Purpose: We aimed to investigate the genetics of antidepressant response in patients with obsessive-compulsive disorder (OCD) in two ethnic groups.

Hypothesis: We postulated that different genetic variations across known OCD candidate genes may predict antidepressant response in OCD patients with different ethnic background.

Method: We examined two independent and ethnically different OCD samples. The Brazilian sample comprises of 222 Caucasian OCD subjects and we investigated 32 single nucleotide polymorphisms (SNPs) across 14 OCD candidate genes and their regulatory regions with antidepressant response data using a custom-made 32-SNP QuantStudio Flex Real-Time PCR System Chip. Individuals were grouped into those who improved following an adequate trial of antidepressant as compared with those who reported “minimal” improvement, “no change”, or “worsening” using the Clinical Global Impression – Improvement scale. Pearson χ² test was performed to detect differences in the number of responders versus non-responders across genotype groups. The Brazilian sample consists of 192 Brazilian OCD individuals and 45 SNPs across 18 OCD candidate genes were genotyped. Of the 192 Brazilian OCD participants, 74 completed an adequate antidepressant trial and change of the Yale-Brown Obsessive-Compulsive Scale severity scores pre- and post-treatment were compared between genotype distributions of each examined SNP.

Results: For the Canadian sample, interesting associations (P<0.05) were detected for the serotonin genes, HTR2A and HTR1B in antidepressant response. For the Brazilian sample, significant associations were detected for a gabergic system gene, GABRA3, and antidepressant response (P<0.05).

Conclusions: These variants may be clinically useful in predicting treatment resistance versus response in patients with OCD, thereby, reducing their duration of suffering via trial-and-error method of prescribing and improving clinical outcome.

Speaker 4: James Kennedy, Canada
Title: The IMPACT Study - “Psychiatry Pharmacogenomics Testing in Clinical Practice”

Abstract
In genomics the amount of information available is increasing rapidly. At the same time our knowledge of inter-individual differences in terms of response and side effects to medications is at an early stage. For example, an important dilemma facing psychiatrists when they need to select an antipsychotic medication for their patient is the forced choice between risk for weight gain and diabetes with the newer generation drugs versus the risk of tardive dyskinesia and other motor side effects with first generation antipsychotics. We have developed a model of seven genes (melanocortin-4 receptor, serotonin 2C, neuropeptide Y, others) that predicts 67% of the variance in risk for this weight gain (Tiwari et al., 2015). In terms of antidepressant treatment there are now several replicated studies showing a significant benefit of gene guided medication selection over treatment as usual (Altar et al., 2015). Genes tested include CYP450, 5HT2A, and 5HTTTLPR. In addition to significant clinical improvement and reduction of side effects there is also a documented reduction in health care costs when genetic guidance is used in antidepressant treatment. Regarding the concern that physicians will not be able to efficiently translate complex genetic information into clinical decision-making, we have surveyed over 200 psychiatrists and family practitioners in our Toronto-based pharmacogenetics study (www.IM-PACT.ca; n=4,900 patients tested) and found that the overwhelming majority of physicians found our user-friendly genetic report to be readily understandable, and over 90% believe that pharmacogenetics testing will become standard of care in the future. We are now working on relevant epigenetic changes in the cortisol system genes, and in the serotonin transporter gene, that may affect medication response and side effects.

14.45 – 16.30

S6: Predicting therapeutic response in depression
Chair: Siegfried Kasper, Austria
Co-Chair: Yu Xin, China

Speaker 1: Siegfried Kasper, Austria
Title: Clinical and genetic findings in treatment response

Abstract
The Group for the Study of Resistant Depression (GSRD), a collaborative project between eight centers in Belgium, France, Greece, Italy, Israel and Austria developed a staging model that distinguishes between “non-responders” (patients who fail to respond to one form of treatment, administered for six to eight weeks), a condition which is now termed “insufficient response” by the European Medicines Agency (EMA), “treatment resistant depression” (TRD, patients that fail to respond to two or more adequate antidepressant trials of different classes of antidepressants), and “chronic resistant depression” (CRD, patients being treated with several antidepressants for more than twelve months). The clinical findings of the GSRD provide a set of eleven variables associated with treatment response, among them comorbid anxiety disorders as well as melancholic features (Souery et al., 2007, Journal of Clinical Psychiatry 68: 1062–1070). Although there is a plethora of hints in textbooks that switching the mechanism of action should be obtained when a patient does not respond to one medication, the results of the GSRD challenge this notion by describing that staying on the same antidepressant mechanism of action for a longer time is more beneficial than switching (Souery et al., 2011; World Journal of Biological Psychiatry 12: 364–375). The clinical and genetic findings of the GSRD European multicenter project have been summarized by Schosser et al. (European Neuropsychopharmacology; 2012; 22: 259–266) and recently expanded by Kautzky et al (European Neuropsychopharmacology; 2015; 25: 441–453) including machine learning techniques to handle the large amount of data obtained in this ongoing research protocol.

