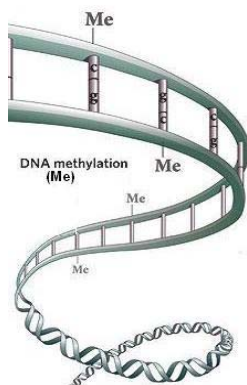


Lab Newsletter, Summer 2011

We want to thank all the people who have generously volunteered to participate in our research studies! We

would not have made any progress without the participation of so many people. This newsletter is to share with you what you have helped achieve. We are particularly excited by the recent advances in technology that allow us to look at our genome for changes in DNA methylation. DNA methylation influences how genes are turned on and off; this opens up new insights into how genes are regulated during development and how the environment can influence this process. We believe the **placenta is key** to understanding human development and pregnancy complications therefore we focus much of our work on this **fascinating** organ.



embryology.med.unsw.edu.au



<http://www.nlm.nih.gov/medlineplus/ency/imagepages/17010.htm>

CURRENT LAB MEMBERS

- Wendy P. Robinson, PhD, Professor, Dept. of Medical Genetics UBC.
- Ryan K.C. Yuen, PhD (DNA methylation in placental and fetal development)
- Courtney Hanna, PhD student (recurrent miscarriage and infertility)
- Magda Price, MSc student (nutrition and global methylation)
- John Blair, MSc student (preeclampsia and DNA methylation)
- Dan Diego-Alvarez, PhD, postdoctoral fellow (trisomy in the placenta)
- Irina Manokhina, PhD, postdoctoral fellow (non-invasive prenatal diagnosis)
- Maria S. Peñaherrera, PhD, Research scientist
- Ruby Jiang- Research associate/tech
- Kristal Louie, Msc - Research coordinator

To find out more about our research studies please contact us: mosaic@interchange.ubc.ca or see our website: www.robinsonresearch.ca

INTRAUTERINE GROWTH RESTRICTION (IUGR)

About 5% of babies are born smaller than expected due to the inability of the placenta to fully support their growth. This is called **intrauterine growth restriction (IUGR)**. We want to understand what goes wrong in the placenta to cause IUGR, and have explored two possible causes:

1) **Trisomy**: Sometimes chromosomes do not separate properly when cells divide. This can lead to an extra chromosome in some cells, called trisomy. We found trisomy in the placenta in 1 of 10 pregnancies associated with IUGR newborns. These findings were published in 2010, but we continue to collect new cases to refine our understanding of how trisomy affects placental function and when clinical testing for this might be warranted.

2) **Altered DNA methylation**: While DNA codes for the genes in our cells, chemical modifications to the DNA, such as methylation, influence how genes are turned on and off. Such chemical changes can be altered by the environment, such as maternal nutrition or smoking. Danielle Bourque, a former master's student in the lab, wanted to know if DNA methylation was altered at the *IGF2* (insulin growth factor 2) gene in placentas from IUGR pregnancies. She found that indeed there was less methylation at *IGF2*, which suggests that IUGR-associated placentas produce less of this important growth factor. We think this change may occur when the placenta is not getting enough nutrients from the mother and thus tries to slow baby's growth to compensate. We think that this change may actually benefit the mother by reducing the risk of maternal high blood pressure (hypertension). Danielle has moved on to Medical School at the U of Toronto, but the lab continues to be interested in how the placenta regulates baby's growth!

Robinson WP, Peñaherrera MS, Jiang R, Avila L, Sloan J, McFadden DE, Langlois S, von Dadelszen P. Assessing the role of placental trisomy in preeclampsia and intrauterine growth restriction. *Prenatal Diag* 2010 Jan;30:1-8
Bourque D, Avila L, Peñaherrera M, von Dadelszen P, Robinson WP. Decreased Placental Methylation at the H19/IGF2 Imprinting Control Region is Associated with Normotensive Intrauterine Growth Placenta. 2010 Mar;31(3):197-20

PREECLAMPSIA

Maternal preeclampsia (hypertension plus protein in the urine) is a serious complication of pregnancy that puts both mother and baby at serious risk. Early identification of at-risk women allows for more careful monitoring for clinical signs of the disease and saves lives. Early-onset preeclampsia (EOPET) which is diagnosed prior to 34 weeks gestation, is thought to be due to poor invasion of the placenta into the maternal uterus, which in turn leads to secondary changes due to the lack of sufficient blood flow, and therefore oxygen, to the placental cells.

