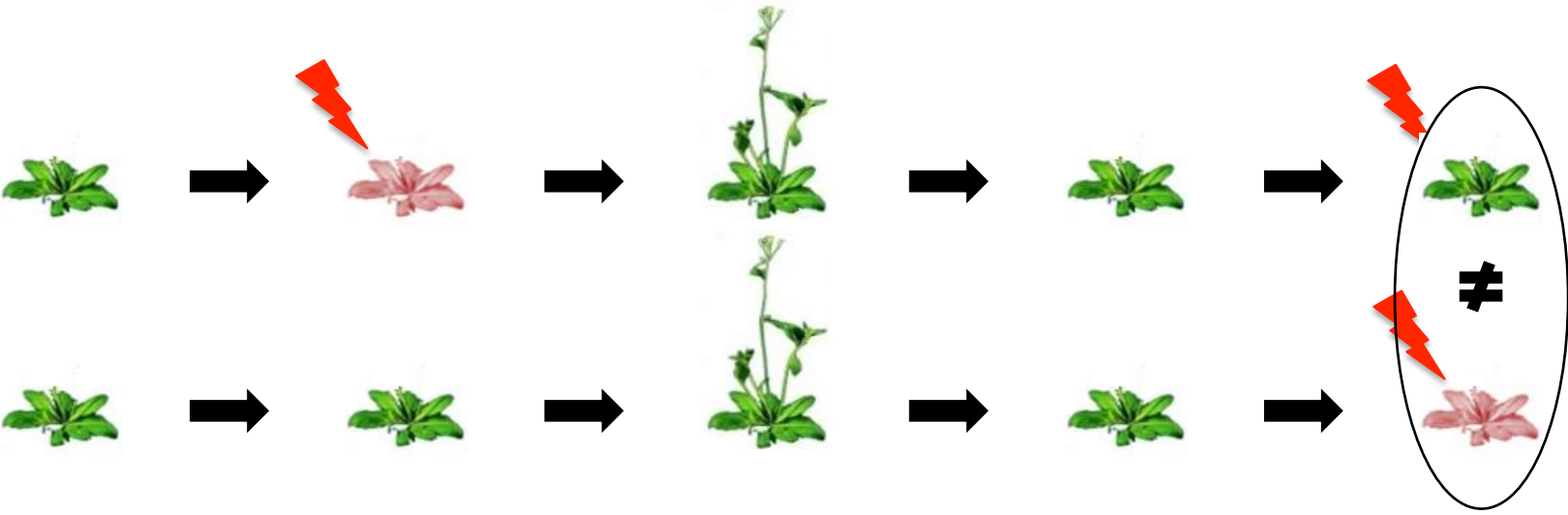
L. Quadrana, V. Colot et al (in preparation) :  
« Environmentally-responsive genes are chromatin targets for transposon-induced mutations »

Colloque – 8-9 Avril 2019

# Can the environment induce memory?



Priming against stress  
(herbivores, pathogens,  
cold, heat, etc.)



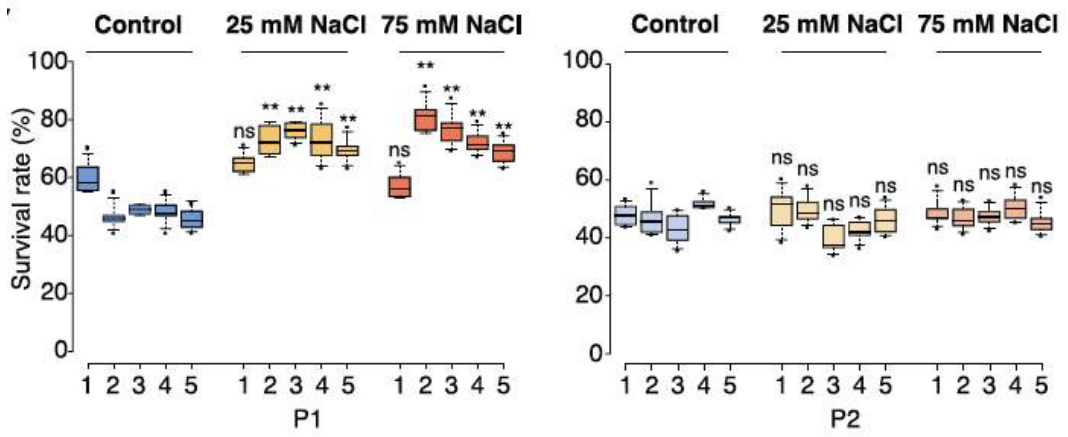
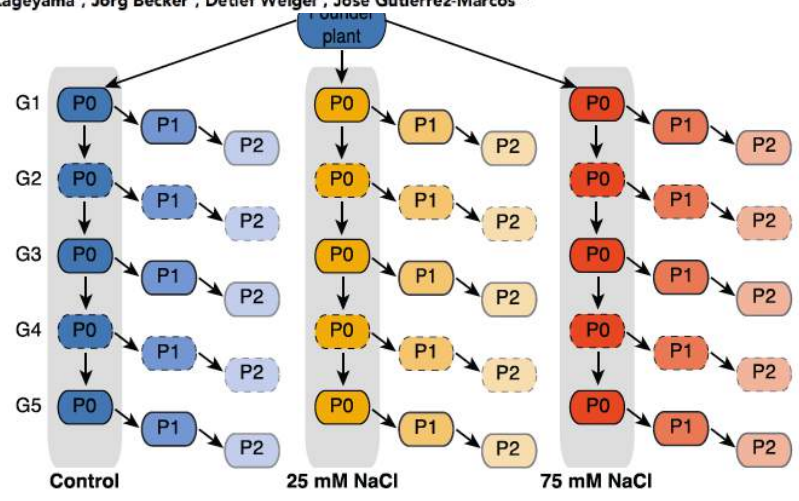
Trans-  
generational  
Stress  
memory  
???

