Art Petronis
Tapscott Chair in Schizophrenia Studies
Department of Psychiatry
University of Toronto

Report 2015-2016

PUBLICATIONS

1. Oh G, Wang SC, Pal M, Chen ZF, Khare T, Tochigi M, Ng C, Yang YA, Kwan A, Kaminsky ZA, Mill J, Gunasinghe C, Tackett JL, Gottesman II, Willemsen G, de Geus EJ, Vink JM, Slagboom PE, Wray NR, Heath AC, Montgomery GW, Turecki G, Martin NG, Boomsma DI, McGuffin P, Kustra R, **Petronis A**. DNA modification study of major depressive disorder: beyond locus-by-locus comparisons. *Biological Psychiatry*. 2015; 77(3):246-55.

   In this article, we performed a series of exploratory analyses and demonstrated how various epigenomic strategies can be applied in psychiatric research.

2. Pal M, Ebrahimi S, Oh G, Khare T, Zhang A, Kaminsky ZA, Wang SC, **Petronis A**. High precision DNA modification analysis of HCG9 in major psychosis. *Schizophr Bull.* 2016 Jan;42(1):170-7.

   This article exemplifies our effort in studying epigenetic marks in the brain at very high resolution.

3. Oh G, Ebrahimi S, Wang SC, Cortese R, Kaminsky ZA, Gottesman II, Burke JR, Plassman BL, **Petronis A**. Epigenetic assimilation in the aging human brain. *Genome Biol*. 2016; 17(1):76.

   In this article we described a new epigenetic phenomenon related to aging. We detected that epigenomes in very old brains become more similar to each other despite them becoming more different in earlier stages of life. This somewhat paradoxical phenomenon is called epigenetic assimilation.

4. Labrie V, Buske OJ, Oh E, Jeremian R, Ptak C, Gasiūnas G, Maleckas A, Petereit R, Žvirbliene A, Adamonis K, Kriukienė E, Koncevičius K, Gordevičius J, Nair A, Zhang A, Ebrahimi S, Oh G, Šikšnys V, Kupčinskas L, Brudno M, **Petronis A**. Lactase nonpersistence is directed by DNA-variation-dependent epigenetic aging. *Nat Struct Mol Biol*. 2016; 23(6):566-73.

   In this article, we present the most comprehensive epigenomic analysis of human and mouse lactose intolerance. We selected this trait as a proof of principle showing that epigenomes can change dramatically over years, and regulation of the same gene in the first years of life can be very different from the one a decade or two later. We learned several very important lessons how epigenetic studies should be performed in human tissues, and now we use this experience in our epigenomic studies of psychiatric disease. Schizophrenia and other psychiatric diseases, similarly to lactose intolerance, have a delayed age of onset, and it takes about 2 decades to present its first clinical manifestations.

5. Gagliano SA, Ptak C, Mak DY, Shamsi M, Oh G, Knight J, Boutros PC, **Petronis A**. Allele-Skewed DNA Modification in the Brain: Relevance to a Schizophrenia GWAS. *Am J Hum Genet.* 2016; 98(5):956-62.

   This is a comprehensive epigenetic study of a very large human brain collection (more than 200 samples) which demonstrates that epigenetics studies can lead to new insights if combined with DNA sequence (genetic) data.

   All papers were accepted and published in very good and highly competitive journals. This particularly applies to the last 3 articles which were published in the journals with an impact factor more than 10. Only ~2% of journals have impact factor of 10 or higher.

STUDENTS WHO GRADUATED IN 2015-16

Pal, M.	PhD student	HCG9 in major psychosis	Graduated 2016
Kwan, A.	MSc student	Epigenetics of cancer	Graduated 2015

GRANTS (ONGOING)

Divergent meiotic recombination in bipolar disorder (R01MH105409)
National Institute of Mental Health (NIMH)
2014-1018
$986,000 USD

Epigenomics of major depression: dissecting environmental, heritable, and stochastic contributions
Canadian Institutes of Health Research (CIHR)
2014-2019
$ 1,180,000

Epigenomics of schizophrenia (MOP-119451)
Canadian Institutes of Health Research (CIHR)
2012-2017
$1,876,137

NEW GRANT

The Aging Brain: Circadian, Transcriptomic, and Epigenomic Dimensions
CIHR and Brain Canada
2016-2019
$2,140,000

This project worth more that $2 million has been successful in both CIHR and Brain Canada competitions. This project marks a beginning of an important new development in the lab – chronoepigenomics of psychiatric disease. The main principles of this multidimensional project are delineated below.

