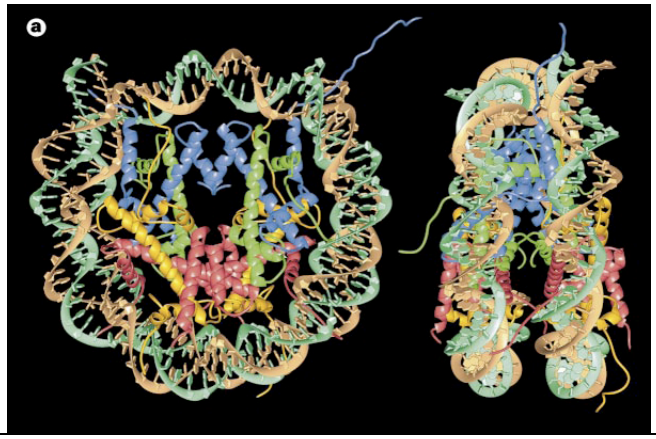
BIOD19 Epigenetics in Health and Disease

Winter 2018

Professor: Dr. Patrick McGowan; **TA:** Samantha Lauby



A lecture/seminar/discussion class on the emerging field of environmental epigenetics. Course will cover basic epigenetic mechanisms, methods in epigenetic research, epigenetic control of gene function, and the role of epigenetics in normal development and human disease.

Environmental epigenetics is a new field of study focusing on mitotically or meiotically heritable changes in gene regulation caused by *environmental factors*. There is evidence that epigenetic changes can occur through diet, toxicants (xenobiotics) and social factors (e.g. parental care). This course will focus on the environmental epigenetic mechanisms that impact human health and disease.

Office hours: Wednesdays: 1PM-3PM or by appointment. My office is in SW-548.

Course email address: epigeneticsD19@gmail.com

Please note that it may take up to 2 business days (48 hrs) for a response.

Lectures: BV-355 Fridays 10AM-12PM

A course calendar with the schedule for lectures and presentations will be available on Blackboard. This schedule is subject to change, so check back regularly.

- Weeks 1-2: Prof. McGowan's lectures on **(1)** foundation topics in environmental epigenetics, **(2)** foundations part 2; how to read/present a research article,
- Week 3: Recap of core principles/methods. How to design and present a poster (Samantha Lauby)
- Weeks 4-10: Student seminars on research articles.
- Weeks 11-12: Poster presentations on research articles.

Textbook: There is NO textbook for this class. Prof. McGowan's power point presentations and journal articles will be supplied on Blackboard as PDF files or linked.

Exams: There are NO exams in this class.

Grading scheme overview:

Assignments (4x2.5%)	10%
Seminar presentation	35%
Seminar discussion	15%
Poster Presentation	35%
Attendance	5%
	100%

Deadlines (midnight to course email):

Take-home assignments (3): Variable, but one week after assignment.
Seminar Presentation: Choice of articles (top 3): Friday January 12
Poster Presentation: Topic choice (top 3): Friday January 26
PDF of poster presentation: Thursday before your Poster Session

Take-home assignments: Four take-home assignments of short answer questions (brief: 3-5 sentences each question) addressing one of the articles presented in the class. You will be required to answer basic questions about the background, methods used, results and conclusions of the paper. The specific paper used for the questions is Prof. McGowan's choice, and you will have one week after assignment to submit your answers. Each assignment will contribute to 2.5% of your final grade (total **10%**).

Seminar Presentation: Seminars will be based on research articles chosen by Prof. McGowan, or you can suggest an article. Each person and a classmate will lead a 15 min presentation of a research article, followed by a 10 min discussion period. Only a maximum of 5 minutes should be spent on the introduction. When presenting, students are expected to provide handouts, which will be given to the class at the beginning of the seminar. Seminars will be graded based on clarity, style and delivery, use of visual aids, content, and ability to answer questions. Your slides and handout document must be submitted the night before your presentation via email (epigeneticsD19@gmail.com). The handout documents will be made available to the class by the instructor via Blackboard before the presentation. The seminar will contribute to **35%** of your final grade.

Seminar Discussion: An important part of your mark in this class is based on contribution to discussions. For each article presented, 4 students will be randomly assigned one week before the presentation to lead a 10-minute discussion (you won't present and lead the discussion on the same article). Each student will lead 2 paper discussions during the course. You will be graded based on your capacity to engage other students in discussion, as well as on your critical analysis and understanding of the article. This mark contributes **15%** to your final grade.

