CAMH Science: Centred on Discovery

Science Synopsis from the Research Program

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From the Desk of Bruce Pollock, Vice President of Research

In 2006, I returned to Canada and joined CAMH's Research program on its journey to change the face of mental illness and addiction. As a scientist in geriatric psychopharmacology, I am searching for better ways to treat depression and the psychiatric symptoms dementia. There is an urgent public health need to improve our understanding of medication effects in this rapidly growing segment of our community, but this is only one aspect of CAMH science.

Since taking on the role of Vice President of Research in February, I've come to appreciate just how vast our scientific scope really is. From neurons to neighbourhoods, from cells to clinic care, these past few weeks have opened my eyes to the remarkable depth and breadth of our scientific work and scientific achievement. In this newsletter you'll read just a few highlights of our recent successes, and there is only more to come from this extraordinary group of scientists, scientific staff, and administrators who I now have the pleasure of guiding to new heights of achievement.

The innovative leadership of my predecessors Drs. Louis Gliksman and Shitij Kapur, fostered a commitment to research excellence that translates into improved care. My goal as VP is to nurture this compassionate approach to science and foster synergies among the diversity of

disciplines and paradigms within our research program. We will also need to increase our communication with government and the public that provides our resources, if we are to advance mental illness and addiction research.

Our dedication to discovery with a human impact means that CAMH science now stands as a beacon of hope to patients and families in our community, throughout the province and around the world. Our work, today or ten years from today, changes how we understand mental illness and addiction, enabling CAMH to improve diagnosis, prevention, intervention, treatment and public policy initiatives.

In this new role, I look forward to working with all facets of the Research Program, and other parts of CAMH, as we continue to transform lives.

In this Issue

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News and Events - Volume Two, Issue Four

Triumphs & Honours

- **CAMH Research & AUTO21: Working Together to Tackle Social Issues & The Automobile**
  Dr. Robert Mann will continue guiding research investigating anti-social driving behaviour (including impaired driving and road rage), public policy and the automotive industry, and issues affecting the automotive workforce, thanks to the Government of Canada's $23.2 million renewal of the Auto21 Network of Centres of Excellence. more
- **Canadian to Lead American Association of Geriatric Psychiatry**
  Vice President of Research Dr. Bruce G. Pollock is the new president of the 2000-member American Association for Geriatric Psychiatry (AAGP). Internationally recognized for his work in geriatric psychopharmacology, as AAGP president Dr. Pollock will use his expertise to guide priorities in the safety and efficacy of psychiatric medications for the elderly, and access to quality mental health care for older adults. more
- **CIHR Champions Pharmacogenetics Lab's Quest for New Ways to Quit Smoking**
  Over 20% of Canadian adults are smokers; an addiction that has huge preventable personal and societal costs. But what is CAMH doing to help smokers quit? Thanks to renewed financial support from the Canadian Institutes of Health Research (CIHR), Dr. Rachel Tyndale and her expert team in the Pharmacogenetics lab are figuring out how genes may provide the key to quitting and investigating a new strategy that may improved smoking cessation treatment. more
- **Nicotine Addiction Treatment**

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Investigation Continues

Dr. Fang Liu, senior scientist and section head for the molecular neuroscience section in the neuroscience research department, received funding from Ontario Research Commercialization Program through BioDiscovery Toronto to continue her work investigating a peptide for treating nicotine addiction. The application, prepared in conjunction with CAMH's Technology Transfer Office, was ranked number one in the grant competition. This project enables Dr. Liu to test her novel peptide in *in vivo* models of nicotine dependence developed by Dr. Anh Le, senior scientist and head of the neurobiology of alcohol section in the neuroscience research department. This is a critical milestone in the development of Dr. Liu's peptide as a possible smoking cessation agent.

- **Work and Well-being Research Boosted by New CIHR Chair**

  Dr. Carolyn Dewa received an Applied Public Health Chair from the Canadian Institutes of Health Research (CIHR) Institute of Public and Population Health and the Public Health Agency of Canada for her project, "developing effective interventions for mental illness and mental health in the working population."
  This prestigious five-year award, for almost one million dollars, supports Dr. Dewa's high-quality and focused policy and program intervention research, which has national relevance to public health.

  The Chair further supports Dr. Dewa's work as program head for the work and well-being research and evaluation program and senior scientist in the health systems research and consulting unit. At CAMH, Dr. Dewa uses a trans-disciplinary approach to investigating workplace mental health by examining the impact of work on people with mental illness, and the workplace's impact on mental health. The chair will also help to strengthen and extend the program's knowledge translation and exchange network activities. It will also be used to increase the research capacity in this area by training new researchers and students.

