

# SHOW ME THE EVIDENCE

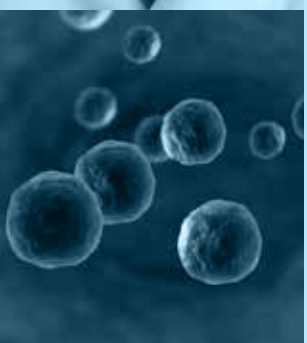
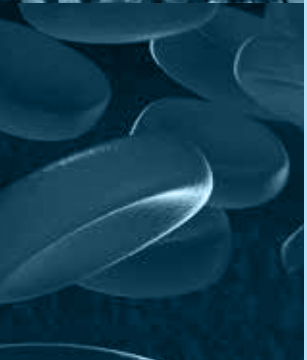
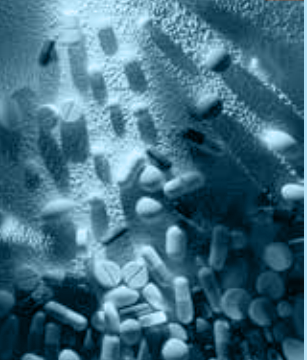
Canadian Institutes  
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# EPIGENETICS: THE ON/OFF SWITCH

**How lifestyle  
and environment  
interact with  
your genes**





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CIHR'S Canadian Epigenetics, Environment and Health Research Consortium

## STAY CONNECTED

As the Government of Canada's health research investment agency, the Canadian Institutes of Health Research (CIHR) enables the creation of evidence-based knowledge and its transformation into improved treatments, prevention and diagnoses, new products and services, and a stronger, patient-oriented health care system. Composed of 13 internationally recognized Institutes, CIHR supports health researchers and trainees across Canada. *Show me the Evidence* highlights CIHR's strategic investments and their impact on research, policy and delivery of care. In each issue, we have in-depth stories about research evidence that is already being applied, shorter profiles of promising new projects, and descriptions of CIHR's strategic priorities. For more information, visit [www.cihr-irsc.gc.ca](http://www.cihr-irsc.gc.ca).

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# WELCOME TO THE SPRING 2015 ISSUE OF SHOW ME THE EVIDENCE

## EPIGENETICS: CHOOSING THE ADVENTURE

The genome is often described as a blueprint or a recipe – a step-by-step set of instructions for creating a living thing. But, in reality, these instructions are more dynamic than that – more like a choose-your-own-adventure book than a set of steps that must be followed in sequence. While the genetic code itself is essentially unchangeable, the way in which it gets read and acted upon can change.

The field of epigenetics – meaning “above” genetics – explores how environmental factors, such as nutrition and stress, create long-term changes in gene activity. Epigenetic changes are molecular tags that attach themselves to the genome without changing the DNA code. These tags serve as notes, telling a cell whether or not to read a gene. An epigenetic tag can determine which sentences are magnified, or which pages of the book are open at a given time.

So far, researchers have focused on studying a few types of epigenetic change, particularly a process known as methylation, in which small molecules called methyl groups bind with DNA or the proteins that package DNA, altering gene activity. Researchers are just beginning to understand how these changes impact our health. For example, cancer researchers are trying to determine the role that epigenetic changes might play in switching on and off the genes that can turn a healthy cell into a cancerous one. Other researchers are exploring how stress during critical periods in development can affect a child’s risk of developing a range of illnesses, from depression to diabetes, later in life.

As the Government of Canada’s health research investment agency, the Canadian Institutes of Health Research (CIHR) sets strategic priorities to respond to key health and health system challenges. In this issue of *Show me the Evidence*, we profile the Canadian Epigenetics, Environment and Health Research Consortium (CEEHRC), a Signature Initiative to support leading-edge research on the role of DNA and environment interactions in human health and disease. CIHR’s Signature Initiatives capitalize on Canada’s research strengths and help us make strategic investments in promising areas of health research.