Poster Presentation: You and a classmate will design and present a poster based on an article from a list of articles provided on Blackboard. Alternatively, you can

suggest an article. This will be a separate article from the one you present in class and cannot be repeated from any other article presented orally or in poster format by your classmates. You and your partner will present the poster on-demand to your classmates and other interested people from the Biological Sciences department. Grading of your poster design, content and presentation will be performed by anonymous evaluators. You may be asked to evaluate some of your classmates posters on the day of the poster sessions. Your poster's PDF file must be submitted 4 days before your presentation via email (epigeneticsD19@gmail.com). You are responsible for printing your own poster (dimensions 3ft x 4 ft). The poster presentation contributes **35%** to your final grade.

Attendance: You are expected to be present on time in this seminar/discussion class. Attendance contributes **5%** to your final grade.

Foundation Reviews (Optional reading for background information):

Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. Nature Reviews Genetics. 2007 Apr;8(4):253-62. PubMed PMID: 17363974.

Fagiolini, M., Jensen, C. L. & Champagne, F. A. Epigenetic influences on brain development and plasticity. Current Opinion in Neurobiology 19, 207–212 (2009).

Petronis A. Epigenetics as a unifying principle in the aetiology of complex traits and diseases. Nature. 2010 Jun 10;465(7299):721-7. PubMed PMID: 20535201.

Youngson NA, Whitelaw E. Transgenerational epigenetic effects. Annual Reviews in Genomics and Human Genetics 2008;9:233-57. PubMed PMID: 18767965.

Epigenetics, Second Edition. 2015. Eds. CD Allis, M Caparros, T Jenuwein, D Reinberg. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York.

AccessAbility statement:

Students with diverse learning styles and needs are welcome in this course. In particular, if you have a disability/health consideration that may require accommodations, please feel free to approach me and/or the AccessAbility Services Office as soon as possible. AccessAbility Services staff (located in Rm SW302, Science Wing) are available by appointment to assess specific needs, provide referrals and arrange appropriate accommodations 416-287-7560 or email ability@utsc.utoronto.ca. The sooner you let us know your needs the quicker we can assist you in achieving your learning goals in this course.

Academic Integrity:

The University treats cases of cheating and plagiarism very seriously. The University of Toronto's Code of Behaviour on Academic Matters (http://www.governingcouncil.utoronto.ca/policies/behaveac.htm) outlines the behaviours that constitute academic dishonesty and the processes for addressing academic offences.

Potential offences in papers and assignments include using someone else's ideas or words without appropriate acknowledgement, submitting your own work in more than one course without the permission of the instructor, making up sources or facts, obtaining or providing unauthorized assistance on any assignment.
On tests and exams cheating includes using or possessing unauthorized aids, looking at someone else's answers during an exam or test, misrepresenting your identity, or falsifying or altering any documentation required by the University, including (but not limited to) doctor's notes.

Intellectual Property:

Recording or photographing any aspect of this course without prior approval of all involved and written approval from the instructor is not permitted.

Articles:

Articles to present will be assigned on a first-come first-served basis.
Send an email with your top 3 choices to: epigeneticsD19@gmail.com
YOU CAN ALSO SUGGEST AN ARTICLE.
Deadline: **Friday January 12, 2018**. After the deadline, an article will be assigned to you.

Nutrition:

1. Lillycrop KA, Slater-Jefferies JL, Hanson MA, Godfrey KM, Jackson AA, Burdge GC. Induction of altered epigenetic regulation of the hepatic glucocorticoid receptor in the offspring of rats fed a protein-restricted diet during pregnancy suggests that reduced DNA methyltransferase-1 expression is involved in impaired DNA methylation and changes in histone modifications. Br J Nutr 2007;97:1064–1073. [PubMed: 17433129]
Illustrates the impact of methyl donors in the maternal diet on offspring DNA methylation and histone acetylation patterns, providing an important link between nutrition and gene regulation.

2. Weaver, I. C. et al. Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life. J. Neurosci. 25, 11045–11054 (2005).
Describes the role of methyl donors in altering epigenetic programming of the stress response and behaviours in adult rats.

3. Dunn GA, Bale TL. Maternal high-fat diet effects on third-generation female body size via the paternal lineage. Endocrinology. 2011 Jun;152(6):2228-36. Epub 2011 Mar 29. PubMed PMID: 21447631; PubMed Central PMCID: PMC3100614.
This study implicates environmental influences on developmental regulation of growth and body size as the result of broad programming events at imprinted loci.

