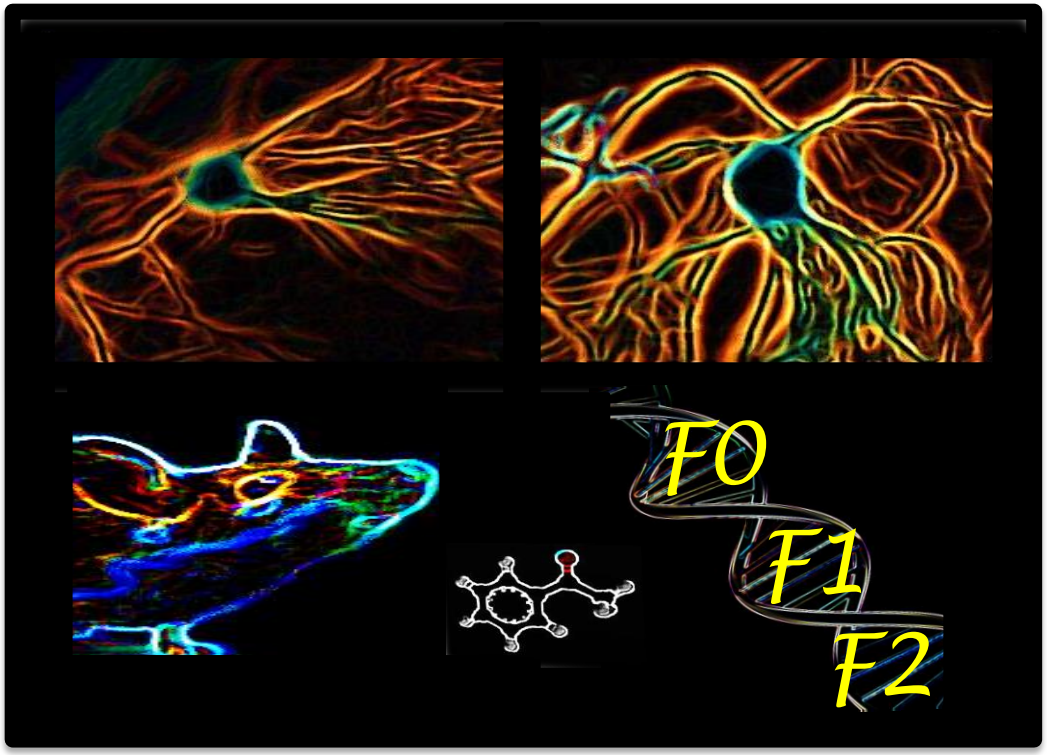
Ancestral influences on descendant generations: a case study using the olfactory system in rodents



Brian Dias, PhD.

Assistant Professor, Emory University School of Medicine
Department of Psychiatry and Behavioral Sciences
Yerkes National Primate Research Center

66th EAAP Annual Meeting: September 1, 2015 (Warsaw, Poland)

Standing on the shoulders of helpful giants…

THANK YOU

- **Kerry Ressler**

- Yerkes Animal Care

- Michael deBelis, Carrie Bearden, Jeremy Veenstra-VanderWeele (Mentors at ACNP, SOBP)

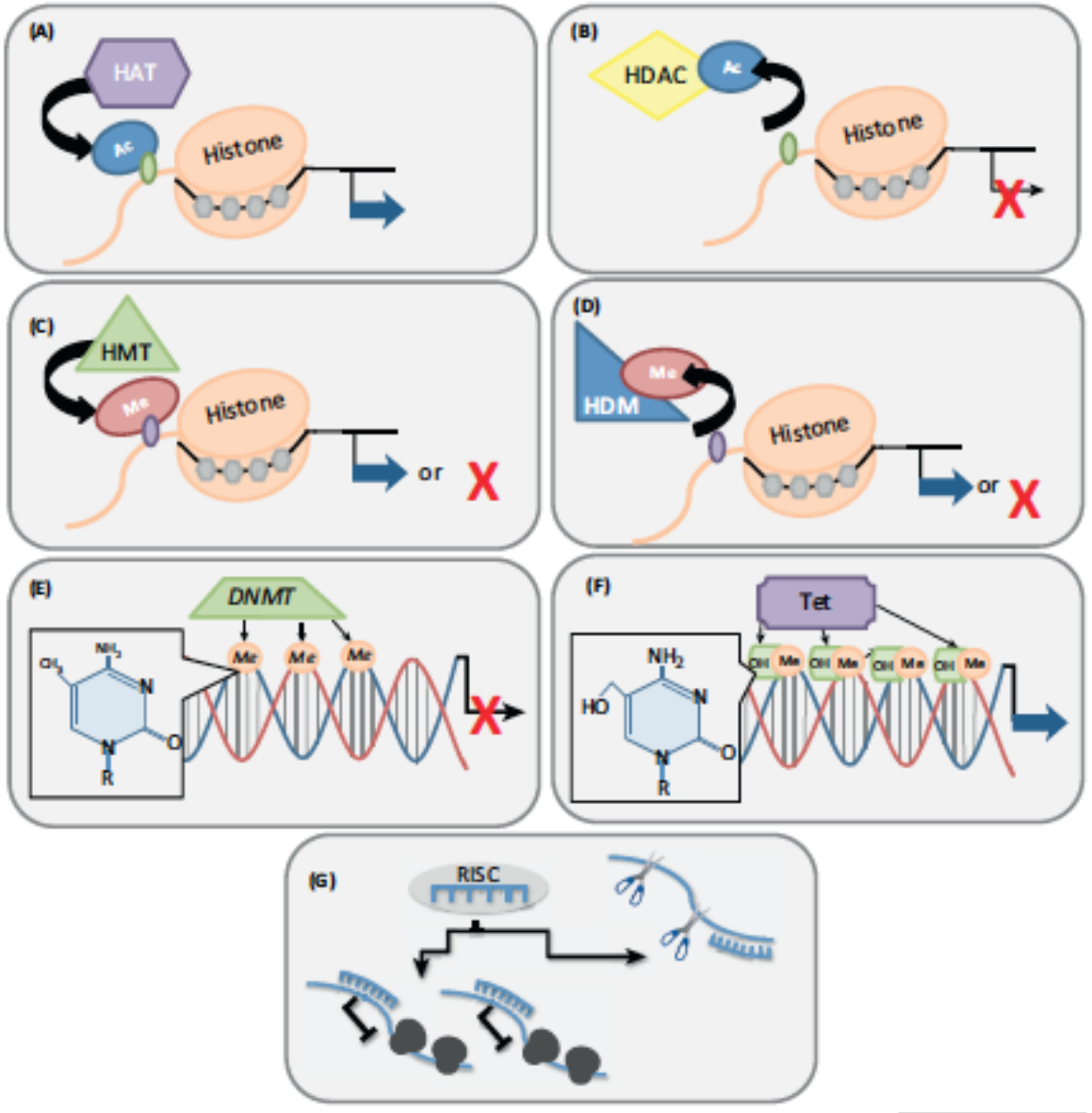
- Mueller, Morgan, Rodgers, Bale
- Debiec, Sullivan, Francis Lee
- Milad (K & M), Graham
- Rick Richardson
- Russo, Dietz, Nestler
- Roth, Sweatt
- Tottenham
- Jovanovic
- Yehuda
- Meaney, Szyf
- Manusuy
- Axel, Buck, Mombaerts, Dulac, Anderson
- Kandel
- Rene Hen, McEwen
- LeDoux, Fanselow, Davis, Josselyn
- Quirk, Luthi, Andrew Holmes, Tye