# Improved salt resistance of progeny from parents exposed to hyperosmotic stress in the next generation (but not beyond)



**Hyperosmotic stress memory in Arabidopsis is mediated by distinct epigenetically labile sites in the genome and is restricted in the male germline by DNA glycosylase activity**

Anjar Wibowo<sup>1†</sup>, Claude Becker<sup>2†</sup>, Gianpiero Marconi<sup>1,3</sup>, Julius Durr<sup>1</sup>, Jonathan Price<sup>1</sup>, Jorg Hagmann<sup>2</sup>, Ranjith Papareddy<sup>1</sup>, Hadi Putra<sup>1</sup>, Jorge Kageyama<sup>2</sup>, Jorg Becker<sup>4</sup>, Detlef Weigel<sup>2</sup>, Jose Gutierrez-Marcos<sup>1\*</sup>



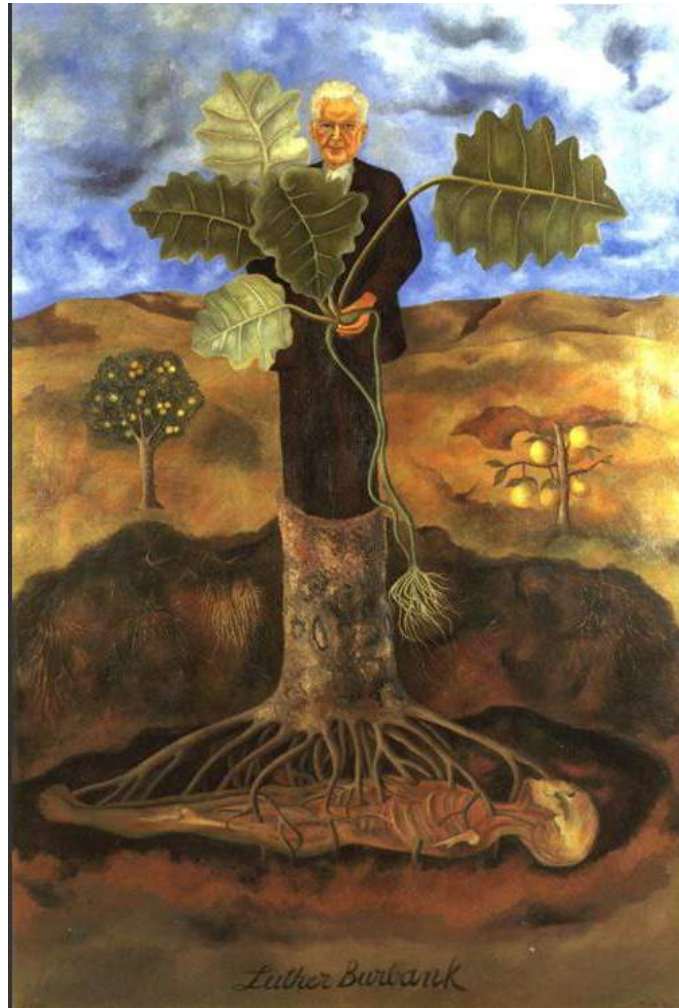


# What is the influence of the environment on epigenetic modifications and their transmission?

**“Heredity is only the sum of all past environment”**  
in *“The Training of the Human Plant.”*

American Botanist and Horticulturist and one of the pioneers of agricultural science. Burbank developed over 800 plant varieties and strains. Including the Russet Burbank potato, most common potato used in processed food preparation (eg MacDonald’s french fries)

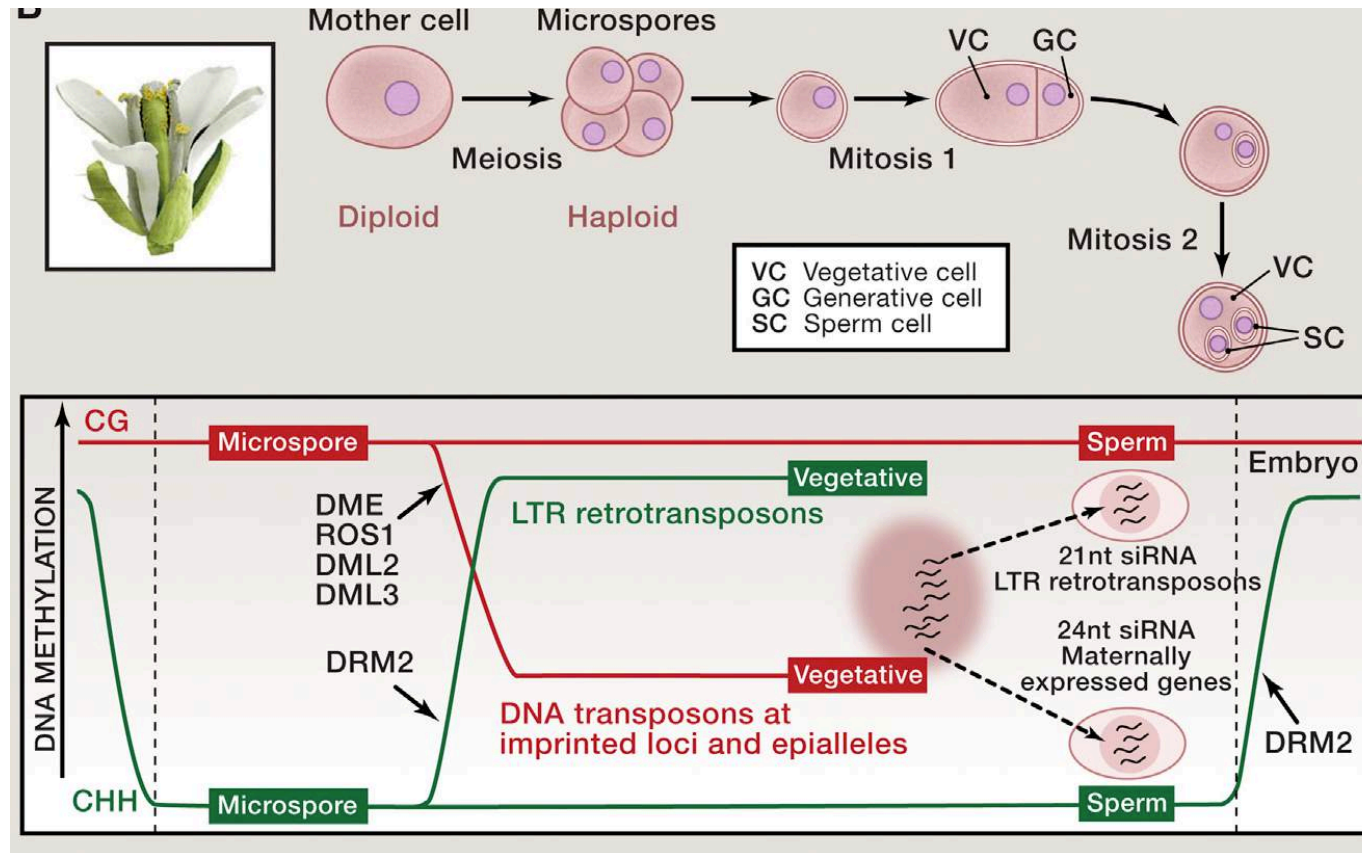
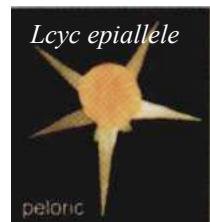
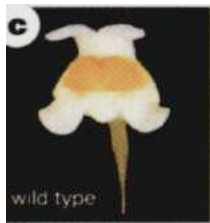
Famous for his crossbreeding projects. Supported by Carnegie institute but was criticised for his record keeping and that his methods were not scientific enough – though he was a man of his time