4. Kucharski R*,* Maleszka J*,* Foret S*,* Maleszka R. 2008*.* Nutritional control of reproductive status in honeybees via DNA methylation*.* Science 319*:* 1827–1830*.*
Early life nutrition induces epigenetic changes that determine whether a honeybee will become a queen or worker bee.

5. Gao Y, Han Z, Li Q, Wu Y, Shi X, Ai Z, Du J, Li W, Guo Z, Zhang Y. Vitamin C-induced pluripotent state in mouse embryonic stem cells by modulating microRNA expression. FEBS J. 2014 Dec 9. doi: 10.1111/febs.13173.

Examines the effects of vitamin C on the epigenetic machinery, including micro RNA expression, in embryonic stem cells.

6. Dominguez-Salas P, Moore SE, Baker MS, Bergen AW, Cox SE, Dyer RA, Fulford AJ, Guan Y, Laritsky E, Silver MJ, Swan GE, Zeisel SH, Innis SM, Waterland RA, Prentice AM, Hennig BJ. Maternal nutrition at conception modulates DNA methylation of human metastable epialleles. Nat Commun. 2014 Apr 29;5:3746.
Study of seasonal variations in methyl-donor nutrient intake of mothers in rural Gambia around the time of conception and their influence on 13 plasma biomarkers and DNA methylation.

Xenobiotics:

7. Anway MD, Leathers C, Skinner MK. Endocrine disruptor vinclozolin induced epigenetic transgenerational adult-onset disease. Endocrinology. 2006 Dec;147(12):5515-23.
Demonstrates the ability of an endocrine disruptor to induce an epigenetic transgenerational disease phenotype for four generations.

8. Dolinoy DC, Huang D, Jirtle RL. 2007. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proc Natl Acad Sci USA 104:13056–13061.
Shows that early developmental exposure to an environmental toxin can change offspring phenotype by stably altering the epigenome, an effect that can be counter-acted by maternal dietary supplements.

9. Wu J, Basha MR, Brock B, Cox DP, Cardozo-Pelaez F, McPherson CA, Harry J, Rice DC, Maloney B, Chen D, Lahiri DK, Zawia NH. Alzheimer's disease (AD)-like pathology in aged monkeys after infantile exposure to environmental metal lead (Pb): evidence for a developmental origin and environmental link for AD. J Neurosci. 2008 Jan 2;28(1):3-9.
This study in primates finds that early exposure to lead (Pb) results in decreased DNA methyltransferase activity in the brain 23 years later.

Stress:

10. Weaver, I. C. G. et al. Epigenetic programming by maternal behavior. Nature Neurosci. 7, 847–854 (2004).
Describes the role of maternal care in epigenetic programming of the stress response and behaviours in rats.

11. Franklin TB, Russig H, Weiss IC, Graff J, Linder N, Michalon A, et al. Epigenetic transmission of the impact of early stress across generations. Biol Psychiatry 2010; 68:408-15.
These findings highlight the negative impact of early stress on behavioral responses across generations and on the regulation of DNA methylation in the germline.

12. Rodgers, A. B., Morgan, C. P., Leu, N. A., & Bale, T. L. (2015). Transgenerational epigenetic programming via sperm microRNA recapitulates effects of paternal stress. *Proceedings of the National Academy of Sciences*, *112*(44), 13699-13704.
In this study, through zygote microinjection of nine specific sperm miRs previously identified in a paternal stress mouse model, the authors demonstrate that sperm miRs function to reduce maternal mRNA stores in early zygotes, ultimately reprogramming gene expression in the offspring hypothalamus and recapitulating the offspring stress dysregulation phenotype.

13. Roth TL, Lubin FD, Funk AJ, Sweatt JD. Lasting Epigenetic Influence of Early-Life Adversity on the BDNF Gene. Biol Psychiatry. 2009.

Study of the transgenerational impact of exposure to maternal abuse in infancy and the role of differential methylation of a growth factor gene in the prefrontal cortex in mediating these effects.

14. Murgatroyd C, Patchev AV, Wu Y, Micale V, Bockmühl Y, Fischer D, Holsboer F, Wotjak CT, Almeida OFX, Spengler D (2009) Dynamic DNA methylation programs persistent adverse effects of early-life stress. Nat Neurosci 12:1559–1566.
Shows that early life stress can dynamically control DNA methylation in neurons to generate stable changes in gene expression and phenotypic alterations that are frequent features in depression.