Funding:
HHMI,
NIH Base Grant to Yerkes National Primate Research Center

Social Media Statement

Reality and Promises of Epigenetics for Animal Science

Epigenetics



Dias et al, *Trends in Neurosci* (2015)

G x E

Ancestral environments affect biology of descendants

0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(7):4115–4118

doi: 10.1210/jc.2005-0550

BRIEF REPORT

Transgenerational Effects of Posttraumatic Stress Disorder in Babies of Mothers Exposed to the World Trade Center Attacks during Pregnancy

Rachel Yehuda, Stephanie Mulherin Engel, Sarah R. Brand, Jonathan Seckl, Sue M. Marcus, and Gertrud S. Berkowitz

Ancestral environments affect biology of descendants

Journal of Child Psychology and Psychiatry **:* (2011), pp **–** doi:10.1111/j.1469-7610.2011.02410.x

Physiological markers of anxiety are increased in children of abused mothers

Tanja Jovanovic,[1] Ami Smith,[1] Asante Kamkwalala,[1] James Poole,[1] Tara Samples,[1,5] Seth D. Norrholm,[1,2] Kerry J. Ressler,[1,3,4] and Bekh Bradley[1,2]

Ancestral environments affect biology of descendants

European Journal of Human Genetics (2002) 10, 682–688

www.nature.com/ejhg

ARTICLE

Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth period

G Kaati[1], LO Bygren*,[1] and S Edvinsson[2]

How do descendants inherit information from ancestors?

Information about ancestral nutritional environment can be inherited by descendants

LETTER

doi:10.1038/nature09491

Chronic high-fat diet in fathers programs β-cell dysfunction in female rat offspring

Sheau-Fang Ng[1], Ruby C. Y. Lin[2], D. Ross Laybutt[3], Romain Barres[4], Julie A. Owens[5] & Margaret J. Morris[1]

Nature, 2010

Paternally Induced Transgenerational Environmental Reprogramming of Metabolic Gene Expression in Mammals

Benjamin R. Carone,[1,10] Lucas Fauquier,[1,10] Naomi Habib,[4,5,10] Jeremy M. Shea,[1,10] Caroline E. Hart,[1] Ruowang Li,[2] Christoph Bock,[6,7] Chengjian Li,[1] Hongcang Gu,[6] Phillip D. Zamore,[1,3] Alexander Meissner,[6,7] Zhiping Weng,[2] Hans A. Hofmann,[8] Nir Friedman,[4,9] and Oliver J. Rando[1,*]

Cell, 2010

Ancestral environment prior to conception affects behavior of descendant generations

F0 female rats exposed to fungicide – Mate preference affected in F3 generation

Transgenerational epigenetic imprints on mate preference

David Crews*, Andrea C. Gore[†‡], Timothy S. Hsu[†], Nygerma L. Dangleben[†], Michael Spinetta[§], Timothy Schallert[§], Matthew D. Anway[¶], and Michael K. Skinner[¶]

PNAS, 2007

Social defeat of F0 male mice – F1 generation showed depression-like behavior

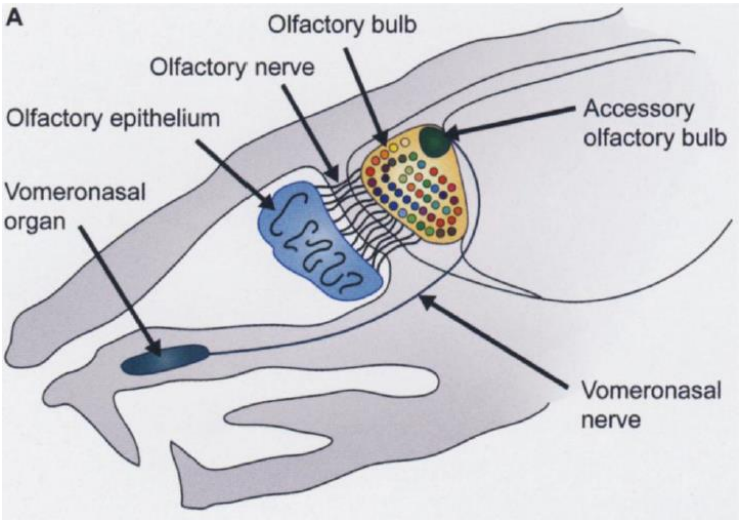
Paternal Transmission of Stress-Induced Pathologies