- *Collecting Biological Samples from Drivers and Party-goers: Implications*

for Alcohol and Drug Intervention Programs -- Dr. Robert Voas presents at the 15th Annual Archibald Lecture on April 17, 2008

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CAMH's Pharmacogenetics Clinic - a new era of precise prescription based on your genes

Prescribing medications is a combination of clinical arts and inexact sciences, and each day physicians face the same dilemma: What is the right drug? Should I start with a lower or higher than standard dose? Will this patient be more susceptible to side effects?

"From the moment a pill passes a patient's lips, there are a many ways the body processes the medication, resulting in an often bewildering variety of responses," explains Dr. Daniel J. Mueller, the recently recruited head of CAMH's new pharmacogenetics clinic. "The solution for harnessing these unruly responses lies in understanding the cause using the blueprint for human sameness and differences -- our DNA."

Medical training and clinical experience teaches physicians some of the considerations important in deciding how best to treat a patient with medication (e.g. age, sex, and ethnicity), but there continues to be huge inconsistencies in how patients respond. CAMH's pharmacogenetics clinic -- the first in the world dedicated to understanding the genetics of psychiatric medication response and side effects --is the opportunity to lead us out of the dark ages of prescribing by trial-and-error and into a new era of precise prescribing of antipsychotic and antidepressant medications based on your genes.

In the new clinic, Dr. Mueller and an expert panel of CAMH's pharmacogeneticists will measure variations in CYP2D6 and CYP2C19, two genes that break down commonly used antidepressant and antipsychotic medications in the liver. These variations will determine if a person

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is a poor, intermediate, extensive, or ultrarapid metabolizer and will ultimately help physicians choose the medication dose that will most effectively treat the illness.

This approach to care has very tangible implications for psychiatric illnesses. For example, despite the wide array of medicines available, more than twenty percent of people with schizophrenia do not initially respond to treatment with antipsychotic drug therapy. Also, twenty to thirty percent who do respond early on eventually relapse, and some develop serious side effects that cause them to stop taking the medication.

As Dr. Mueller explains, “We’ll be able to identify clients with schizophrenia who are slow metablolizers of perphenzine or olanzapine, for example. This information tells us that their bodies hold onto medication for a long time, making them prone to adverse side effects even with low doses.”

If on the other hand you’re a rapid metabolizers, the medication usually leaves your body too quickly to be effective. In this scenario, for example, physicians need to prescribe higher doses or can more confidently prescribe an antipsychotic that leaves the body through the kidneys, such as the recently introduced antipsychotic paliperidone. “In our clinic,” says Dr. Mueller, “we’ll give patients a card that outlines their metabolic rate, giving doctors a prescription road map that will increase the medications efficacy and decrease side effects.”

This clinic will also help provide critical information on side effects. Using a diagnostic kit, which includes a critical component discovered at CAMH, we can help indentify individuals at risk for developing tardive dyskinesia. The clinic will also use genetic information to help pinpoint individuals who have an increased risk for antipsychotic–induced weight gain (see also: Müller & Kennedy, 2006).

But the pharmacogenetics clinic will offer more than just genetic testing. During phase one, CAMH clients, (referred to the clinic by their CAMH psychiatrist because of intolerable side effects or non-response to medication) will receive high-quality care in an environment that includes pharmacology expertise (how drugs work in the body to address an illness), combined with

comprehensive clinical management that will include a general exam, and medical and medication history review. This novel approach to care and treatment is a comprehensive way to translate basic research in psychiatric pharmacogenetics into quality clinical care

"By combining our intellectually and clinically powerful resources, this timely, valuable and unique resource can help both physicians and patients," says Dr. Mueller. "We look forward to the day that all physicians can offer personalize prescriptions that transform patients' lives."

For more information on the pharmacogenetics clinic, contact Dr. Daniel Mueller at Daniel_Mueller@camh.net.

References: Müller DJ & Kennedy JL. Genetics of antipsychotic treatment emergent weight gain in schizophrenia. Pharmacogenomics. 2006; 7: 863-887.

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Drinking and Aggression: How Important are Where, with Whom, and How Much Students Drink?

Heavy drinking and alcohol-related harm, including aggression, are significant problems on university and college campuses, with evidence showing that about fifty percent of violent episodes involve alcohol. A new study lead by Dr. Samantha Wells, a scientist in the social and community prevention research section, helps explain how aggressive behaviour is influenced by where students drink, who they drinking with, and how much they are drinking. These results support experimental evidence showing a direct role of alcohol in aggression and point to characteristics of the drinking context that might be targeted in future prevention initiatives.