15. Cao-Lei L, Massart R, Suderman MJ, Machnes Z, Elgbeili G, Laplante DP, Szyf M, King S. DNA methylation signatures triggered by prenatal maternal stress exposure to a natural disaster: Project Ice Storm. PLoS One. 2014 Sep 19;9(9):e107653.
Study of effects of the 1998 Quebec Ice Storm on methylation in T-cells and saliva of children in utero at the time.

Learning and Memory/Addiction:

16. Fischer A, Sananbenesi F, Wang X, Dobbin M, Tsai LH. Recovery of learning and memory is associated with chromatin remodelling. Nature 2007;447:178–182. [PubMed: 17468743]
Rodent study showing that environmental enrichment increases histone acetylation in the hippocampus. Histone deacetylase inhibitors induce increased spatial memory in a neurodegenerative disorder mouse model.

17. Lubin FD, Roth TL, Sweatt JD. Epigenetic regulation of BDNF gene transcription in the consolidation of fear memory. J Neurosci 2008;28:10576–10586. [PubMed: 18923034]
Illustrates the dynamic changes to DNA methylation which occur during the process of learning and the critical role of these modifications in the consolidation of memory.

18. Guan JS, Haggarty SJ, Giacometti E, Dannenberg JH, Joseph N, Gao J, Nieland TJ, Zhou Y, Wang X, Mazitschek R, et al. HDAC2 negatively regulates memory formation and synaptic plasticity. Nature 2009;459:55–60. [PubMed: 19424149]
Study in mice examining the particular histone deacetylase target through which histone deacetylase inhibitors exert enhancements in synaptic plasticity and memory. The authors illustrate the importance of levels of this enzyme in mediating cognitive enhancement.

19. Vassoler FM, White SL, Schmidt HD, Sadri-Vakili G, Pierce RC Epigenetic inheritance of a cocain-resistance phenotype. Nat Neurosci. 2013 Jan;16(1):42-7. doi: 10.1038/nn.3280. Epub 2012 Dec 16. [PMID: 23242310]
In a case of sex-linked epigenetic inheritance, paternal cocaine use results in a heritable increase in cortical *Bdnf* gene expression that confers a cocaine-resistant phenotype in male, but not female, progeny.

20. Dias BG, Ressler KJ. Parental olfactory experience influences behavior and neural structure in subsequent generations. Nat Neurosci. 2014 Jan;17(1):89-96.
This study shows that when mice are taught to fear an odor, both their offspring and the next generation are born fearing it. The gene for an olfactory receptor activated by the odor is specifically demethylated in the germ line and the olfactory circuits for detecting the odor are enhanced.

21. Wang H, Duclot F, Liu Y, Wang Z, Kabbaj M. Histone deacetylase inhibitors facilitate partner preference formation in female prairie voles. Nat Neurosci 2013; 16: 919-24.

Examines the epigenetics of pair bond formation in the monogamous prairie vole, and uses a pharmacological method to alter epigenetic status and partner preference.

22. Zovkic IB, Paulukaitis BS, Day JJ, Etikala DM, Sweatt JD. Histone H2A.Z subunit exchange controls consolidation of recent and remote memory. Nature. 2014 Nov 27;515(7528):582-6. doi: 10.1038/nature13707.
Examines the role of histone variant exchange in memory in a mouse model.

Human Transgenerational/Health and Disease:

23. (A) Pembrey, M. E. et al. Sex-specific, male-line transgenerational responses in humans. Eur. J. Hum. Genet. 14, 159–166 (2006).
(B) Kaati G, Bygren LO, Pembrey M, Sjöström M. Transgenerational response to nutrition, early life circumstances and longevity. Eur J Hum Genet 2007; 15:784-90.
These two short reports (A-B) should be considered together. The first study demonstrates an inherited disease phenotype in humans that is potentially induced by an epigenetic phenomena. The second study follows on those data with evidence of a transgenerational response to ancestors' nutrition as a main influence on longevity.