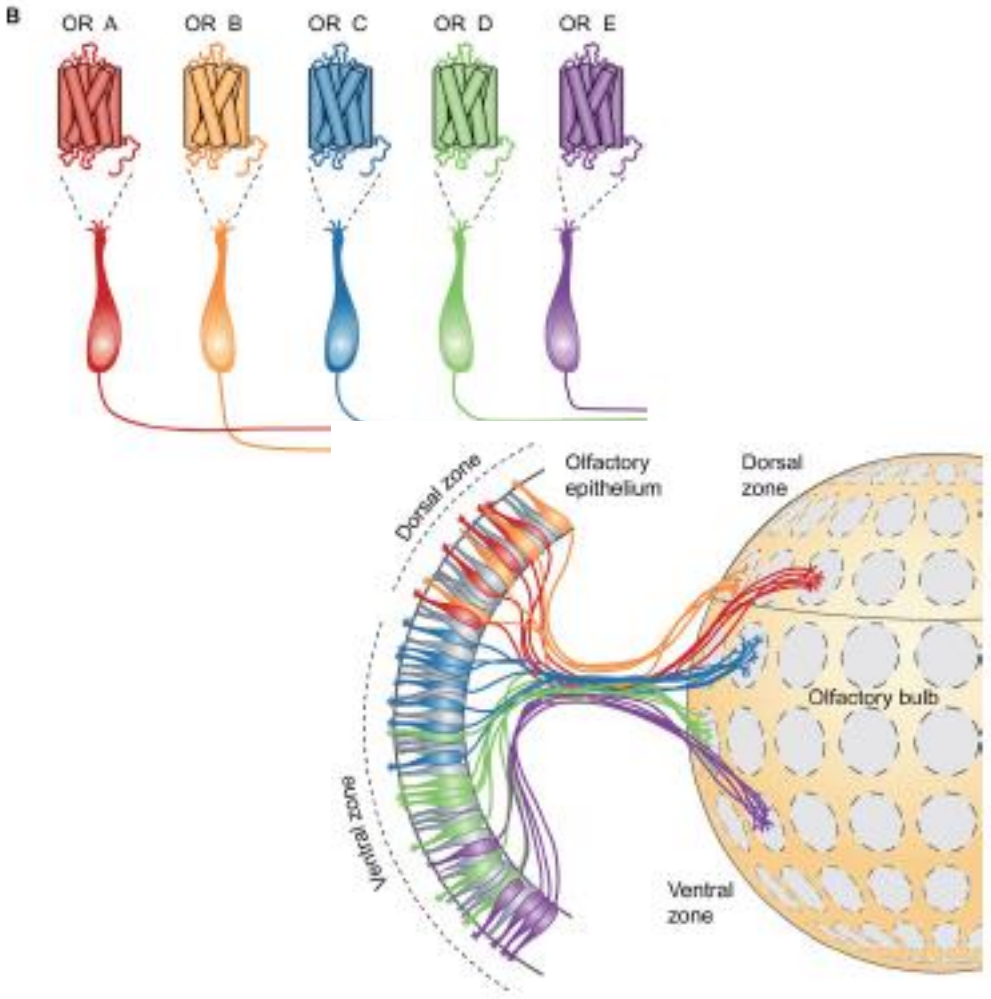
David M. Dietz, Quincey LaPlant, Emily L. Watts, Georgia E. Hodes, Scott J. Russo, Jian Feng, Ronald S. Oosting, Vincent Vialou, and Eric J. Nestler

Biol Psychiatry, 2011

Also: Franklin (Mansuy), Roth (Sweatt), Rodgers (Bale) and others

Mammalian olfactory system

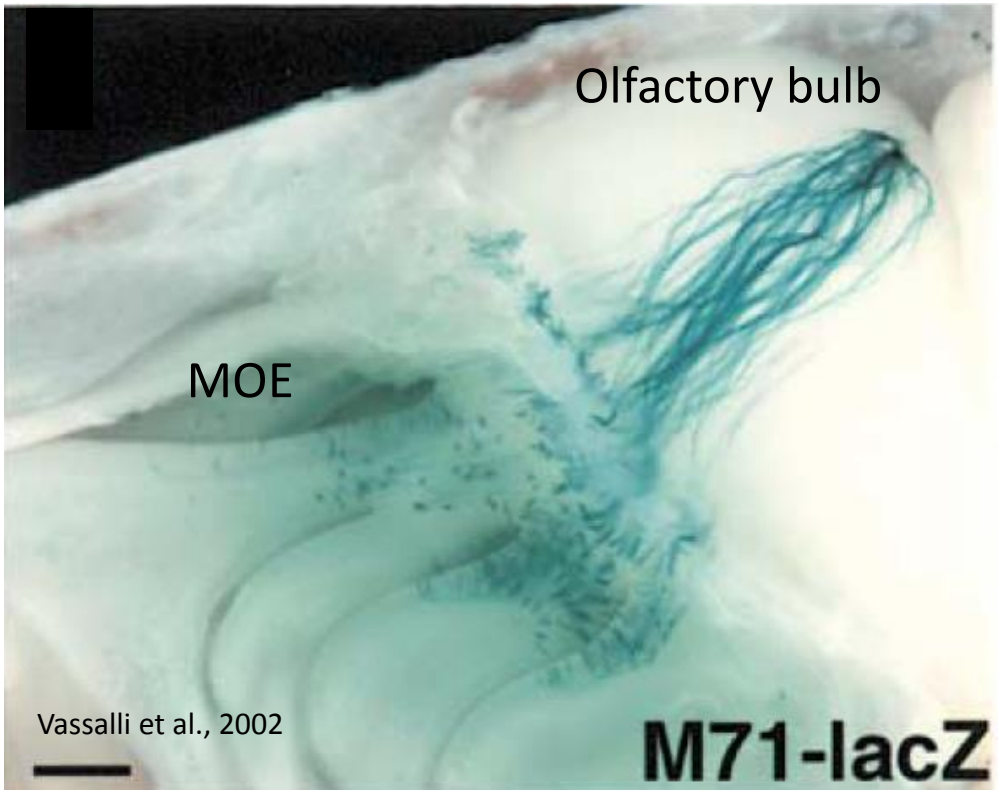




DeMaria & Ngai, 2010

All olfactory sensory neurons (OSNs) in the nose expressing a single odorant receptor, project to a discrete region called a glomerulus in the olfactory bulb.

M71-LacZ transgenic mice
M71 receptor (*Olfr151*) expressing neurons stained blue



Acetophenone activates M71 OSNs (Bozza et al., 2002). Propanol does not.