Speaker 2: Heon-Jeong Lee, Republic of Korea
Title: A hypothesis of circadian rhythm on the treatment response in depression

Speaker 3: Shigeto Yamawaki, Japan
Title: Impact of neuroimaging on treatment response in depression

Abstract
Major depressive disorder (MDD) is a heterogeneous condition in which a wide range of etiologies, risk factors and symptom profiles may be associated with a threshold diagnosis. Response rates in drug treatment are variable and often less than 50% due to a trial-and-error prescription of antidepressants. Despite significant
advances in neuroscience, no widely accepted biomarker is available to assist diagnostics or treatment choice for individual patients. Neuroimaging using fMRI is useful to investigate the pathophysiology of MDD and aid in the identification of biomarkers of treatment response. Traditional task-based fMRI analysis has used statistical approaches to locate areas of the brain which are activated differently between patients and control subjects. Several fMRI studies on responses to emotional stimuli found an association between greater baseline activity in regions throughout the dorsal-ventral extent of anterior cingulate (ACC) - medial prefrontal cortex (mPFC) and better treatment response to SSRI medications in depression. Another fMRI study reported that greater pretreatment amygdala activity predicted better outcome of cognitive-behavioral therapy (CBT). These studies suggest that measures of activity in ACC, mPFC and amygdala may differ in patients who benefit from psychotherapy compared with SSRIs.

More recently, resting-state fMRI has become increasingly popular to study for understanding brain network dynamics in MDD. The key findings in neural circuits supporting implicit emotion regulation and reward processing indicate either abnormally increased resting connectivity between amygdala and striatum, and ACC and ventromedial PFC, and decreased resting connectivity between subgenual ACC and cortical areas. Subcortical-ACC resting-state connectivity has shown an increase after SSRI treatment. Such abnormal resting-state connectivity between brain regions may be possible predictors of antidepressant response.

However, it is unlikely that a single clinical or biological marker can guide treatment selection, therefore multiple biological measures may be needed to provide more reliable markers to guide treatment. Recently, computational neuroscience techniques using machine learning are also applied for neuroimaging studies. In our laboratory, we found that the combination measurement of Childhood Abuse Trauma Scale (CATS) and the resting-state connectivity between angular and default mode network - executive network may be able to predict the non-responder for SSRI.

In this lecture, the recent neuroimaging studies including our current research on treatment response in depression will be reviewed and discussed.

Speaker 4: Brian Dean, Australia
Title: Serotonin 2A receptor in depression and suicide

Abstract
The serotonin 2A receptor is one of the most abundant serotonin receptors in the human CNS and is a target for drugs designed to treat psychiatric disorders (McCorvy and Roth, 2015). Significantly, levels of serotonin 2A receptors have been shown to be altered in the CNS of subjects with schizophrenia (Dean, 2003), major depressive disorders (Arora and Meltzer, 1989; Dean et al., 2014) and suicide completers (Mann et al., 1986; Dean et al., 2014). These findings raise the issue of whether or not changes in levels of the serotonin 2A receptor are involved in a drive to suicide or are changed in the CNS of suicide completers because they have suffered from disorders such as schizophrenia or major depressive disorders in which there are changed levels of the receptor. In this presentation the current literature on changes in serotonin 2A receptors, as measured by neuroimaging and postmortem CNS studies, will be reviewed in the context of unravelling the role of these changes in the aetiology of psychiatric disorders versus a drive to suicide completion. In addition, the growing understanding of the regulation of levels of serotonin 2A receptors in the CNS will be discussed within the framework of understanding how changes in the receptors may have a role in the aetiologies of psychiatric disorders and their involvement in a drive to suicide.

References
Arora RC, Meltzer HY (1989) AmJPsychiatr 146:730–736. Dean B (2003) J Neurochem 85:1–13. Dean B et al. (2014) Int J Neuropsychopharmacol 17:895 - 906. Mann JJ et al. (1986) ArchGenPsychiatry 43:954–959. McCorvy JD, Roth BL (2015) Pharmacol Ther 150:129–142.

S7: The role of Short and Long Non-coding RNA in Mental Illness
Chair: Gustavo Turecki, Canada
Co-Chair: Alexandra Sulcova, Czech Republic

Speaker 1: Alon Chen, Germany & Israel
Title: The role of specific microRNAs in regulating stress-linked behaviors
Alon Chen
Department of Stress Neurobiology and Neurogenetics, Max Planck Institute of Psychiatry, Munich, Germany and Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel

Abstract
The role of specific microRNAs in regulating stress-linked behaviors

The fine-tuning of gene expression determines both normal and pathological behavior. Posttranscriptional regulation by microRNAs (miRNAs) offers a new approach for studying dysregulation of psychopathology-related behaviors. Recent studies reveal that miRNAs expression profile in blood circulation correlates with psychiatric disorders, and may offer a novel diagnostic tool. Furthermore, manipulating the levels of miRNAs is emerging as a potential treatment of stress-linked psychopathologies. In this lecture, we will discuss the experimental approaches using human subjects, animal models, cellular systems and bioinformatics to advance our knowledge on miRNAs role in stress-related mental conditions and will describe our recent findings in this field (describe in part at the below publication).

References
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Speaker 2: Claes Wahlestedt, USA
Title: Understanding and Drugging the Epigenome and the Non-Coding Transcriptome
Claes Wahlestedt, MD PhD