Portrait of Luther Burbank (1849- 1926)  
Frida Kahlo 1931

# Epigenetic memory across generations?

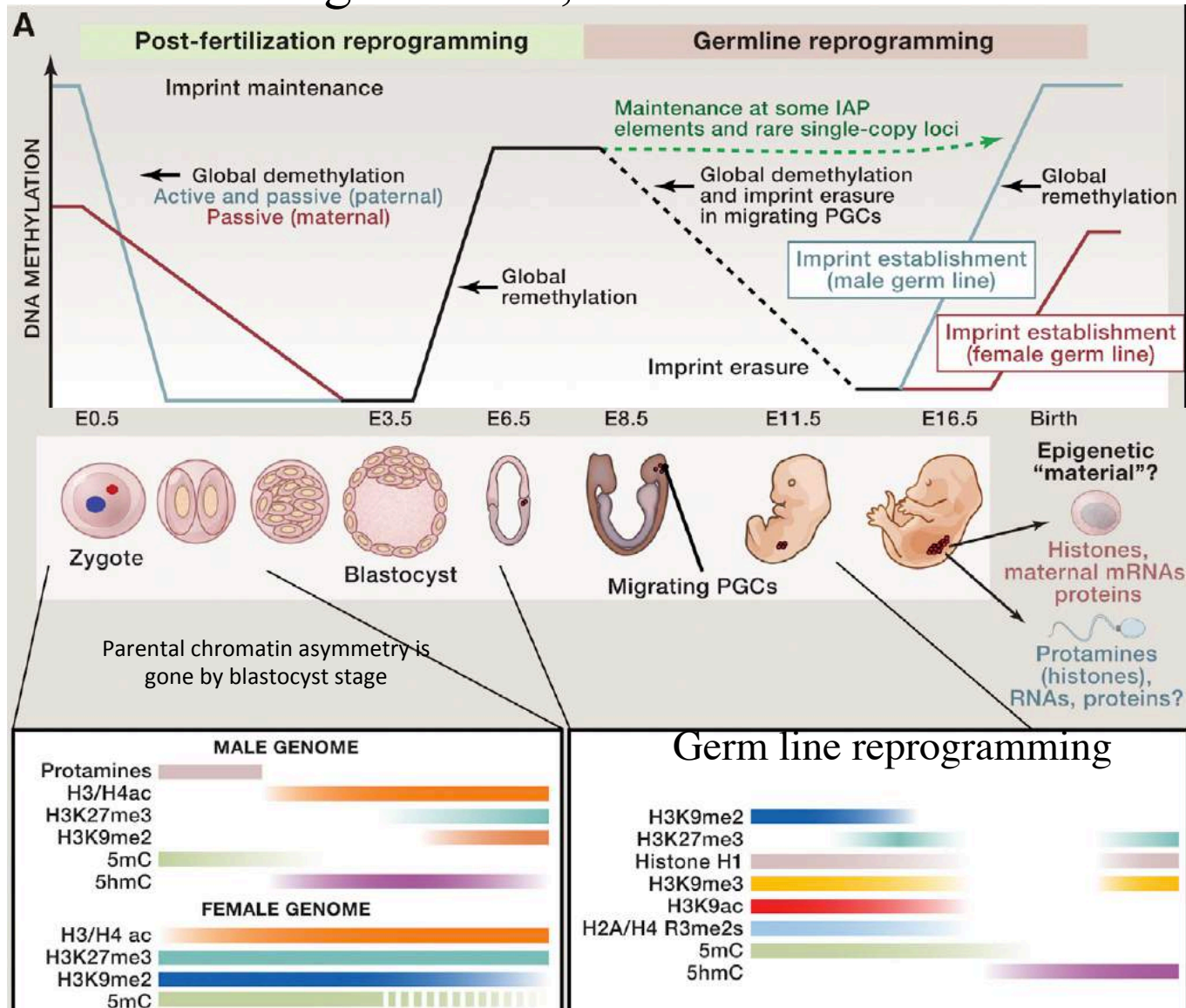
- In plants, unlike animals, there is no early separation of germline and soma thus epigenetic marks acquired throughout their lifetime can be included in the gametes e.g. *Peloric* (*Lcyc* CpG me).
- Most plant developmental genes involve **non-CpG** DNA methylation which requires a continuous remethylation cue and as such is continually reprogrammed
- Transposable elements (**CpG methylation**) are probably key targets for trans-generational effects
- Both spontaneous and environmentally induced trans-generational effects



From  
 Heard and  
 Martienssen,  
 Cell 2014

# Epigenetic memory across generations?

In mammals, most epigenetic marks are erased at each generation, but some are not...