How do descendants inherit information from ancestors?

Condition F0 generation with Odor (Odor+Shock)

Mate

Test descendant generations

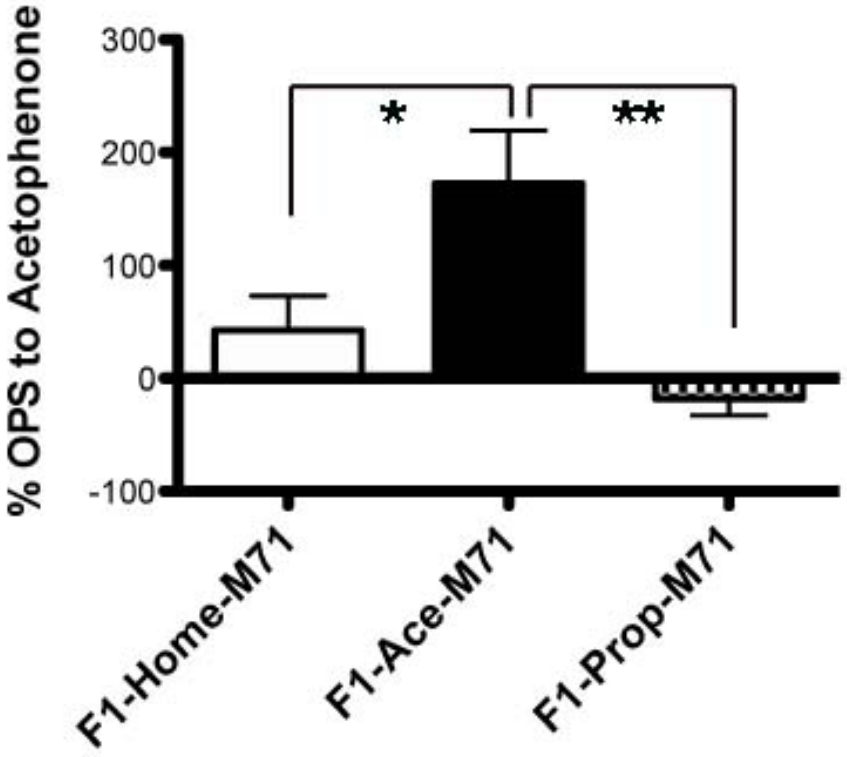
How do descendants inherit information from ancestors?

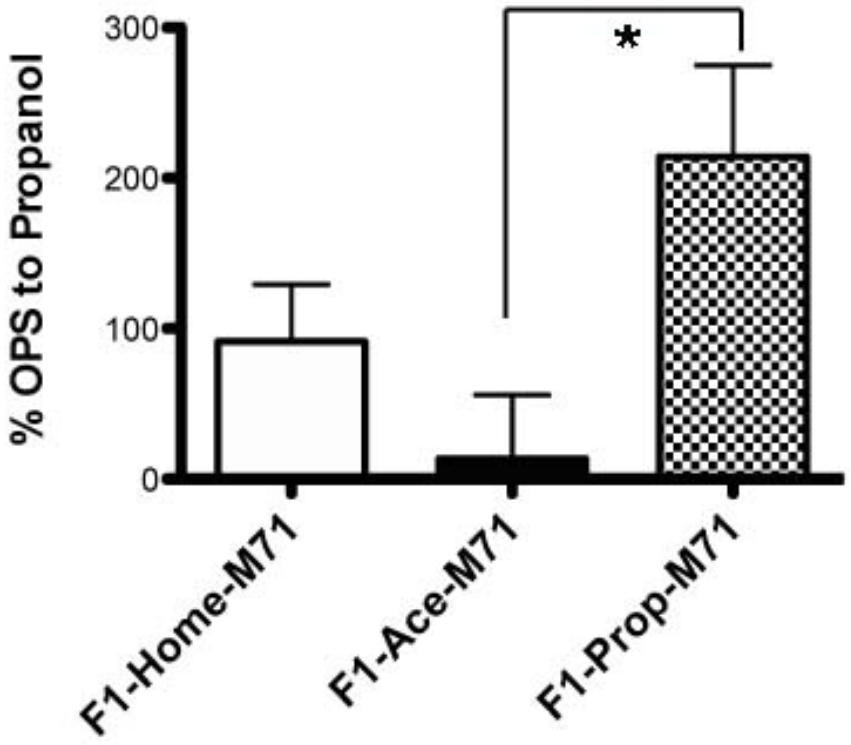
Condition F0 generation with Odor (Odor+Shock)

Mate

Test descendant generations

F0 olfactory fear conditioning results in F1 generation being sensitive to F0 conditioned odor

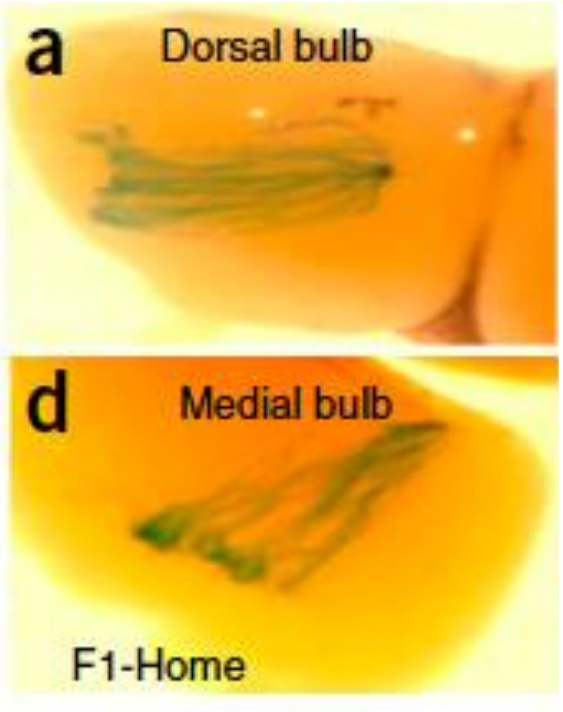




n = 9-13

Dias & Ressler, *Nat Neurosci* (2014)

F0 olfactory fear conditioning results in enhanced neuroanatomical representation in F1 generation



