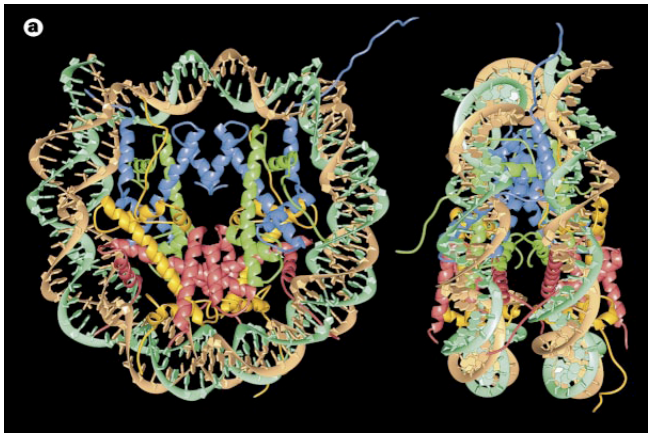
BIOD19H3 Epigenetics in Health and Disease

Winter 2013

Professor: Patrick McGowan; **TA:** Wilfred de Vega



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). When such factors influence brain development, they can increase the risk for psychopathology. This course will focus on the environmental epigenetic changes that occur in early life with consequences for health and disease throughout the lifespan.

Office hours: Friday: 11-12PM or by appointment. My office is in SW-564.

Course email address: epigeneticsD19@gmail.com

Lectures: BV-355 Tuesdays 10am-12am

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 1-3: Prof. McGowan's lectures on **(1)** foundation topics in environmental epigenetics, **(2)** how to read/present a research article, **(3)** how to write a minireview.
- Weeks 4-12: Student seminars 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.

Exams: There are NO exams in this class.

Grading scheme overview:

Assignments (3x5%)	15%
Seminar presentations	35%
Seminar questions	10%
Minireview	35%
Attendance	5%
	100%

Deadlines (5:00PM to course email):

Take-home assignments: Variable, but one week after assignment.
Seminar Presentation: Choice of articles: Tuesday Jan 15th.
Minireview: Topic choice: Jan 22nd.
Abstract and Title: Feb 5th.
Final Document **(also Hardcopy)**: April 2nd.

Take-home assignments: Three take-home assignments of 5 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 5% of your final grade (total **15%**).

Seminar Presentation: Seminars will be based on research articles chosen by Prof. McGowan. Each person will lead a 15 min discussion of a research article, followed by a 10 min question 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. The seminar will contribute to **35%** of your final grade.

Seminar Questions: An important part of your mark in this class is based on contribution to discussions. You will be graded based on the number of quality questions that you ask over the course of the student presentations. This mark contributes **10%** to your final grade.

Minireview: You will complete a summary/analysis of a topic in environmental epigenetics. This could stem from the article that you will present, but it could also be on another topic (note: must at least be related to a foundation review). Choose your topic by week 3 of class **(5:00PM Jan 22nd)** and email us with your topic choice. Your Title and Abstract must be submitted two weeks after that for evaluation **(5:00PM Feb 5).** The final document will be due the final week of class (**5:00PM, Apr 2**) both as a hard copy and emailed as a PDF file to the class email address. See the **Minireview Guidelines** section for detailed instructions. The minireview 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.

Minireview Guidelines

A minireview provides a concise, focused review of the literature related to a question of current interest in environmental epigenetics. Scientists may read minirviews to quickly get up to speed on a particular topic that may not be their area of specialty. Sometimes minireviews also raise questions or suggest new hypotheses or attempt to reconcile conflicting data that has recently been published. Writing a minireview is a good way to organize your thoughts and summarize the knowledge you have obtained about a particular topic that you have acquired from reading the literature and thinking and discussing with others and is a good exercise in scientific writing.

Example description of a minireview (from the Journal of Biological Chemistry):

"The goal of the Minireviews is to provide a concise summary of a particular field in a manner understandable to [scientists] working in any area."

Your minireview should have the following organization:

Title. The title of a review article should be clear, concise and comprehensible to all readers with the purpose of quickly identifying the focus of the reported work.

Author information. Your name, student number, course (BioD19), prof, TA and date.

Brief Abstract. Summarize what the minireview is about as concisely as possible in an introductory paragraph. Provide necessary background/context for the reader. Should indicate why the chosen topic is important and timely.

Body of the minireview. This section should contain the most relevant aspects and achievements in the reviewed scientific area. The review itself should not be an assembly of detailed information but present a summarization of critically selected and evaluated literature which should reflect the most important findings. It may be subdivided with short, informative headings.

References. You will be obliged to perform literature searches and to cite original research articles.

Additional guidelines. Submit your minireview, typed, double-spaced, with pages numbered, using 12 point font (Arial), 2 cm margins. The maximum length for the minireview is 10 pages including any Figures you make yourself and EXCLUDING References. Include a reference list at the end in one of the following styles: American Psychological Association (APA), Vancouver, Nature, and PLoS. Endnote is a useful program for generating a reference list.

Foundation Reviews (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.

Choose 1 of the following to present:

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
Deadline: **Tuesday Jan 15th, 5:00PM**. After the deadline, an article will be assigned to you.

Nutrition:

1. Waterland, R. A. & Jirtle, R. L. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. Mol. Cell. Biol. 23, 5293–5300 (2003).
This study demonstrates that maternal methyl donor supplementation during gestation can alter offspring phenotype by methylating the epigenome.

2. 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.

3. 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.

4. 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.

Xenobiotics:

5. Anway MD, Leathers C, Skinner MK. Endocrine disruptor vinclozolin induced epigenetic transgenerational adult-onset disease. Endocrinology. 2006 Dec;147(12):5515-23. Epub 2006 Sep 14. PubMed PMID: 16973726.
Demonstrates the ability of an endocrine disruptor to induce an epigenetic transgenerational disease phenotype for four generations.

6. 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.

7. 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. PubMed PMID: 18171917; PubMed Central PMCID: PMC2486412.
This study in primates finds that early exposure to lead (Pb) results in decreased DNA methyltransferase activity in the brain 23 years later.

Stress:

8. 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.

9. 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.

10. Mueller BR, Bale TL. Sex-specific programming of offspring emotionality after stress early in pregnancy. J Neurosci 2008;28:9055–9065. [PubMed: 18768700]
Illustrates alterations in DNA methylation of placental and brain tissue following exposure to gestational stress, providing a possible mechanism mediating the long-term neurobiological effects of prenatal exposure to elevated maternal stress response activity.

11. 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.

12. 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.

Learning and Memory/Addiction:

13. 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.

14. 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.

15. 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.

16. 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.

Human Transgenerational/Health and Disease:

17. (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.

18. (C) Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci USA 2008; 105:17046-9.
(D) Tobi EW, Lumey LH, Talens RP, et al. DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. Hum Mol Genet 2009;18:4046–53.
These two short reports (C-D) should be considered together. They both examine evidence for transgenerational epigenetic changes associated with famine during the Dutch Hunger Winter of World War II.

Human Development/Health and Disease:

19. 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.

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

Accessibility: Students with diverse learning styles and needs are welcome in this course. If you have a disability/health consideration that may require accommodations, please notify me and contact the AccessAbility Services Office (located in SW302) as soon as possible. I will work with you and AccessAbility services to ensure you can achieve your learning goals in this course. Enquiries are confidential, and the staff is available to assess your specific needs, provide referrals, and arrange appropriate accommodations (Tel/TTY: 416-287-7560 or ability@utsc.utoronto.ca).