Using data from the 2004 Canadian Campus Survey, a national survey of 6,282 university students at 40 Canadian universities, Dr. Wells and her team discovered that the likelihood of experiencing an argument or fight increased when students:

- drank more alcohol -- with each additional standard drink consumed, the likelihood of aggression increased by about 12%;
- drank at a fraternity, sorority, or residence;
- drank at three or more different places; or
- had a partner present during the drinking event.

A pattern of heavy episodic drinking also increased the likelihood of aggression. Parties were linked to a greater likelihood of aggression, and this risk was especially high for female university students. The likelihood of aggression was actually reduced, however, when students had a

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meal.

While more research is needed, Dr. Wells points out that these findings can be used for policy and prevention purposes. She suggests that measures to reduce the risk of aggression and violence need to address not only reducing conflict and stress in drinking situations, but also moderating the amount young people drink. She notes that risky drinking locations should be targeted in prevention planning, such as student residences and fraternities/ sororities. Dr. Wells adds that programs focusing on preventing partner violence and other relationship-related conflicts may be highly effective, in addition to programs that promote the consumption of food.

For more information visit Where, With Whom, and How Much Alcohol Is Consumed on Drinking Events Involving Aggression? Event-Level Associations in a Canadian National Survey of University Students.

This study was funded by the Canadian Institues of Health Research's (CIHR) Research in Addictions: Innovative Approaches in Health Research - Secondary Analysis Grant (RAS – 79983).

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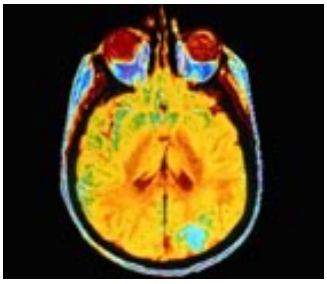
Epigenetic Changes Discovered in Major Psychosis: New Clues for Uncovering the Mysteries of Mental Illness



CAMH scientists in the Krembil Family Epigenetics Laboratory -- the only psychiatric epigenetics laboratory in North America, one of the few programs in North America that is exploring this field -- have discovered epigenetic changes (i.e. chemical changes to a gene that do not alter the DNA sequence) in individuals with schizophrenia and bipolar disorder. This is the first epigenome-wide investigation in psychiatric research, and this groundbreaking data may be a significant step on the journey to fully understanding major psychosis.

Senior scientist Dr. Arturas Petronis and his team studied 12,000 locations on the genome using an epigenomic profiling technology developed at CAMH. Approximately one in every two hundred of these genes showed an epigenetic difference in the brains of psychiatric patients. Significantly, these changes were noted on genes involved in neurotransmission (the exchange of chemical messages within the brain), brain development, and other processes linked to disease origins.

Dr. Petronis explains that these epigenetic changes may be the missing link in understanding what causes an illness. “The DNA sequence of genes for someone with an illness like schizophrenia and a for someone without a mental illness often look the same; there are no visible changes that explain the cause of a disease. But we now have tools that show us changes in the second code, the epigenetic code, which may give us some very important clues for uncovering the mysteries of major psychosis and other complex non-

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Mendelian illnesses."

This proof-of-principle study is the first demonstration of what CAMH epigeneticists have hypothesized for the last 10 years. "Until now, we only had theories that epigenetic changes were important to understanding what causes major psychosis," explains Dr. Petronis. "Now we have the tools and expertise to support our theories and we can look at conducting larger studies, which will hopefully give us an even better understanding of psychiatric illnesses. And once we understand the primary molecular causes of an illness, we can advance diagnosis and treatment approaches, and possibly even prevent illness."

The March 12th edition of the *Globe and Mail* covered this story. Visit Scientists solve a psychiatric mystery to view a copy of the article. An article was also featured on the CBC web site at 2nd genetic code could provide clues to schizophrenia, bipolar disorder.

Visit Epigenomic Profiling Reveals DNA-Methylation Changes Associated with Major Psychosis for more information on this study in the *American Journal of Human Genetics*.

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Teaching Case Peport: Recognizing 22q11.2 Deletion Syndrome

Dr. Anne Bassett, an internationally renowned expert in the genetics of schizophrenia, describes the case of a young woman with 22q11.2 deletion syndrome (an under-recognized subtype of schizophrenia) in the February edition of *Canadian Medical Association Journal*. Dr. Bassett also presents a summary of common features, along with suggestions for managing and treating people with this syndrome, who commonly experience delayed or missed diagnosis. Visit Recognizing a common genetic syndrome: 22q11.2 deletion syndrome -- Kapadia and Bassett 178 (4): 391 -- Canadian Medical Association Journal to view this case report.