Our ultimate goal is to identify some of the early placental changes associated with EOPET that could be used to predict complications before they occur. Using new advanced technologies, Ryan Yuen, PhD, has made some interesting findings concerning DNA methylation in normal and EOPET associated placentas. He found many genes showed less methylation in placentas from EOPET-pregnancies as compared to controls. He further identified methylation of the *TIMP3* gene as a possible marker for EOPET. Dan Diego-Alvarez, a postdoctoral fellow, observed many of these same changes in placentas with trisomy 16 (confined to the placenta), a condition with a high risk of preeclampsia. This raises our hopes that looking at specific trisomies, which can be more easily identified early in pregnancy, can provide clues to the sequence of changes that occur over pregnancy with EOPET. This is work that will be continued by John Blair, a new Master's student in the lab.

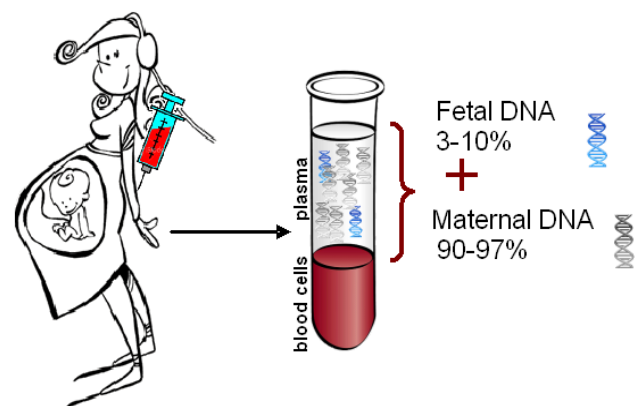
Yuen RKC, Avila L, Peñaherrera MS, von Dadelszen P, Lefebvre L, Kobor MS and Robinson WP. Human placental-specific epipolymorphism and its association with adverse pregnancy outcomes. *PLoS One*. 2009 Oct 19;4(10):e7389.

Yuen RKC, Peñaherrera MS, von Dadelszen P, McFadden DE, and Robinson WP. DNA methylation profiling of human placenta reveals promoter hypomethylation of multiple genes in early-onset preeclampsia. *Eur J Hum Genet*. 2010 Sep;18(9):1006-1

NON-INVASIVE PRENATAL TESTING

The ability to safely and accurately screen pregnancies for potential complication offers enormous benefit to maternal health and pregnancy management. However, current methods of prenatal diagnosis are largely invasive (thus put mother and baby at risk) and are limited in the types of problems identified (mainly limited to chromosome changes and neural tube defects). However, it is now known that a baby's cells (really placental) and cell-free DNA can be found in a pregnant woman's blood. DNA methylation differences between the placenta and blood exist and can be used to distinguish cell-free fetal DNA (cffDNA) in the mother's blood for direct testing.

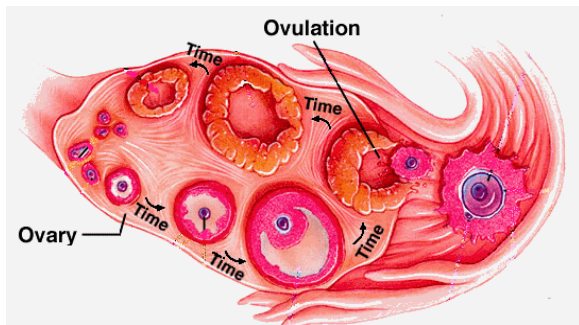
Irina Manokhina is a new postdoctoral fellow in the lab who completed her PhD at the I.M. Sechenov Moscow Medical Academy. Her focus is to use DNA methylation differences in the placenta to develop new tests to screen for EOPET and other fetal conditions and pregnancy complications. To do this we need to collect many blood samples from pregnant women at different gestational ages!