The CIHR-supported research highlighted in this issue has not only helped improve our understanding of epigenetics, it’s also laying the foundation for improvements in diagnosis and treatment of a wide range of diseases. The stories describe:

- **INCREASED AWARENESS OF THE CONNECTIONS BETWEEN CHILDHOOD TRAUMA AND MENTAL HEALTH**
- **A NEW AVENUE OF DRUG DEVELOPMENT FOR CANCER AND INFLAMMATION-RELATED ILLNESSES**
- **AN IMPROVED UNDERSTANDING OF BLOOD STEM CELLS, AND HOW THEY CONTRIBUTE TO LEUKEMIA**

### GLOSSARY

**CHEMICAL PROBE** – A small molecule that has been designed to interact with a specific protein, so that researchers can better understand the protein’s function.

**CHROMATIN** – Within a cell, DNA molecules are tightly wrapped around proteins. This condensed DNA-protein structure is called chromatin, and it makes up chromosomes.

**CHROMOSOME** – The DNA in a cell is divided into structures called chromosomes. Different species have different numbers of chromosomes. For example, humans have two sets of 23 chromosomes (with one set inherited from each parent).

**DNA** – Short for deoxyribonucleic acid, DNA is a very long molecule that contains biological information and transmits this information from one generation to the next in living things. It consists of a code that provides instructions for the structures and processes necessary for life. Your DNA sequence is unique to you (unless you have an identical twin).

**EPIGENETICS** – This field of scientific study explores how environmental factors create long-term changes in gene activity.

**EPIGENOMICS** – The study of all the epigenetic modifications in a genome.

**GENE** – A gene is a stretch of DNA sequence with a specific function. In general, a gene contains the code for a protein, which has a defined role in the body.

**GENETICS** – The study of genes and how they work.

**GENE EXPRESSION** – Genes aren’t active all the time. When a cell is making a protein based on the instructions contained in a gene, scientists say the gene is being “expressed.”

**GENOME** – Genome is the term for an organism’s complete genetic material. For example, an individual human genome is all of the genetic information contained in a person’s 23 pairs of chromosomes. **Genomics** is the study of the information contained in the genome.

**METHYLATION** – This is a type of chemical reaction in which a small molecule, known as a methyl group, is attached to a DNA strand or a histone protein. These chemical changes are epigenetic modifications that can increase or decrease the activity of a gene.

# THE TRACES OF TRAUMA

## Researchers draw links between early childhood abuse and suicide

**In the mid-2000s, a Canadian researcher showed that early life experiences could have lasting effects on rat behaviour. Dr. Michael Meaney found that rat pups exhibit anxious behaviours if they receive less favourable care from their mothers, and that these behaviours were associated with changes in gene activity. This work opened up a new line of research for Dr. Gustavo Turecki, a CIHR-funded researcher based at the Douglas Mental Health University Institute.**

Dr. Turecki wondered whether similar results could be observed in humans. Drawing on the Douglas-Bell Canada Brain Bank for tissue samples, Dr. Turecki, together with Dr. Meaney and a third researcher, Dr. Moshe Szyf, went on to show, for the first time, that childhood abuse leaves molecular traces in the brain.

“We’ve known for a long time, clinically, that many people who have been abused in childhood can have a hard time regulating their emotions later in life,” says Dr. Turecki, who directs a multidisciplinary team at the McGill Group for Suicide Studies (MGSS). “Little is known about the molecular mechanisms that lead to long-lasting consequences in behaviour, including suicide.”

Dr. Turecki is now helping uncover these mechanisms through the emerging field of epigenetics.

“We are all born with a genetic code that is immutable,” says Dr. Turecki. “Epigenetics is the science that investigates how the genome is regulated – how it adapts to

stimuli, and decides which processes to ‘turn on’ or ‘turn off.’ The cells in a brain and a liver share the same DNA, for example, but function differently because certain genes are active, and others are dormant.”

He likens the genetic code to a book with many chapters that can be read selectively. “When you’re reading Chapter 10, it doesn’t mean the text in Chapter 1 isn’t there,” he says. “Epigenetics regulates which pages are open at what times, and what ‘sentences’ are magnified.”

In 2009, with funding from the Canadian Institutes of Health Research, Drs. Turecki, Meaney and Szyf showed that individuals who had experienced childhood abuse had different epigenetic markings on the DNA in the hippocampus, a part of the brain involved in the formation of memories.<sup>1</sup>

“There was a lot of excitement about the project,” says Dr. Naguib Mechawar, who was setting up his own lab at MGSS at the time. “The study made a lot of headlines.”