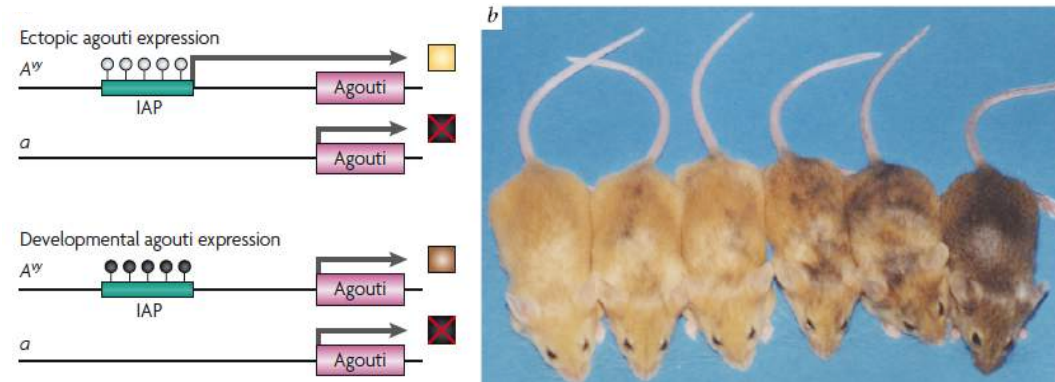


From  
Heard and  
Martienssen,  
Cell 2014



# Epigenetic memory across generations?

Resistance of some retrotransposons to reprogramming may lead to trans-generational epigenetic effects in mammals?  
*Agouti* is a classic eg of a IAP-induced metastable epiallele



*Agouti<sup>vy</sup>*  
*Morgan et al, 1999*

- In Mouse germ line: 4730 loci escape demethylation (>40% 5mC) in the germ line: mainly IAP -TR1 elements (most active elements); 233 were single-copy loci (**COURS 2015**)
- In Human germ line: 116000 loci escape reprogramming, 7000 of these were CpG islands not in TEs/repeats – but located in/near genes associated with metabolism and neurological function (obesity, multiple sclerosis and schizophrenia) (Tang et al, Cell 2015)



# Trans-generational epigenetic inheritance of metastable alleles is reconstructed at each generation

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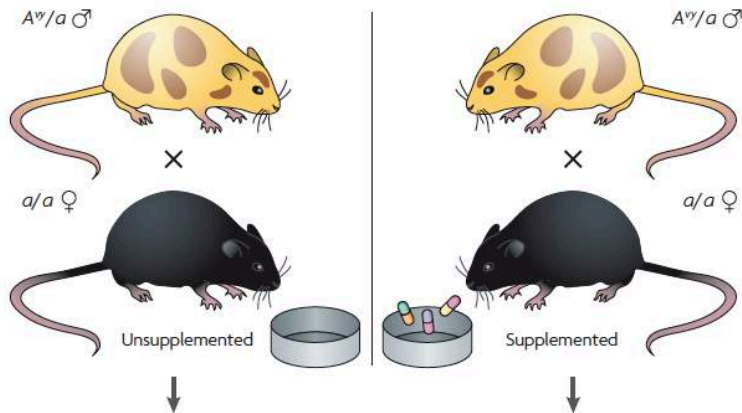
## Highlights

- Repertoire of variably methylated repeat elements defined in inbred mice
- VM-IAPs are flanked by CTCF binding sites, and very few act as promoters
- Methylation variability is re-established from one generation to the next
- Memory of parental methylation state is an exception rather than the rule

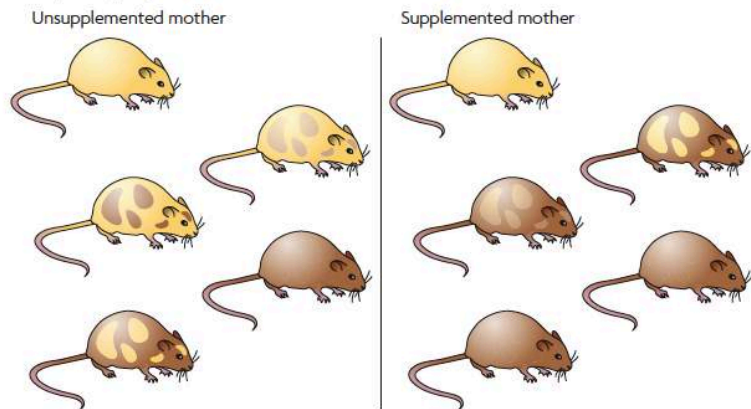
- Multiple C57BL/6J murine IAPs with Avy-like epigenetic properties.
- Each exhibits a stable methylation state within an individual but varies between individuals.
- Variably methylated IAPs are reprogrammed after fertilization and re-established as variable loci in the next generation, indicating reconstruction of metastable epigenetic states and challenging the generalizability of non-genetic inheritance at these regions.

# Nutritional Influence on Trans-generational Epimutations?

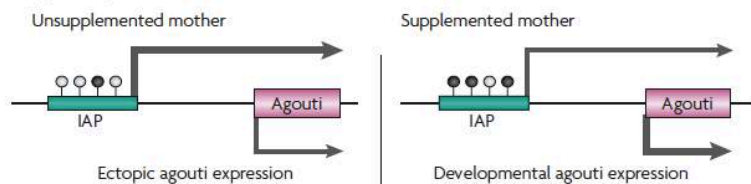
## a Dietary supplementation during pregnancy