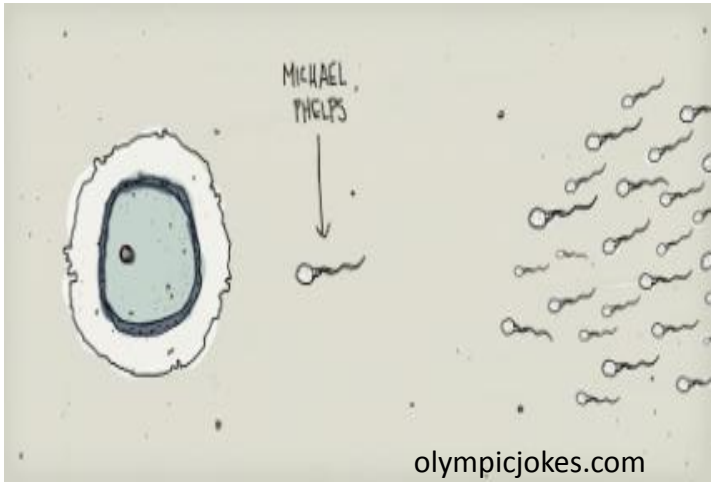
n = 18-38

Dias & Ressler, *Nat Neurosci* (2014)

Like Father – Like Son : How?

Transmitted

vs



Inherited

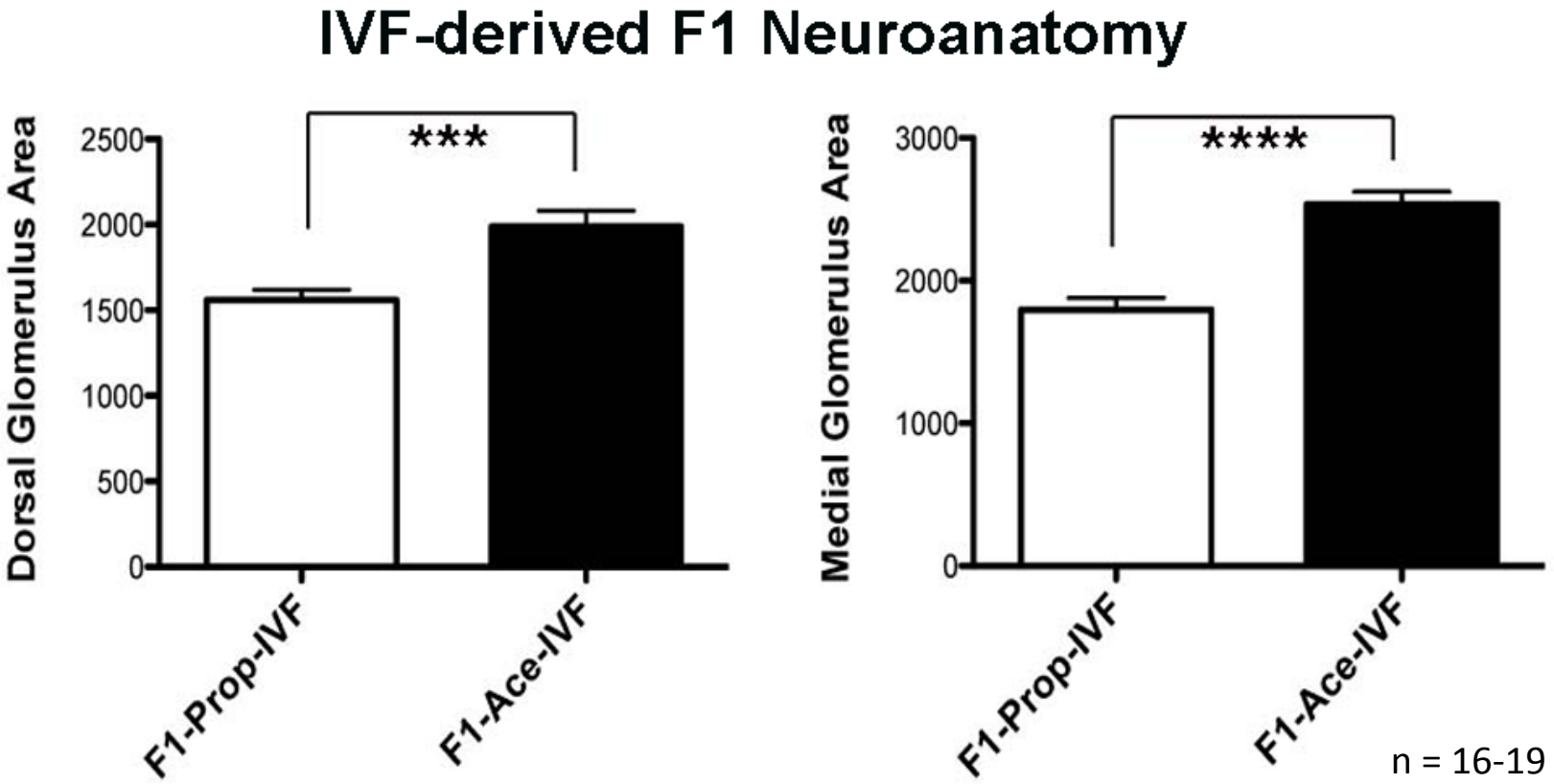
Inheritance **of structure and function**