Chronoepigenomics of Schizophrenia and other Psychiatric Diseases

- Rhythmicity is a fundamental aspect of the universe at every level, and serves as a critical foundation for life on this planet. **Every organism - from algae to humans - has their own biological clocks.**

- Biological clocks are incredibly intricate. They are composed of genes and proteins that operate in a feedback loop. Clock genes contain instructions for making clock proteins, whose levels rise and fall in a regular cyclic pattern. This pattern in turn regulates the activity of the genes. Whether we're awake or asleep, our clocks keep ticking. **Nearly everything about how our body works is tied to biological clocks.** Our clocks influence alertness, hunger, metabolism, memory, cognition, fertility, cognition, mood and numerous, if not all, other physiological conditions.

- **Many of these clocks run on a cycle of about 24 hours and such are called** "**circadian"** ("circa" comes from the Latin word "around" and "diem" means "day"). Under normal circumstances we are not aware of circadian clocks "ticking" in our cells but even small deviation from the routine day activities or sleep at night do remind about the disrupted rhythms in the body. The best example is jet lag caused by passing through several time zones which offsets the body's clock from one's wrist watch. "Losing" or "gaining" time during air travel can leave one feeling disoriented, groggy, and tired. Eventually the body is able to adjust its circadian rhythms to the new environment. But return travel will disrupt it again, requiring another reset.

- Brain is particularly interesting organ from the circadian perspective. Different brain regions exhibit different types of 24 hour rhythmicity. Circadian cycles reach their peaks and troughs at different times in amygdala, hippocampus, striatum, cortex and other critically important parts of the brain. **Brain can be compared to a large orchestra consisting of violins, flutes, cellos, string basses, bassoons, trombones, drums and numerous other instruments.** Each instrument plays its separate melody and each melody contributes to a complex and sophisticated musical performance. However, if one instrument is off, the entire performance is ruined. Very likely, similar problems occur in the brain; if one out of numerous brain regional "clocks" starts ticking too fast or too slow, sooner or later it may have a detrimental effect on the overall brain performance and present with the symptoms of psychiatric or neurological disease.

- Circadian rhythm abnormalities have been detected in patients with schizophrenia, bipolar and other mood disorders for more than 60 years, and such include changes in wake - sleep cycle, cognitive parameters, hormone secretion, brain neuromediators, among numerous other deviations from the norm. **It has been suggested that circadian dysfunction of the**

brain "multiclock" system is a risk factor contributor to major psychiatric disease, including schizophrenia, however, concrete molecular mechanisms remain unclear.

- **The team of the Krembil Family Epigenetics Laboratory (CAMH) has recently discovered a surprising phenomenon that even epigenomes in the cells and tissues undergo significant circadian rearrangements.** Millions and millions of DNA bases in the nucleus of each cell are subjected to epigenomic "tides" every day and night. Given that different brain regions have their own circadian rhythm, it is evident that the overall organization of epigenomic "tides" in the brain is really very complex.

- Epigenomics has been a recent and very promising development in etiological studies of psychiatric and other diseases, which can explain various clinical and molecular aspects of brain dysfunction. Traditionally, epigenomic studies have been performed using single time specimens ("snapshots"). Our circadian epigenomic discoveries bring one critically important component to the equation: time. The time dimension has been rarely investigated in molecular studies of the brain, however, it can bring new insights into the circadian origin of psychiatric diseases. **The <u>chrono-epigenomic</u> ("*chrono*" means time in Greek) investigation of schizophrenia, bipolar disorder and other psychiatric diseases may help understanding numerous important questions which directly pertain to the uncovering the origin of these severe brain disease**.

- We plan to perform a series of original and highly innovative chronoepigenomic experiments. We will collect skin cells (fibroblasts) from individuals affected with major psychosis and controls, convert them into induced pluripotent stem cells (NB induction of pluripotency is an epigenetic process), and then differentiate them into neuronal cells. **Such samples of a dish-grown neurons will be subjected to a detailed chronoepigenomic analysis, which will detect specific genes exhibiting circadian epigenetic misregulation.**

- **The key element of the chronoepigenomic approach is that each patient can be analyzed individually as opposed to the traditional studies based on group-wise comparisons.** In the latter, individual specific diseases causes and related differences can be masked by the group effects. Genetic, imaging and pathophysiological studies failed to detect common major disease gene or disease specific aberration in the brains of psychiatric patients, therefore, it is logical to assume that each patient is unique.

- In parallel to the chronoepigenomic studies, **the same patients and control individuals will be subjected to the circadian analysis of their brains** (this idea is now being discussed with the CAMH Imaging Center; it is not trivial but potentially can be very powerful). For this, the brain of each subject will be MRI scanned two or more times during the 24 hour period. This will enable us to identify the parts of the brain which are misregulated in each specific patient. Ultimately, we will analyze the dynamic brain imaging patterns and chronoepigenomic data in order to link the brain specific changes in each bipolar disease patient with their specific chronoepigenetic aberrations.

- All this effort may be **a significant step towards personalized psychiatry**. Uncovering the specific mechanisms, which predispose to and/or support schizophrenia and other psychiatric disease in each concrete individual, will play a major role in diagnostics and highly selective treatment strategies.