What is an **Epigenetic** Mechanism and why is it important?
Epigenetics

- Programming of gene expression that:
  - does not depend on the DNA code
  - (relatively) stable, i.e., replicated through:
    - cell mitosis
    - meiosis, i.e. transgenerational (limited evidence in humans)

- Characteristics of epigenetic programming
  - Modifiable (can be reprogrammed)
  - Active or poised to be activated:
    - Potentially associated with current health states or predict future events
A musical example

DNA

Phenotype

Epigenetics

Andrea Baccarelli – Laboratory of Environmental Epigenetics
Epigenetics & Music Use the Same Markings

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- pencil markings (can be erased)
- markings in ink (permanent)
**Epigenetic markings**

**DNA methylation**
Methyl marks added to certain DNA bases **repress** gene transcription

**Histone modifications**
A combination of different molecules can attach to the ‘tails’ of proteins called histones. These **alter** the activity of the DNA wrapped around them.

**microRNAs**
Small non-coding RNAs that **block translation** of messenger RNAs into proteins
DNA methylation suppresses RNA expression

(more accurately: it is **usually** associated with suppressed RNA)

- **DNA methylation**
  - inactive

- **DNA demethylation**
  - active or poised to be activated

**Cytosine-phosphate-Guanine**

CpG sites

[Diagram showing 5-Methylcytosine and Cytoine with methyl groups at specific positions]
Lamarck vs. Darwin

Jean-Baptiste Lamarck
(1744-1829)

Charles Darwin
(1809-1882)
Giraffes stretching their necks to reach leaves high in trees (especially Acacias), strengthen and gradually lengthen their necks.

These giraffes have offspring with slightly longer necks (also known as "soft inheritance").
Lamarck’s examples: the blacksmith

A blacksmith, through his work, strengthens the muscles in his arms. His sons will have similar muscular development when they mature.
When Brian Dias became a father last October, he was, like any new parent, mindful of the enormous responsibility that lay before him. From that moment on, every choice he made could affect his newborn son’s physical and psychological development. But, unlike most new parents, Dias was also aware of the influence of his past experiences — not to mention those of his parents, his grandparents and beyond.

Where one’s ancestors lived, or how much they valued education, can clearly have effects that pass down through the generations. But what about the legacy of their health: whether they smoked, endured famine or fought in a war?

As a postdoc in Kerry Ressler’s laboratory at Emory University in Atlanta, Georgia, Dias had spent much of the two years before his son’s birth studying these kinds of questions in mice. Specifically, he looked at how fear associated with a particular smell affects the animals and leaves an imprint on the brains of their descendants.

Dias had been exposing male mice to acetophenone — a chemical with a sweet, almond-like smell — and then giving them a mild foot shock. After being exposed to this treatment five times a day for three days, the mice became reliably fearful, freezing in the presence of acetophenone even when they received no shock.

Ten days later, Dias allowed the mice to mate with unexposed females. When their young grew up, many of the animals were more sensitive to acetophenone than to other odours, and more likely to be startled by an unexpected noise during exposure to the smell. Their offspring — the ‘grandchildren’ of the mice trained to fear the smell — were also jumpier in the presence of acetophenone. What’s more, all three generations had larger-than-normal ‘M71 glomeruli,’ structures where acetophenone-sensitive neurons in the nose connect with neurons in the olfactory bulb. In the January issue of *Nature Neuroscience*, Dias and Ressler suggested that this hereditary transmission of environmental information was the result of epigenetics — chemical changes to the genome that affect how DNA is packaged and expressed without altering its sequence.

Biologists first observed this ‘transgenerational epigenetic inheritance’ in plants. Tomatoes, for example, pass along chemical markings that control an important ripening
Parental olfactory experience influences behavior and neural structure in subsequent generations.

Dias & Ressler, Nature Neuroscience 2014
(Graphics adapted from Szyf Nature Neuroscience 2014)
Dias & Ressler’s experiment

• Offspring mice inherited conditioned fear to acetone odor
  – The father mouse experienced odor in conjunction with electric shock (after repeated experience, the mouse was conditioned to get a fear reaction upon exposure to odor alone)
  – The offspring mouse experienced fear to the acetone odor although never exposed to electric shock
• Experiment repeated with IVF to exclude any behavioral transmission through mothers
• Altered DNA methylation in an odorant gene found in the mouse sperm
Disease programming throughout the lifecourse

Figure adapted from Fleisch, Wright & Baccarelli, J Mol Endocrinol, 2012
Can we reverse our epigenetic programs?

A way forward for epigenetic translation?
Can diet (flavonoids) protect us from air pollution?

**High flavonoid intake**

- Flavonoid = Midpoint of Q4 (673 mg/d)
- Flavonoid = Midpoint of Q3 (370 mg/d)
- Flavonoid = Midpoint of Q2 (228 mg/d)
- Flavonoid = Midpoint of Q1 (128 mg/d)

**Low flavonoid intake**

- Flavonoid = Midpoint of Q4 (673 mg/d)
- Flavonoid = Midpoint of Q3 (370 mg/d)
- Flavonoid = Midpoint of Q2 (228 mg/d)
- Flavonoid = Midpoint of Q1 (128 mg/d)

**Conclusions**

- Differential methylation in innate immunity genes may confer susceptibility to adverse cardiac autonomic effects of PM2.5 exposure in older individuals
- Higher flavonoid intake may attenuate these effects, possibly by decreasing TLR2 methylation.

Zhong et al, JAHA 2014

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Are we finally going to have the “Cool Juice”? 

- In the 1990s’ sitcom “Family Matters”, America’s undisputed King of Nerds Steve Urkel (to the left) drank his “Cool Juice” and transformed himself in Stefan Urquelle (to the right).
- Can a “cool juice” make our epigenome (and lives) healthier?
Summary & discussion

• Epigenetics can provide
  – Molecular traces of recent or past exposures
  – Possible biomarkers of future risks
  – Insight on potential mechanisms of disease programming

• Transgenerational effects
  – The most intriguing aspect of epigenetic programming
  – Are there transgenerational cycles of exposures, stressors, disparities?
  – Examples are sparse both in animals and humans

• Can we keep our epigenome healthy?
  – Opportunities for research leading to primordial, primary, secondary interventions