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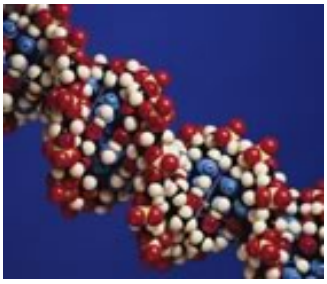

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Sexual Harassment and School Safety

Under the leadership of Dr. David Wolfe, CAMH's Centre for Prevention Science surveyed 1819 Grade 9 and 11 students in rural and city schools between 2004 and 2007 to measure both the victimization and perpetration of harassment and bullying and overall school safety. The recently released report conducted at 23 schools in Southwestern Ontario shows some cause for concern.

When surveyed on sexual pressures, four percent of males in grade 11 admitted trying to force someone to have sex with them, while 10 percent of males and 27 percent of females admitted being pressured into doing something sexual that they did not want to. Not surprisingly, the data shows that girls are feeling this pressure more than boys, with 15 percent reporting that they had oral sex just to avoid having intercourse.

The survey also revealed the following:

- In terms of sexual harassment in school, girls were much more likely to report having received sexual comments, unwanted looks or touches, and having parts of their body commented on or rated.
- In contrast, boys were much more likely to report being called homophobic insults (such as "gay" or "fag") than girls (e.g., "lezzie," "dyke").
- This pattern of homophobic insults continued mostly unchanged from grade 9 (34 percent) to grade 11 (30 percent) for boys, but declined by almost half for girls, from 22 percent to 12 percent.
- Sixteen percent of girls and 32 percent of boys reported being physically harmed (on or off school property)
- Ten percent of girls and 25 percent of boys admit to being the perpetrators of

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such violence.
- In a trend that has emerged with the widespread use of the web and social networking sites, 12 percent of males and 14 percent of females reported being harassed over the Internet.

Based on these and previous findings, this report points out that there is ample evidence to conclude that harassment and abuse are occurring at high rates among high school students. Although many of these behaviours are not as visible or extreme as other forms of violence, these acts of "everyday violence" are likely to have significant impact on the lives of youth. While some of these behaviours show a decline over the course of adolescence (such as hitting others), it is clear that students worry about their safety throughout high school.

On a positive note, the researchers emphasize that many school boards across the province are listening more to students and responding to their concerns. Schools are playing a more active role in violence prevention and promoting healthy relationships by implementing innovative school-based programs and curricula as well as involving community professionals. Students, parents and staff have to be partners in ensuring school safety. It's never too early to start - many of these negative patterns begin in elementary school, and the long-term solution will involve education that teaches positive relationship skills and respect for others.

For more information, including a copy of the report, visit Sexual harassment and school safety: How safe do students feel?

In response to this report, and other related information from other organizations, the Ontario government is reengaging its Safe Schools Action Team to combat harassment and

violence in schools. Visit Ontario Ministry of Education - Preventing Violence And Harassment In Schools

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Centre for Addiction and Mental Health

Interim STOP Study Results Show Promising Results

One out of every 13 participants has remained smoke-free for 12 months – a result that indicates smokers who have access to effective counselling and nicotine replacement therapies (NRT) are up to four times more likely to quit - according to the interim report from the STOP (Smoking Treatment for Ontario Patients) Study.

"This is the first time such a study has been implemented in Canada on such a large scale," said Dr. Peter Selby, CAMH's clinical director of addiction programs and principal investigator of the STOP Study. "The STOP Study is most likely unique in the world due to the innovative methods of distributing free NRT linked to supportive counselling that are being investigated. It is clear there's both a demand and a need for nicotine replacement therapy, and with the Ontario government's help, we're committed to finding the most effective ways to help smokers quit."

The study has reached more than 42,000 smokers in its first two and a half years. That represents more than 24 per cent of the estimated 175,000 Ontario smokers eligible to participate. With the Ontario government's recent announcement of an additional $2 million to add 15,000 more smokers to the study, the STOP Study will continue to explore the most effective methods to help Ontarians quit smoking.

For information on how to participate in the STOP Study, visit www.ontario.ca/smokefree or call 1-800-350-5305.

Additional information is also available at Research shows promising results for smokers to "go weedless"

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