## b *Avy/a* offspring



## c Agouti expression



### Transposable Elements: Targets for Early Nutritional Effects on Epigenetic Gene Regulation

Robert A. Waterland and Randy L. Jirtle\*

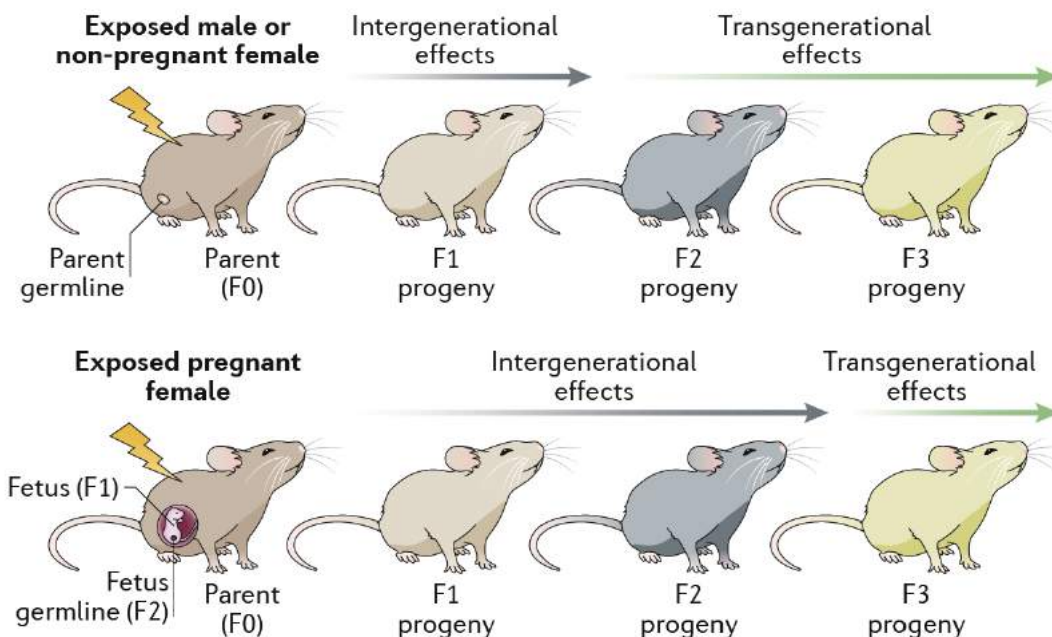
- Early nutrition affects adult metabolism in humans and other mammals, potentially via persistent alterations in DNA methylation.
  - Dietary methyl supplementation of *a/a* dams with extra folic acid, vitamin B12, choline, and betaine alter the phenotype of their *Avy/a* offspring.
  - **The methyl-donor-induced shift in coat-colour distribution** was shown to result from an **increase in DNA methylation at CpG sites in the upstream IAP transposable element.**
  - Genistein, when given at a level that is comparable to that consumed by humans with high soy diets, also shift the Agouti coat colour increases DNA methylation even though it is not a methyl-donating compound – the mechanism for this is unknown.
- ⇒ dietary supplementation, long presumed to be purely beneficial, may have unintended deleterious influences on the establishment of epigenetic gene regulation in humans?

**However, the shift in coat colour induced by diet is NOT stable across generations (in the absence of methyl supplemented diet).**

**Diet-induced hypermethylation at *agouti viable yellow* is not inherited transgenerationally through the female**

Robert A. Waterland,<sup>\*1</sup> Michael Travisano,<sup>+2</sup> and Kajal G. Tahiliani\*

# Can the Environment Induce/Influence Epialleles in Mammals?



*From review by Skvortsova et al, NRCMB 2018*

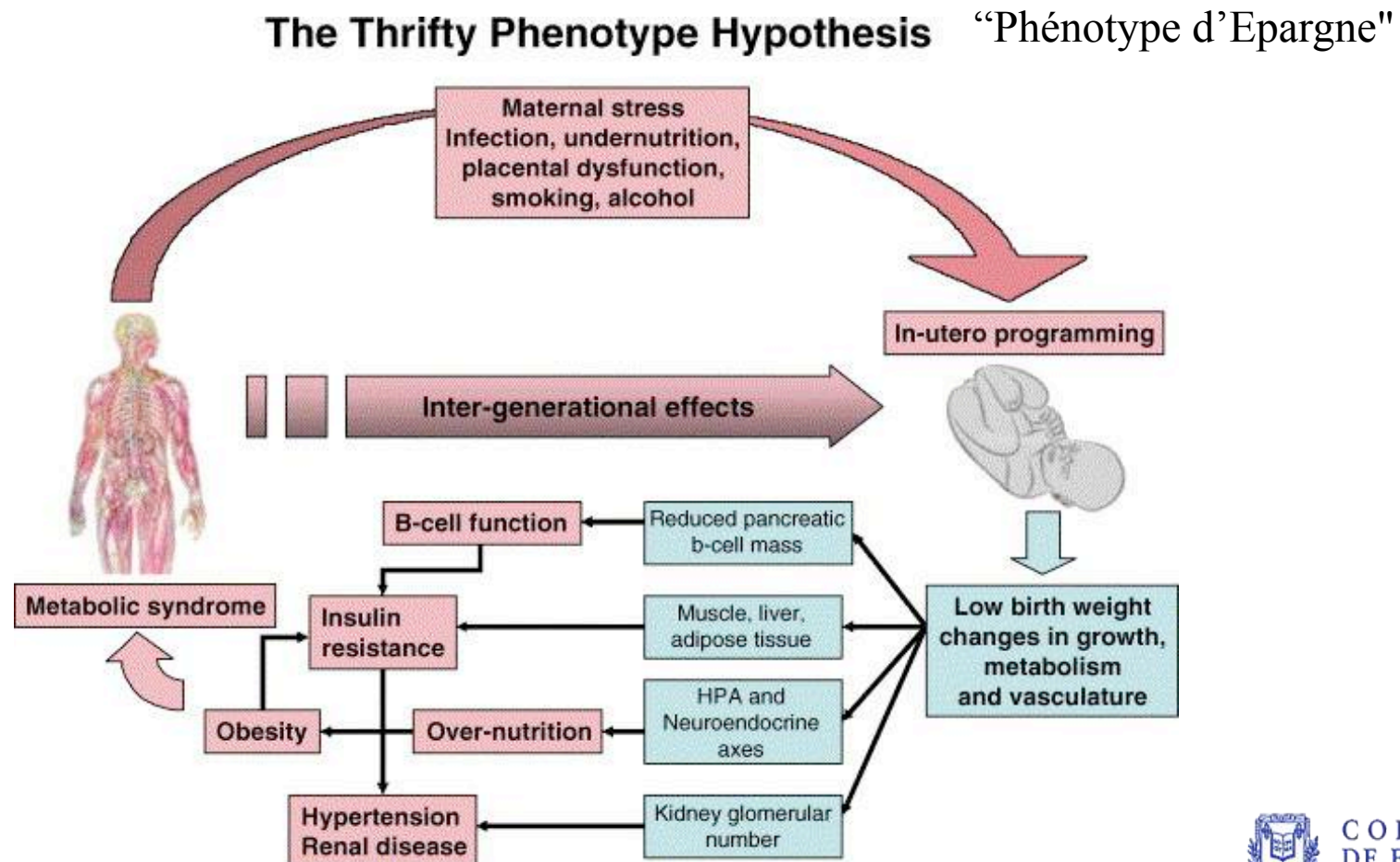
Laboratory models allow epigenetic changes to be distinguished from DNA sequence changes; ideally would like individuals that are:

- Genetically identical => *uniform* genetic information
- ⇒ identify specific effects of different environmental influences
- ⇒ precise time at which sensitivity to the environment may occur
- ⇒ extent to which stochastic events contribute to phenotypic change
- ⇒ Father – to – offspring transmission excludes variable oocyte and gestational effects
- ⇒ Exclude « Cultural » effects

# Influence of environmental fluctuations during early mammalian development?

Nutritional conditions during uterine development may have effects later in life, and influence the occurrence of adult metabolism and diseases

Eg Dutch famine – at the end of WWII, individuals exposed to famine during gestation had a poorer glucose tolerance than those born the year before the famine.





# Influence of environmental fluctuations during early mammalian development?

Nutritional conditions during uterine development may have effects later in life, and influence the occurrence of adult metabolism and diseases

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## The Thrifty Phenotype Hypothesis “Phénotype d’Epargne”

Maternal stress  
Infection, undernutrition,  
placental dysfunction,  
smoking, alcohol

The evolution of developmental plasticity, which enables an organism to adapt to environmental signals during early life, can also increase the risk of developing chronic diseases when there is a mismatch between the perceived environment and that which is encountered in adulthood.

High number of confounding possible effect in humans:

*Genetic polymorphisms*  
*Unmeasured environmental variables*  
*Cultural effects*  
*Etc etc*

Hypertension  
Renal disease

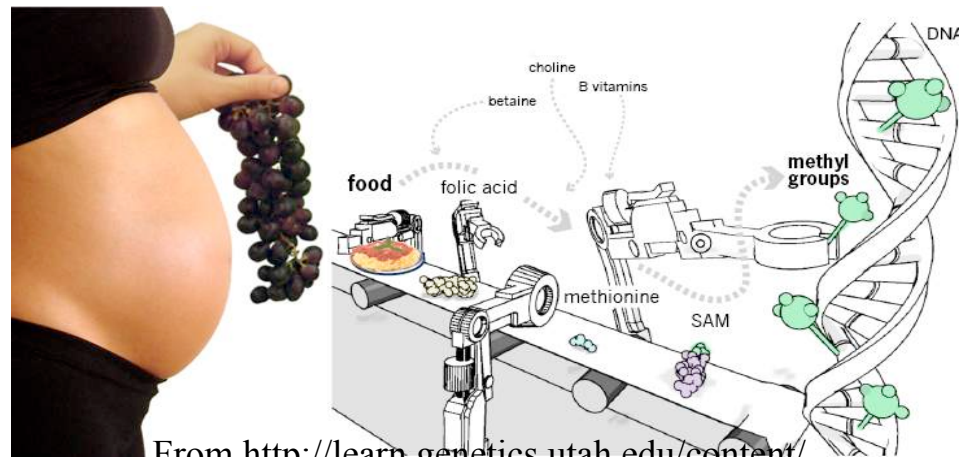
Kidney glomerular  
number





# Nutritional Influence and Inter-generational Effects

Understanding how the environment affects the human epigenome and how potentially acquired traits can be propagated through generations remains an area of intense investigation



From <http://learn.genetics.utah.edu/content/epigenetics/nutrition/>

"the environment can influence the degree to which these so-called "epigenetic marks" are covalently bonded onto the genome during early development.