Alongside their lab work to discover traces of abuse in the brains of suicide victims, the researchers conduct structured interviews with family members to piece together the victim's past. Understanding the extent and nature of the abuse or neglect helps inform the researchers' interpretation of molecular changes in the brain.

"For years, epidemiological studies told us that bad experiences and social position can lead to differential rates of morbidity (sickness) and mortality," says Dr. Stephanie Lloyd, an anthropologist working with the team. "Ultimately, [epigenetic] research is trying to throw the 'nature versus nurture' debate out the window, and move into a co-production space where nature and nurture are constantly informing each other."

Findings in the celebrated 2009 study focused on one variant of NR3C1, a receptor involved in the brain's response to stress. Dr. Turecki's team found fewer copies of the receptor in the brains of suicide victims with a history of childhood abuse. This suggests that early life events can affect genes in a way that could heighten risk for emotional distress in later life.

The study reaffirmed previous studies on animals, and prompted the team to expand the scope of its research across the genome. In 2012, they found that early-life trauma induced alterations in DNA methylation – a type of chemical modification that affects gene regulation – in several genes.<sup>2</sup>

## Evidence in Action

**Drs. Mechawar and Turecki co-direct the Douglas-Bell Canada Brain Bank, which is essential to the research at MGSS. The Bank is home to tissue samples from thousands of human brains. Known for its speciality in suicide, the Bank distributes some 1,000 brain tissue samples annually to researchers in Canada and around the world. Each year, more than 20 scientific articles draw on these samples.**

Without access to these samples, Dr. Turecki and his colleagues wouldn't be able to study epigenetic changes in brain tissue. But the Bank does have some limitations. Through their research on rats, Drs. Meaney and Szyf showed early life experience can shape the brain, and that some effects can even be reversed. But similar studies aren't possible in humans. "You can manipulate and expose animals to certain conditions," says Dr. Turecki. "Obviously, in humans, we can't take people in and out of abusive situations and observe the difference."

Another ongoing challenge is understanding the brains of "resilient victims" – those who experienced childhood trauma but did not commit suicide. The Bank also lacks control samples from people who had no neurological disorders.

"This makes it challenging to tackle questions as deeply as we would like," says Dr. Mechawar. "We may be excited about findings, but we know the limits of our study,



“Epigenetics regulates which pages are open at what times, and what ‘sentences’ are magnified.”

and try not to go overboard with our conclusions.”

The MGSS takes care to interpret their findings cautiously, says Dr. Lloyd. “If we say suicide is an outcome of methylation, it reduces the act of suicide to early childhood abuse, which I don’t think anyone at MGSS would claim.”

But the growing understanding of epigenetic changes could one day lead to improved treatments and interventions for people at risk of suicide. In the meantime, Dr. Turecki works hard to maintain a link between the work he does in the lab and the needs of people living with depression. Early in his career, he realized that he wanted to combine research with work as a psychiatrist.

“If I didn’t have contact with patients, I became more detached from the problems,” he says. “Having clinical experience helped me gain insight and generate hypotheses.”

At the Douglas Institute, he follows about 250 patients who often arrive with depression that family doctors were unable to treat.

“Each person has a different story. Sometimes you can’t help people, but when you can, it’s extremely rewarding. That’s what keeps me going.”

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#### FOR MORE INFORMATION

McGill Group for Suicide Studies

[http://mgss.ca/Douglas-Bell Canada Brain Bank](http://mgss.ca/Douglas-Bell%20Canada%20Brain%20Bank)

<http://www.douglas.qc.ca/page/brain-bank>

Gustavo Turecki: Childhood abuse affects the brain. Have you heard of epigenetics?

<http://podcasts.mcgill.ca/health-2/gustavo-turecki-childhood-abuse-affects-the-brain-have-you-heard-of-epigenetics-en/>

Video with Dr. Turecki <https://www.youtube.com/watch?v=ieTBLLQovM>

# A NEW FRONTIER OF DRUG DISCOVERY

Epigenetics is providing protein targets and chemical bullets to make powerful new cancer and inflammation-related drugs

**In her office at the University of Toronto, Dr. Cheryl Arrowsmith opens a complex, colour image on her computer screen. The image could be post-modern art: interconnected blue lines, hinged at red circular joints set against a globular multicolored background. To Dr. Arrowsmith, a structural biologist, the image represents a new, largely unexplored frontier of drug development.**

The colourful blob is a protein that controls whether specific genes are turned on or off. Dr. Arrowsmith refers to these as epigenetic proteins. The image also shows a new chemical probe her lab has developed, a molecule meticulously designed to fit snugly into the protein's structure.