Modified from Bustamante-Aragones (2009). *Boletin de la AEGH*, 1:8

RECURRENT MISCARRIAGE AND INFERTILITY

The inability to get pregnant is devastating for couples trying to start a family. Recurrent miscarriage affects 3-5% of couples and often has no explanation. PhD candidate Courtney Hanna is exploring several possible explanations for such problems. We know maternal age is the greatest risk factor for miscarriage, but what is different about egg maturation in older women than younger women?



legacy.owensboro.kctcs.edu/.../Image690.gif

One of several possibilities Courtney has considered is that the hormonal environment in which the egg matures may be important. As a first step in women with recurrent miscarriages, she looked at genetic variants (i.e. differences in the DNA code) in genes of hormones involved in egg development and maturation. She found some genetic changes in the prolactin receptor, glucocorticoid receptor and estrogen receptor genes. However, these will need to be followed up in a larger group of women. Courtney is continuing these studies and also joining the lab trend in studying DNA methylation changes in miscarriages to understand this important problem further!

One thing we need for these studies is a large number of blood samples from healthy control women who have not had any difficulties achieving pregnancy and carrying the pregnancy to term. We are specifically looking for women who have given birth later in their reproductive life (>37y) to reduce the possibility that they might experience premature menopause.

Hanna CW, Bretherick KL, Liu CC, Stephenson MD, Robinson WP. Genetic variation within the hypothalamus-pituitary-ovarian axis in women with recurrent miscarriage. *Hum Reprod.* 2010 25(10):2664-7

NEURAL TUBE DEFECTS (NTDs)

Our lab is extremely interested in the interplay between genes and environment. We think that studying DNA-methylation, will shed new light on how early exposures to a baby in utero can have long-lasting effects on health. Neural Tube defects (NTDs), affecting the brain and spinal cord, are influenced by both genetic factors and environmental exposures. Low folate intake has been clearly associated with increased risk of NTDs, but it is unknown why. Also some NTDs occur in a folate-independent manner and thus increased folate intake may not reduce the incidence in those cases.



Interestingly, folate is an important contributor to the production of methyl groups involved in DNA and protein methylation. We want to understand how

folate is used and transported across the placenta to the fetus, and how this might affect DNA methylation in both the placenta and fetus. We think that there may be differences in this process in placentas from pregnancies associated with NTDs.

To investigate this Dr. Maria Peñaherrera will compare methylation at 450,000 sites in the genome between placentas from NTD and healthy pregnancies. Magda Price, a Master's student, is also trying to understand the factors that affect methylation in our cells, the role of folate metabolism, and how this might be altered in NTDs.

www.cdc.gov/hcbddd/spinabifida/facts.html

SELECTED PUBLICATION LIST (LAST 3 YEARS)