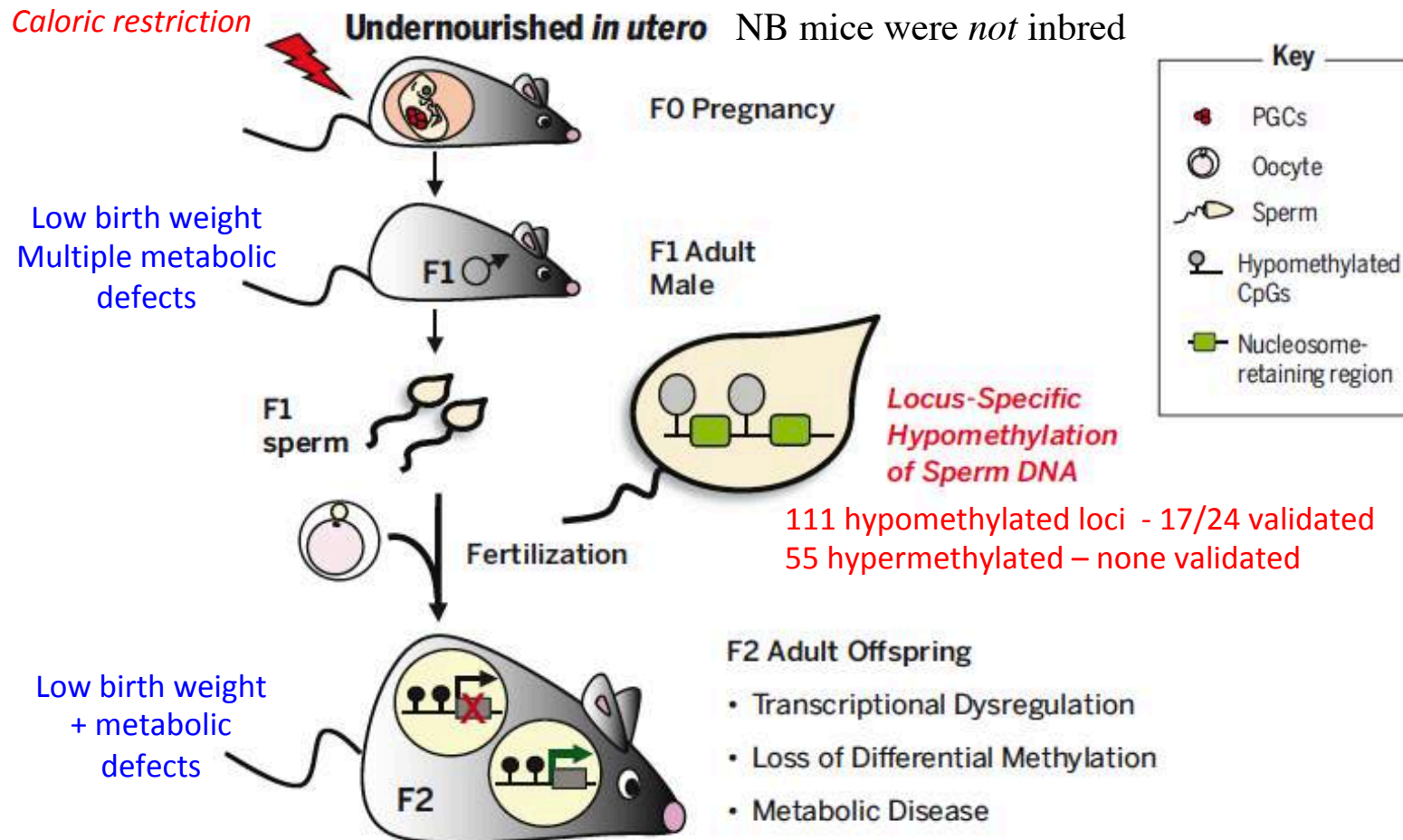
Thus, the thinking goes, **the early environment can modulate gene expression in ways that are long-lasting - even transgenerational.** The idea is a powerful one to be sure. And a scary one as well, as **parents who read this literature, may fret that their children (and grandchildren) can be epigenetically scarred by early nutritional, physical and/or psycho-social stress.**

I must admit that, as a parent of young children myself, I began to wonder if I might be negatively influencing the epigenome of my children.

I'm wondering how much physical and/or social stress is enough to cause changes in the epigenome? Does the concern about epigenetics only apply to exposure to severe stress? or run of the mill forms of stress? How much do we know about this?" [Genes 2 Brains 2 Mind 2 Me](#)

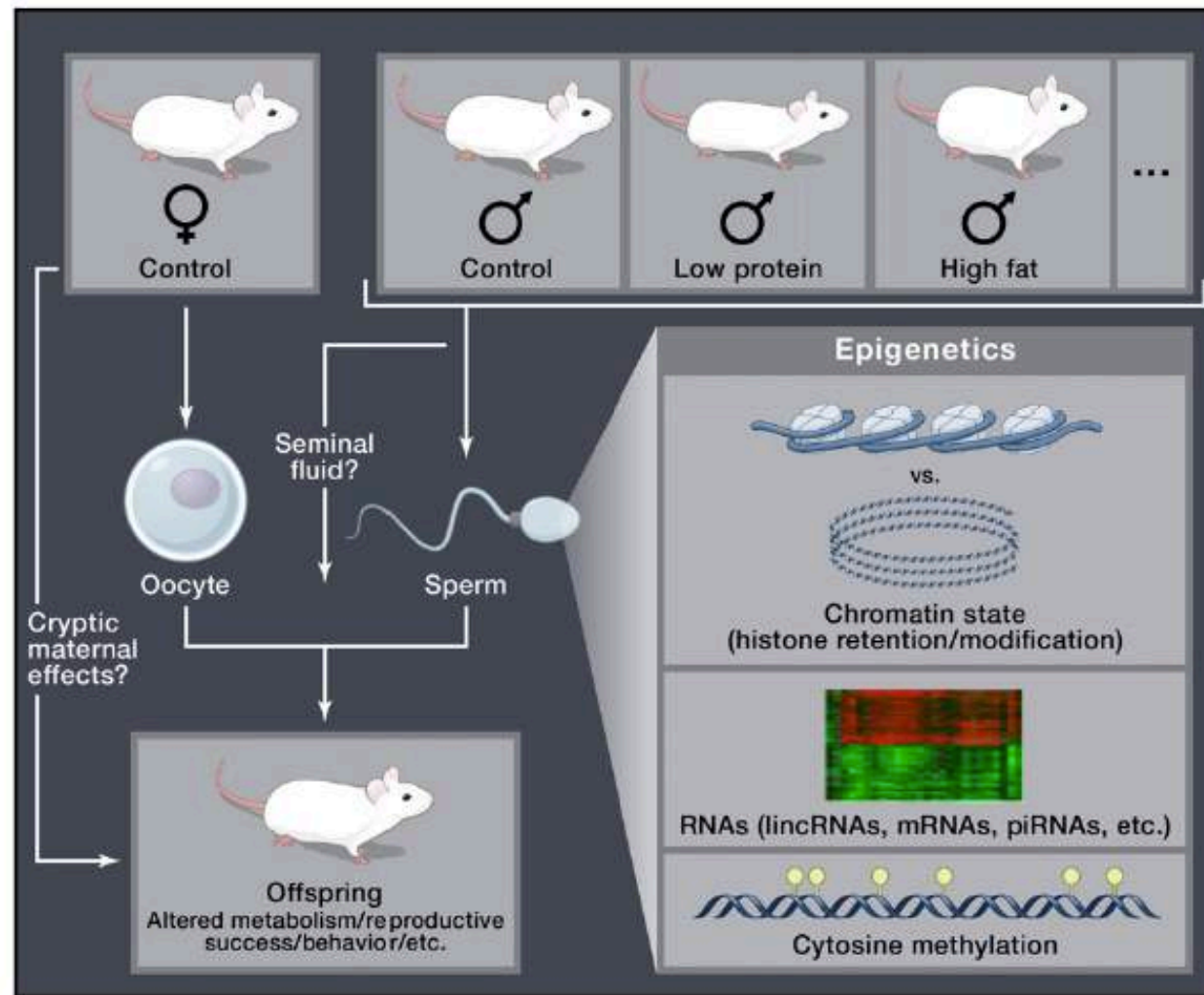
# Nutritional Influence and Inter-generational Effects