Dr. Arrowsmith's lab is part of a collaborative network of researchers that are laying the groundwork for the development of epigenetic-targeted drugs, to treat diseases from cancer to inflammatory disorders.<sup>1</sup>

"There's so much evidence that epigenetic proteins are important in disease and could be potential drug targets that we think the best way to explore this is to create chemical probes and use them to explore as many disease models as possible," she says. In fact, she is so passionate about epigenetics, that her team is generating "Open Access" chemical probes – making them available for the world to test in disease models without licensing or restrictions on use.

Over the past decade, epigenetics – literally meaning "above" genetics – has emerged as a new frontier for understanding what

makes cells tick – and sick.<sup>2</sup> We know that every cell in the body contains exactly the same genes. But there are many different kinds of cells in the body. This raises a question: how can cells that all carry the same instructions develop different functions?

"It's the epigenetic proteins," explains Dr. Arrowsmith.

This collection of several hundred proteins acts to regulate which genes are active in a given cell during its development. This determines, for example, whether the cell matures into a liver cell producing digestive enzymes or a protective skin cell.

The growing awareness of epigenetics has sparked a flurry of medical interest because while genes can't readily be changed, epigenetic proteins can. Their action is reversible, making them excellent potential drug targets.

"Probes against epigenetic [proteins] are the next frontier in medicinal chemistry," says the University of British Columbia's Dr. Colby Zaph, one of Dr. Arrowsmith's Canadian Institutes of Health Research (CIHR)-funded collaborators.



## Chemical Probes

**Dr. Arrowsmith's research involves first using x-ray crystallography and Nuclear Magnetic Resonance (NMR) techniques to determine the precise 3D structure of an epigenetic protein. Team members then identify target areas in the protein where a small molecule might fit and tightly bond with the protein. Working with academic and pharmaceutical company chemists, the Arrowsmith group finds a small molecule, the chemical probe, that will efficiently and durably bind to the protein to slow or accelerate its action.**

As of 2013, there were four epigenetic therapies approved for patients in the United States, all to treat cancers, and there are currently more than a dozen in U.S. clinical trials.<sup>3</sup>

"I think these are just the tip of the iceberg," says Dr. Arrowsmith.

However, pharmaceutical scientists say the bottleneck in developing these new drugs is identifying the small molecules – the chemical probes – that can alter an epigenetic protein's behaviour.<sup>4</sup> This is exactly where Dr. Arrowsmith's lab is a world leader.

In a recent paper in the Proceedings of the National Academy of Sciences, Dr. Arrowsmith and colleagues at Pfizer described how they painstakingly identified the first chemical probe that can inhibit an epigenetic protein called SETD7.<sup>5</sup> The protein plays an important role in regulating tissue size and growth, which are out-of-control in cancer tumours.

Dr. Arrowsmith's team, including more than a dozen collaborators, revealed that a probe named (R)-PFI-2 binds to the protein, inhibiting its function. They also showed that the probe can readily enter cells, a critical feature for any potential drug.

"Researchers interested in understanding epigenetic regulation and pharmaceutical companies interested in SETD7 as a drug target will jump on this work," says Dr. Stephen Burley, Director of the Protein

Data Bank, based at Rutgers University in New Jersey.

The research was done as part of the Structural Genomics Consortium (SGC), a unique academic-industry collaboration of university and pharmaceutical company researchers based on Open Access principles. In this partnership, the SGC identifies 3D protein structures and industry helps develop the drug-like chemical probes – all of which are made fully available to the wider biomedical research community in order to accelerate the pace of discovery.