24. Tobi EW, Goeman JJ, Monajemi R, Gu H, Putter H, Zhang Y, Slieker RC, Stok AP, Thijssen PE, Müller F, van Zwet EW, Bock C, Meissner A, Lumey LH, Eline Slagboom P, Heijmans BT. DNA methylation signatures link prenatal famine exposure to growth and metabolism. Nat Commun. 2014 Nov 26;5:5592.
A genome-scale analysis of differential DNA methylation in whole blood after periconceptional exposure to famine during the Dutch Hunger Winter of World War II.

Human Development/Health and Disease:

25. Kaminsky, Z. A. et al. DNA methylation profiles in monozygotic and dizygotic twins. Nature Genet. 41, 240–245 (2009).
A study of genome-wide epigenetic differences among twins.

26. Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, Heine-Suner D, Cigudosa JC, Urioste M, Benitez J, et al. 2005. Epigenetic differences arise during the lifetime of monozygotic twins. Proc Natl Acad Sci 102: 10604– 10609.
This study examined the global and locus-specific differences in DNA methylation and histone acetylation of a large cohort of monozygotic twins. They find that, compared to differences in the early years of life, older monozygous twins exhibit greater differences in their overall content and genomic distribution of 5-methylcytosine DNA and histone acetylation, affecting their gene-expression portrait.

27. Katari S, Turan N, Bibikova M, et al. DNA methylation and gene expression differences in children conceived in vitro or in vivo. Hum Mol Genet 2009;18:3769–78.
This study examined DNA methylation at more than 700 genes in placenta and cord blood and measured gene expression levels of a subset of genes that differed in methylation levels between children conceived in vitro versus in vivo.

28. Lam LL, Emberly E, Fraser HB, Neumann SM, Chen E, Miller GE, Kobor MS. Factors underlying variable DNA methylation in a human community cohort. Proc Natl Acad Sci U S A. 2012 Oct 16;109 Suppl 2:17253-60. doi: 10.1073/pnas.1121249109. Epub 2012 Oct 8.
Genome-wide epigenetic study of the contributions of stress and other factors in early life to epigenetic variability in humans stratified by socio-economic position.

29. Borghol N, Suderman M, McArdle W, Racine A, Hallett M, Pembrey M, Hertzman C, Power C, Szyf M. Associations with early-life socio-economic position in adult DNA methylation. Int J Epidemiol. 2012 Feb;41(1):62-74.
Study reporting that adult blood DNA methylation profiles show more associations with childhood socio-economic position than adult socio-economic position.

30. Petropoulos, S., Edsgärd, D., Reinius, B., Deng, Q., Panula, S. P., Codeluppi, S., ... & Lanner, F. (2016). Single-Cell RNA-Seq Reveals Lineage and X Chromosome Dynamics in Human Preimplantation Embryos. *Cell*, *165*(4), 1012-1026.
Study of human pre-implantation embryo development at single cell resolution, revealing that the lineage path in the human embryo is distinct from that in the mouse.

Mental health (humans):

31. Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics. 2008 Mar-Apr;3(2):97-106. PubMed PMID: 18536531.
This study examined relationships between prenatal exposure to maternal mood and the methylation status of the human glucocorticoid receptor gene in newborns and HPA stress reactivity at age three months.

32. Davies MN, Krause L, Bell JT, Gao F, Ward KJ, Wu H, Lu H, Liu Y, Tsai PC, Collier DA, Murphy T, Dempster E, Mill J; UK Brain Expression Consortium, Battle A, Mostafavi S, Zhu X, Henders A, Byrne E, Wray NR, Martin NG, Spector TD, Wang J. Hypermethylation in the ZBTB20 gene is associated with major depressive disorder. Genome Biol. 2014 Apr 2;15(4):R56. doi: 10.1186/gb-2014-15-4-r56.
Reports that aberrant methylation profiles affecting the hippocampus are associated with major depressive disorder and shows the potential of the epigenetic twin model in neuro-psychiatric disease.

33. Lunnon K, Smith R, Hannon E, De Jager PL, Srivastava G, Volta M, Troakes C, Al-Sarraj S, Burrage J, Macdonald R, Condliffe D, Harries LW, Katsel P, Haroutunian V, Kaminsky Z, Joachim C, Powell J, Lovestone S, Bennett DA, Schalkwyk LC, Mill J. Methylomic profiling implicates cortical deregulation of ANK1 in Alzheimer's disease. Nat Neurosci. 2014 Sep;17(9):1164-70.
The first epigenome-wide association study of AD employing a sequential replication design across multiple tissues.