Analyse sperm of F1 male offspring from **females (dams) that were undernourished** during a specific window of gestation (period of DNA methylation re-acquisition in the male germ line)  
And analyse the metabolic state of the F2 offspring of these males



Radford et al (2014) In utero undernourishment perturbs the adult sperm methylome and intergenerational metabolism. *Science* 345, 785-790.

# Nutritional Influence and Inter-generational Effects



- Progeny of **males that had been fed on a low protein diet** showed increased expression of genes involved in fat and cholesterol synthesis corresponding to lipid metabolism
- The sperm **epigenome** was modestly altered by diet
- Trans-generational effects (F2 and beyond) not demonstrated...

# What is the influence of the environment on epigenetic modifications and their transmission?

## Developmental Cell

### Genetic and Epigenetic Variation, but Not Diet, Shape the Sperm Methylome

#### Highlights

- Whole genome nucleotide resolution analyses of dietary effects on sperm methylation
- No consistent effects of paternal diet on sperm cytosine methylation pattern
- Epivariation between animals influences methylation pattern differences over diet
- Identification of genetic and epigenetic variability over tandem repeats such as rDNAs

#### Authors

Jeremy M. Shea, Ryan W. Serra, Benjamin R. Carone, ..., Alexander Meissner, Manuel Garber, Oliver J. Rando

#### Correspondence

oliver.rando@umassmed.edu

#### In Brief

Shea et al. characterize genome-wide cytosine methylation patterns in sperm obtained from mice on a variety of dietary paradigms. They show that epivariation between animals exerts far greater influence on cytosine methylation patterns than the diet consumed. Characterization of regions subject to epivariation shows dramatic variation over tandem repeat families.

Article

## Developmental Cell

### Small RNAs Are Trafficked from the Epididymis to Developing Mammalian Sperm

#### Highlights

- Detailed characterization of small RNA dynamics in mammalian sperm maturation
- Caput epididymosomes can deliver small RNAs to testicular spermatozoa *in vitro*
- Metabolic labeling of RNAs in intact animals tracks RNAs from epididymis to sperm

#### Authors

Upasna Sharma, Fengyun Sun, Colin C. Conine, ..., Veronika A. Herzog, Stefan L. Ameres, Oliver J. Rando

#### Correspondence

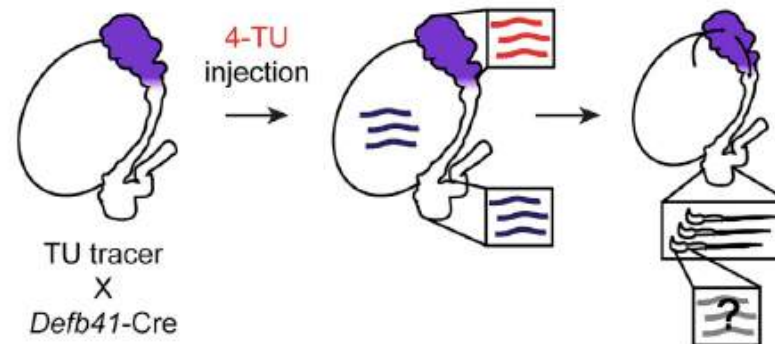
oliver.rando@umassmed.edu

#### In Brief

Recent studies suggest that sperm carry RNAs first synthesized in epididymal somatic cells. Sharma et al. test this hypothesis, characterizing small RNA population dynamics during sperm maturation. They show that caput epididymosomes can deliver RNAs to immature sperm *in vitro* and track RNAs *in vivo* from the epididymis to sperm using metabolic labeling.

Article

Novel epigenetic reprogramming events that occur during mammalian spermatogenesis: Transition from a piRNA-dominated stage of testicular spermatogenesis To **tRNA fragment (tRF)** in epididymal sperm, And a transient loss of clustered microRNAs in the **caput epididymis**.





# What is the influence of the environment on epigenetic modifications and their transmission?

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## Dad's diet – smRNA methylation signatures in sperm pass on disease risk

Zhang, Y. et al. Dnmt2 mediates intergenerational transmission of paternally acquired metabolic disorders through sperm small non-coding RNAs. *Nat. Cell Biol.* 20, 535–540 (2018).

### **Changes in tRNA-derived small RNAs following a high-fat diet.**

A high-fat diet in mice results in changes in tRNA-derived small RNA (tsRNA) expression profiles as well as increased methyl modifications at these tsRNAs, which when injected into zygotes result in phenotypes associated with metabolic disease risk.

This transmission is prevented in mice lacking DNA methyltransferase enzyme (DNMT2; *Dmnt2*<sup>-/-</sup>),  
=> Methyl modifications for tsRNAs are required for the transmission of the environment memories of a high-fat diet.



# Mechanisms of environmentally induced epigenetic transmission : methylation of RNA not DNA, and not associated with chromatin!

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# Maternal and Paternal Stress: Epigenetic impact on offspring (next week)

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# CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

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**Année 2018-2019:**

**“Épigénétique, Environnement et Biodiversité”**

**11 Decembre 2018**

**Cours IV**

**Le role de l'épigénétique dans la plasticité phénotypique et  
l'évolution des réponses adaptatives**

8/04/2019 (LORS DU COLLOQUE)  
5) Épigénétique, Environnement et Biodiversité