### **Evidence in Action: Toward new drugs for IBD**

**Dr. Arrowsmith's current CIHR-funded research projects are demonstrating the potential power of epigenetic drugs in creating new treatments for Inflammatory Bowel Disease (IBD) and cancers, diseases known to involve a high level of epigenetic deregulation.**

**In a recently published study, Dr. Zaph demonstrated that a chemical probe developed in Dr. Arrowsmith's lab blocks the activity of an epigenetic protein thereby inhibiting immune cells' ability to spark inflammation.<sup>6</sup>**

**"The probe allowed us to tease apart the intricate mechanisms of how the epigenetic protein regulates gene expression and cellular differentiation," says Dr. Zaph, noting that the protein is also active in human immune cells.**

"The companies give us libraries of thousands of drug-like molecules that we can use in our assays to identify the few that inhibit a given protein," says





Dr. Arrowsmith, the scientific lead for the Toronto section of the SGC. Experienced chemists in industry then work to optimize the promising molecules based on how the chemicals fit into the 3D proteins structures. “Through this collaboration we’ve developed 27 chemical probes that are now available for the community to use.”

Dr. Arrowsmith says the pace of discovery as a cornerstone lab in the SGC is at times daunting.

“We have to solve a specific number of structures every quarter, and our goal is to develop about ten new chemical probes each year,” she says. But knowing that each intriguing 3D image on her computer screen is the potential building block for a potential new therapy is powerful motivation.

“It’s really exciting,” says Dr. Arrowsmith. “I feel like we’re not only doing our own research, we’re catalyzing other peoples’ research and drug discovery as well.”

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## The Structural Genomics Consortium (SGC)

**The SGC is a not-for-profit, public-private partnership that supports the discovery of new medicines by identifying the 3D structures of medically-relevant proteins. With more than 200 scientists centered at labs in Toronto, Canada, and Oxford, England, it’s the world’s leading source of new protein structure information. These proteins are important to the development of new therapies for cancer, diabetes, obesity, and inflammatory and psychiatric disorders. The SGC is funded by nine pharmaceutical companies, and public partners including CIHR. All of the SGC’s outputs – including chemical probes – are made publically available without restrictions on use.**

### FOR MORE INFORMATION

The Structural Genomics Consortium: <http://www.thesgc.org/>

Dr. Cheryl Arrowsmith’s Lab Group: <http://nmr.uhnres.utoronto.ca/arrowsmith/>

Video with Dr. Arrowsmith <https://www.youtube.com/watch?v=rjTWz7pjIU>

# DOWN TO THE STEM

## Understanding the epigenetics of blood stem cells sheds light on new cancer treatments

**For the past 30 years Dr. John Dick, a blood explorer, has led the way in creating a cellular family tree of how our blood cells mature. Every day our body produces about a trillion new mature blood cells. Each one begins in the bone marrow as a hematopoietic stem cell (HSC), or blood-producing cell, which can mature into one of more than 10 different sub-types of white and red blood cells.<sup>1</sup>**

“Understanding normal blood cell development is crucial to harnessing the regenerative potential of normal blood tissues as well as teasing apart when and how blood cells become cancerous,” says Dr. Dick, a senior researcher at Toronto’s Princess Margaret Cancer Centre.

Now after years of successfully mapping differences in blood cells based on their genetic profiles and surface characteristics, Dr. Dick’s lab is at the forefront of identifying the epigenetic changes at work when a healthy blood stem cell becomes a mature cell type or when a normal cell turns into a leukemic one. Epigenetic changes are those that turn genes on or off without altering the DNA sequence.

Any cancer, whether it’s leukemia or lung cancer, involves a mix of cells that vary in terms of their ability to drive tumor growth over the long term and their resistance to therapy.<sup>2</sup>

“We’ve shown that not every cancer cell is equal. There are some cancer cells, including in leukemia, that are more able to keep the cancer going – they have stem cell properties,” says Dr. Dick.

In 1994, Dr. Dick’s lab group was the first to isolate cancer stem cells in acute myeloid leukemia (AML), and has since shown that these cells are crucial to understanding the initiation and successful treatment of blood cancers.<sup>3</sup> In fact, Dr. Dick’s research revealed that only this minor subset of cancerous cells can cause leukemia when transplanted in mice.

Only about one-in-a-thousand leukemia cells are stem cells, but they are critical to cancer recurrence. Chemotherapy targets rapidly dividing cells, but cancer stem cells can remain dormant and survive treatment.