1. IVF

2. F2 generation

1. Cross-fostering

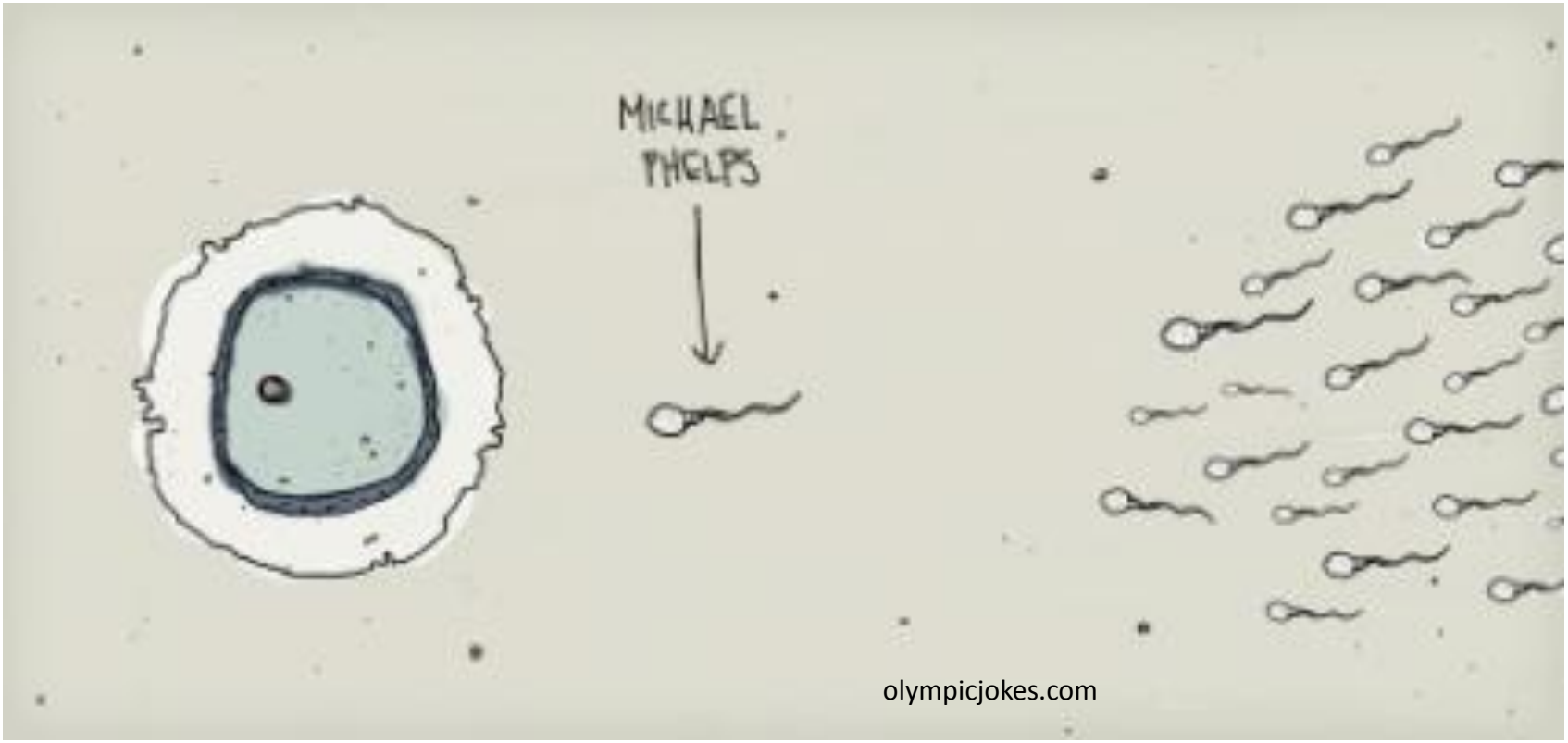
M71 glomeruli in the olfactory bulbs of *F1* males are larger when F0 conditioning occurs with Acetophenone (Offspring derived from F0-sperm via IVF)



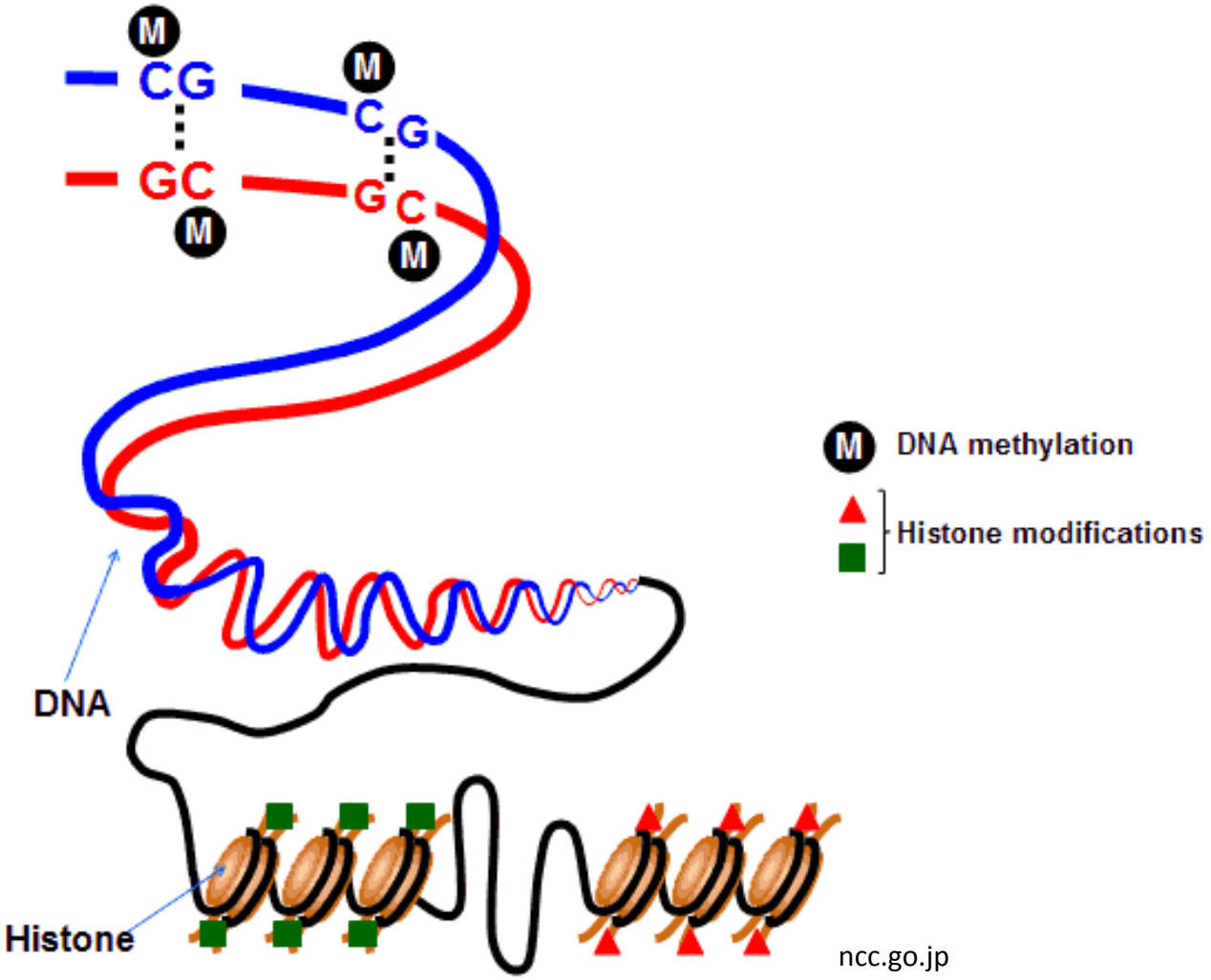
Dias & Ressler, *Nat Neurosci* (2014)