1. Bretherick K, Fairbrother N, Avila L, Harbord S, Robinson WP. Fertility and aging: Do reproductive-aged Canadian women know what they need to know? *Fertil and Steril*. 2009 Mar 16. [Epub ahead of print]
2. Hanna CW, Bretherick KB, Gair JL, Fluker MR, Stephenson MD, Brown CJ, Penaherera MS, Robinson WP. Telomere length and reproductive aging. *Hum Reprod*. 2009 May;24(5):1206-11.
3. Cotton AM, Avila L, Penaherrera MS, Affleck JG, Robinson WP, Brown CJ. Inactive X chromosome - specific reduction in placental DNA methylation.. *Hum Mol Genet*. 2009; 18(19):3544-52.
4. Yong PJ, von Dadelszen P, McFadden DE, Barrett IJ, Kalousek DK, Robinson WP. Placental weight in pregnancies with trisomy confined to the placenta. *J ObstetGynaecol Can*. 2009 Jul;31(7):605-10
5. Yuen RKC, Avila L, Peñaherrera MS, von Dadelszen P, Lefebvre L, Kobor MS and Robinson WP. Human placental-specific epipolymorphism and its association with adverse pregnancy outcomes. *PLoS One*. 2009 Oct 19;4(10):e7389.
6. Bourque D, Avila L, Peñaherrera M, von Dadelszen P, Robinson WP. Decreased Placental Methylation at the H19/IGF2 Imprinting Control Region is Associated with Normotensive Intrauterine Growth Restriction but not Preeclampsia Placenta. 2010 Mar;31(3):197-202.
7. Robinson WP, Peñaherrera MS, Jiang R, Avila L, Sloan J, McFadden DE, Langlois S, von Dadelszen P. Assessing the role of placental trisomy in preeclampsia and intrauterine growth restriction. *Prenatal Diag* 2010 Jan;30(1):1-8
8. Peñaherrera MS, Weindler S, Avila L, Van Allen M, Langlois S, Robinson WP. Methylation Profiling in individuals with Silver-Russell Syndrome. *Am J Med Genet A*. 2010 Jan 15. 152A(2):347-55.
9. Yuen RKC, Peñaherrera MS, von Dadelszen P, McFadden DE, and Robinson WP. DNA methylation profiling of human placentae reveals promoter hypomethylation of multiple genes in early-onset preeclampsia. *Eur J Hum Genet*. 2010 Sep;18(9):1006-12.
10. Bourque D, Peñaherrera M, Yuen R, van Allen MA, McFadden DE, Robinson WP. The utility of quantitative methylation assays at imprinted genes for the diagnosis of fetal and placental disorders. *Clin Genet*. 2011 Feb;79(2):169-75
11. Hanna CW, Bretherick KL, Liu CC, Stephenson MD, Robinson WP. Genetic variation within the hypothalamus-pituitary-ovarian axis in women with recurrent miscarriage. *Hum Reprod*. 2010 25(10):2664-71.
12. Avila L, Yuen RKC, Diego-Alvarez D, Peñaherrera MS, Jiang R, Robinson WP. Evaluating DNA methylation and gene expression variability in the human term placenta Placenta. 2010 Dec;31(12):1070-7
13. Rajcan-Separovic E, Diego-Alvarez D, Robinson WP, Qiao Y, Harvard C, Fawcett C, Tyson C, Stephenson M. Identification of Copy Number Variants (CNV) Associated with Recurrent Pregnancy Loss. *Hum Reprod*. 2010 Nov;25(11):2913-22
14. Ngai YF, Chijiwa C, Mercimek-Mahmutoglu S, Stewart L, Yong SL, Robinson WP, Gibson WT. Pseudohypoparathyroidism type 1a and the GNAS p.R231H mutation: Somatic mosaicism in a mother with two affected sons. *Am J Med Genet A*. 2010 Nov;152A(11):2784-90.
15. Yuen RKC, Robinson WP. A high capacity of the human placenta for genetic and epigenetic variation: implications for assessing pregnancy outcome. *Placenta*. 2011 Mar;32Suppl 2:S136-41
16. Yuen RKC, Neumann SMA, Fok AK, Peñaherrera MS, McFadden DE, Robinson WP, Kobor MS. Extensive epigenetic reprogramming in human somatic tissues between fetus and adult Epigenetics Chromatin. 2011 May 5;4(1):7.

HOW TO PARTICIPATE IN OUR RESEARCH?

We are currently recruiting for a variety of studies:

- ☐ **CONTROL WOMEN WITH SUCCESSFUL PREGNANCIES AT/OVER AGE 37**
- ☐ **ABNORMAL MATERNAL SERUM SCREEN, PREECLAMPSIA and/or IUGR PREGNANCY**
- ☐ **WOMEN WITH RECURRENT MISCARRIAGES OR A TRISOMIC PREGNANCY**
- ☐ **WOMEN WITH PREMATURE OVARIAN FAILURE (POF)**
- ☐ **PRENATAL DIAGNOSIS OF NEURAL TUBE DEFECT**
- ☐ **PRENATAL or POSTNATAL DIAGNOSIS OF TRISOMY MOSAICISM**
- ☐ **IMPRINTING DISORDERS AND UNIPARENTAL DISOMY**
- ☐ **DIAGNOSIS OF HYDATIDIFORM MOLE, TRIPLOIDY or PLACENTAL MESENCHYMAL DYSPLASIA**

To find out more about our research studies please contact **us at :**

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