Dr. Dick is now exploring the role that epigenetics plays in the “stemness” of cancer stem cells and HSCs. These cells have a special ability to self-renew – that is, they can divide to form daughter stem cells, but at the same time they can mature and develop into any kind of blood cell. By understanding the “stemness” of these cells, researchers may be able to directly target them with improved cancer therapies.<sup>4</sup>

### **Making Blood Cells**

**While we generally think of blood as being composed of two types of blood cells, white and red, there are more than a dozen intermediate and mature blood cell development stages. All of these different cells start from hematopoietic stem cells (HSC) in the bone marrow. One of Dr. Dick's key research questions is how genetic and epigenetic factors direct the development of HSC to differentiate and form one kind or another of blood cells – or change to become a leukemia cell.**



## Evidence in Action

Dr. Dick and his lab group are already helping show that it's possible to directly target the epigenetic regulation of "stemness" in certain types of cancer cells.<sup>5</sup>

As with leukemia, colorectal cancer has stem cells – first reported by Dr. Dick and his team in 2007. In a recent study, Dr. Dick and a team of Canadian researchers blocked the action of a key epigenetic protein called BMI-1 that's critical to cancer stem cell self-renewal. The result: by targeting this key "stemness" protein, they prevented self-renewal and stopped growth of colon cancer tumours that had been grafted into mice.<sup>6</sup>

"By targeting epigenetic mechanisms, we may be able to alter the sensitivity of the general characteristics of cancer stem cells, making these cells more sensitive to therapies to directly induce cell death," says Dr. Ola Hermanson, a neuroscientist at Sweden's Karolinska Institute and one of Dr. Dick's fellow epigenetics researchers. Dr. Hermanson's research focuses on the epigenetic regulation of neural stem cells and their relationship with brain cancers.

In another recent study, Dr. Dick and a team of research collaborators found evidence that the extent of "stemness" in patients with AML can help predict a patient's response to treatment and overall survival.<sup>7</sup>

The researchers examined blood samples from 16 AML patients at Toronto hospitals and used the expression, or activity, of "stemness" genes as a measure of leukemic stem cell activity. The results have since been verified, in yet unpublished research, in more than 1,000 AML patients from around the world.

"What we're trying to figure out now is the role of epigenetics in this," says Dr. Dick, of ongoing research with Japanese colleagues at the University of Tokyo as part of a CIHR-supported project to create an epigenetic road map of healthy blood cells and leukemia.

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## FOR MORE INFORMATION

Dr. Dick's laboratory home page: <http://www.jdstemcellresearch.ca/>

Stem Cell and Cancer Research Institute: <http://sccri.mcmaster.ca/>

What is a cancer stem cell? Narrated by Dr. John Dick: <http://vimeo.com/109846660>

# FERTILE IDEAS

## A father's diet may affect the health of his offspring

Researchers suspect some developmental disorders may be linked to epigenetic information contained in a father's sperm. Epigenetic markings are chemical groups that attach to DNA and associated proteins, and can switch genes on or off at key moments in human development. This gene regulation plays an important role in how sperm cells develop, and in how these same cells package the DNA for safe delivery to the egg for fertilization. Alterations to the epigenetic information may have health consequences for the resulting children. "I'm trying to discover how external environmental factors such as diet and toxicants are imprinted on the epigenetic information in sperm," said Dr. Sarah Kimmins of McGill University. "In this way, we can hopefully find ways to pass on a healthy sperm epigenome to reduce disease."

**Research:** Pregnant women have long been encouraged to eat green leafy vegetables full of folate, or vitamin B9, to ward off birth defects. Supported by an eight-year CIHR grant and Genome Québec, Dr. Kimmins has shown that a diet deficient in folate also negatively influenced the sperm epigenome of male mice. "It was the first study to show that a father's diet plays a role in preventing birth defects and ensuring the future health of offspring, perhaps as great a role as the mother's," she says. The research team is now investigating whether harmful epigenetic changes in sperm can be reversed. Ultimately, they will explore whether the findings on mice also hold true for men. It takes three months for males to produce mature sperm, she noted, which may present a brief window for introducing lifestyle changes. "That's the big question," says Dr. Kimmins. "If a man starts eating well, could that fix the effects of a previously poor lifestyle and associated epigenetic errors imprinted in his sperm?"