34. Mehta D, Klengel T, Conneely KN, Smith AK, Altmann A, Pace TW, Rex-Haffner M, Loeschner A, Gonik M, Mercer KB, Bradley B, Müller-Myhsok B, Ressler KJ, Binder EB. Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. Proc Natl Acad Sci U S A. 2013 May 14;110(20):8302-7.
Study of the interaction between childhood maltreatment and PTSD, examining genome-wide gene expression and epigenetic signatures.

35. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, Turecki G, Meaney MJ. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 2009; 12: 342-8.
This study shows epigenetic alterations of a stress-sensitive gene in the brains of suicide victims in association with early life abuse or neglect.

Genetic, tissue-specific, and intergenerational sources of epigenetic variation:

36. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol 2013; 14: R115.
Uses computational methods and DNA methylation microarray data to examine DNA methylation status as a predictor of chronological age in a variety of tissues.

37. Orozco LD, Rubbi L, Martin LJ, Fang F, Hormozdiari F, Che N, Smith AD, Lusis AJ, Pellegrini M. Intergenerational genomic DNA methylation patterns in mouse hybrid strains. Genome Biol. 2014 Apr 30;15(5):R68.
Concludes that the majority of DNA methylation differences among individuals are associated with genetic differences, and a much smaller proportion of these epigenetic differences are due to sex, imprinting or stochastic intergenerational effects.

38. Heijmans, B. T., Kremer, D., Tobi, E. W., Boomsma, D. I. & Slagboom, P. E. Heritable rather than age-related environmental and stochastic factors dominate variation in DNA methylation of the human IGF2/H19 locus. Hum. Mol. Genet. 16, 547–554 (2007).
This study investigated the contribution of heritable influences and the combined effect of environmental and stochastic factors to variation in DNA methylation of the IGF2/H19 locus.

39. Reinius LE, Acevedo N, Joerink M, Pershagen G, Dahlen S-E, Greco D, Soderhall C, Scheynius A, Kere J. Differential DNA methylation in purified human blood cells: Implications for cell lineage and studies on disease susceptibility. PLoS ONE 2012; 7: e41361.
Addresses the tissue-specific nature of epigenetic modifications by examining methylation profiles in subsets of peripheral blood cells, which are commonly used in human clinical investigations.

40. Flanagan, J. M. et al. Intra- and interindividual epigenetic variation in human germ cells. Am. J. Hum. Genet. 79, 67–84 (2006).
This study provides evidence for significant epigenetic variability in human germ cells, which warrants further research to determine whether such epigenetic patterns can be efficiently transmitted across generations and what impact inherited epigenetic individuality may have on phenotypic outcomes in health and disease.

41. Radford EJ, Ito M, Shi H, Corish JA, Yamazawa K, Isganaitis E, Seisenberger S, Hore TA, Reik W, Erkek S, Peters AH, Patti ME, Ferguson-Smith AC. In utero effects. In utero undernourishment perturbs the adult sperm methylome and intergenerational metabolism. Science. 2014 Aug 15;345(6198):1255903.
Reports that prenatal undernutrition can compromise male germline epigenetic reprogramming and thus permanently alter DNA methylation in the sperm of adult offspring at regions resistant to zygotic reprogramming. However, persistence of altered DNA methylation into late-gestation somatic tissues of the subsequent generation is not observed.

<u>Aging and the epigenetic clock:</u>

42. Horvath, S., Gurven, M., Levine, M. E., Trumble, B. C., Kaplan, H., Allayee, H., ... & Jamieson, B. D. (2016). An epigenetic clock analysis of race/ethnicity, sex, and coronary heart disease. *Genome biology*, *17*(1), 171.

43. Levine, M. E., Lu, A. T., Chen, B. H., Hernandez, D. G., Singleton, A. B., Ferrucci, L., ... & Kusters, C. D. (2016). Menopause accelerates biological aging. *Proceedings of the National Academy of Sciences*, *113*(33), 9327-9332.

44. Zannas, A. S., Arloth, J., Carrillo-Roa, T., Iurato, S., Röh, S., Ressler, K. J., ... & Menke, A. (2015). Lifetime stress accelerates epigenetic aging in an urban, African American cohort: relevance of glucocorticoid signaling. *Genome biology*, *16*(1), 266.

45. Lin, Q., & Wagner, W. (2015). Epigenetic aging signatures are coherently modified in cancer. *PLoS genetics*, *11*(6), e1005334.