Thank you: Emory Transgenic Mouse Core

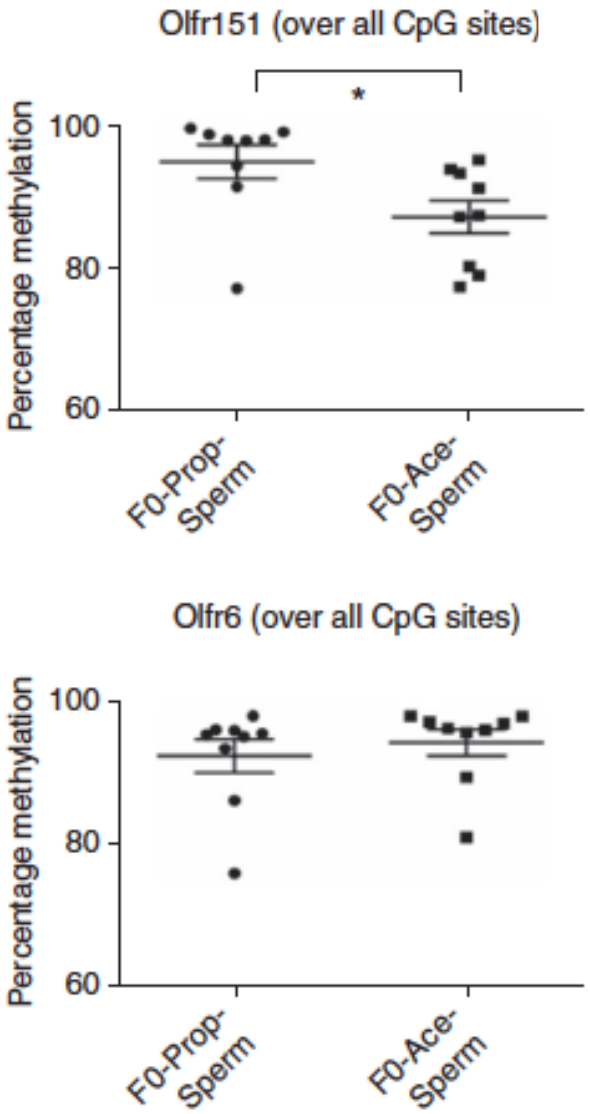
Like Father – Like Son: Inherited BUT How?



Epigenetic mechanisms may explain enhanced transcription of the M71 odorant receptor



Olfr151 (M71) is hypo-methylated in sperm of F0-Ace males

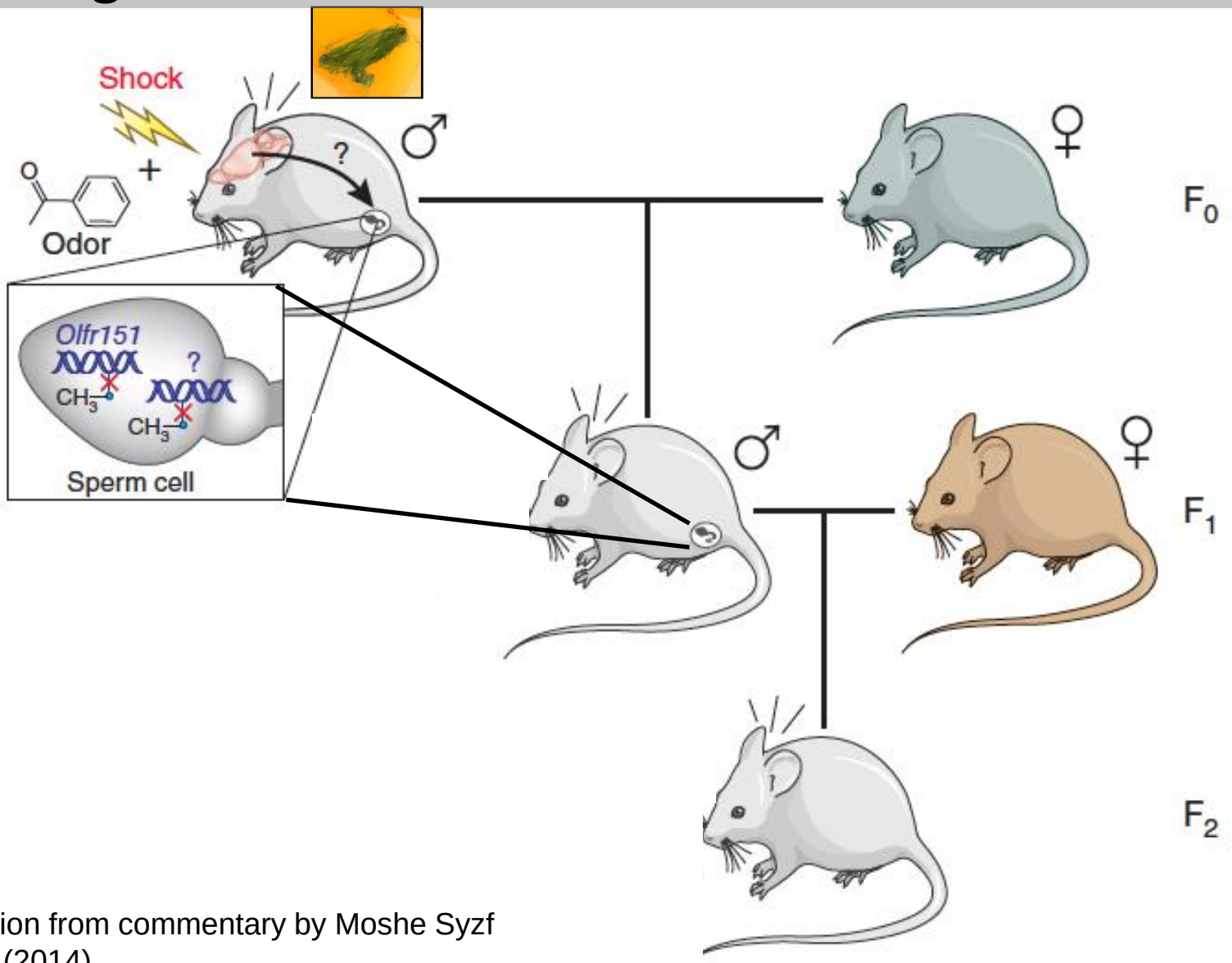


n = 9

Dias & Ressler, *Nat Neurosci* (2014)

Thank you: Active Motif (especially Paul Labhart)

Inheritance of olfactory sensitivity & neuroanatomy from ancestral generation



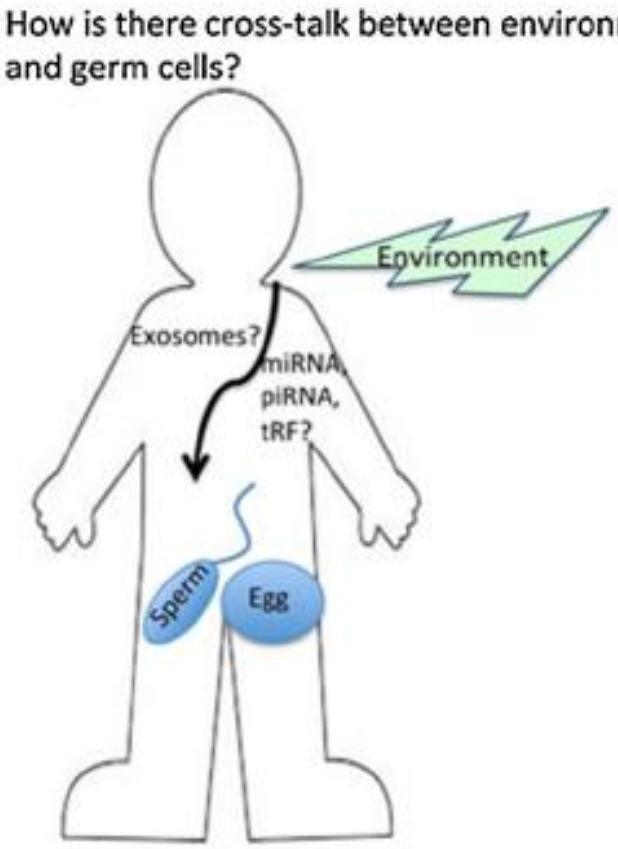
Modified version from commentary by Moshe Syzf
Nat Neurosci (2014)

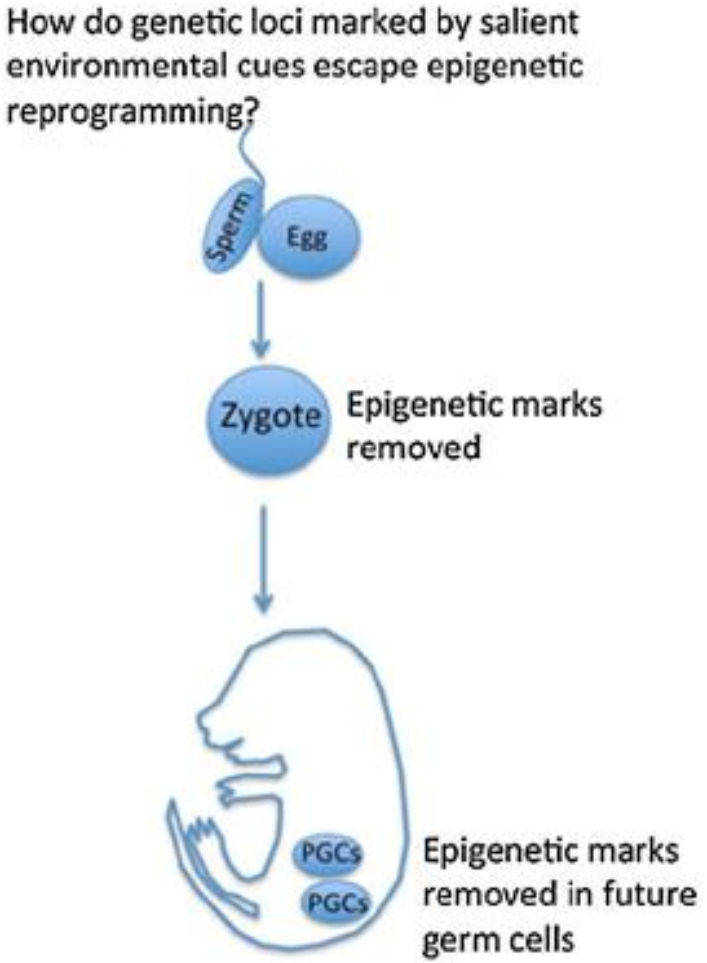
Reality

G x E

Stressful experiences interact with the genome

What can we do with this information?





Dias & Ressler, *Bioessays* (2014)

Reik,
Milekic (Gingrich), Smith (Mill),
Radford (Ferguson-Smith)

Sources of information transfer in sperm

1. **Nose to gametes:** Exosomes containing ncRNA (miRNA, piRNA, tRFs)

   Active project: Profiling circulating exosomes and sperm RNA *(Commercial)*

2. **What is going on in the sperm:** Focus on methylation

   Active project: Genome-wide 5hmC and 5mC analysis *(Collab: Peng Jin)*

Reality

G x E

Stressful experiences interact with the genome

Unknowns

Do positive environments interact with the genome

Reality and Promises of Epigenetics for Animal Science

Reality

G x E

Stressful experiences interact with the genome

Unknowns

Do positive environments interact with the genome

Promises

Manipulating gene expression in sperm and egg