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# RIGHT FROM THE START

## How do maternal and infant diet affect the health of mother and child?

**What women eat during pregnancy may interact with their genes to affect their children's resistance to conditions like obesity, pre-diabetes, allergies and asthma. However, epigenetic effects – such as the influence of external factors like diet on genes – are not fully understood. Moreover, what infants eat can also leave them vulnerable to health problems. Dr. Stephanie Atkinson of McMaster University and her colleagues are looking for ways to give babies the best start in life and improve the health of mothers during pregnancy and the postpartum.**

**Research:** Dr. Atkinson and her colleagues are integrating data from four ongoing birth cohort studies – which follow a child from birth – to better understand the relationship between maternal diet, infant diet and health. Members of the team with expertise in genetics will explore if early diet interacts with genetic variants to set an infant on the path for obesity, allergy and asthma, among other health risks. “In this way, we have a much larger sample size of diverse Canadian populations (white Caucasians, South Asians and Aboriginal peoples) from which to explore genetic and geographic diversity,” says Dr. Atkinson. “This project builds on the investment by CIHR and other donors in the original core studies, allowing us to enhance the value from the data already collected.” All told, the coalition of cohort studies represents 5,000 pairs of women and infants. The researchers will soon have initial findings on the mothers’ dietary patterns and nutrient intakes, and how these patterns relate to maternal health, including postpartum weight retention and gestational diabetes.

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# MAPPING THE CELLULAR LANDSCAPE

## Understanding how epigenetics influences cancer

While cancer has been long viewed as a genetic disease, researchers are discovering that epigenetics – the biological mechanisms that turn genes on or off – also plays a role. The human genome – the entire DNA content of a cell – remains essentially unchanged and is the same throughout the body. Conversely, the epigenome – the chemical compounds that modify, or mark, the genome – evolves over the course of a person's life and can vary from cell to cell. "To understand epigenetic influences on disease, we need to know how a 'normal' epigenome would function," says Dr. Martin Hirst of the BC Cancer Research Centre. "And while we can define a cell by its epigenome, there are hundreds of distinct cell types so it's a significant undertaking to complete the picture."

**Research:** As a member of the International Human Epigenomic Consortium (IHEC), the BC Cancer Research Centre and the University of British Columbia are collaborating with several other partners to create a "reference map" for human cell types. Since the epigenome changes as cells age and in response to environmental influences, researchers are generating multiple reference maps for each cell type. The goal is for partners to develop an open access database of 1,000 reference epigenomes based on standards set by IHEC. With support from clinicians who provide high quality human tissue, the Centre is generating maps of normal and malignant cells related to cancers in the brain, colon and breast, among others. To date, with funding from CIHR, the Centre has profiled 38 cell types, making it on track to reach its goal of 100. "Even now, the project is providing critical references for normal cells that we can compare against disease," says Dr. Hirst. "For example, we're using data we've generated to understand the epigenetic landscape of normal human breast cell types as a foundation to understand breast cancer."

### Sources

Gascard, P. et al. (in review). Epigenetic and transcriptional determinants of the human breast.

Kundaje, A. et al. (in press). Integrative analysis of 111 reference human epigenomes.

# CIHR'S CANADIAN EPIGENETICS, ENVIRONMENT AND HEALTH RESEARCH CONSORTIUM

**Sometimes referred to as the second revolution in genetics, epigenetics research promises to deliver profound new insights into the nature of human health and disease. Here in Canada, talented researchers are expanding our understanding of how epigenetics influences health. The Canadian Epigenetics, Environment and Health Research Consortium (CEEHRC) is a national initiative to direct strategic investments in epigenetic and epigenomic research.**

## **COORDINATING OUR STRENGTHS**

Through CEEHRC, CIHR is promoting the translation of epigenetic discoveries into new diagnostic technologies and treatments for patients. We've identified Canada's research strengths in this field, and areas where there is room to build. CEEHRC is accomplishing this in a number of ways:

- It has established two national epigenetics platforms that are serving as an essential resource for generating epigenomic data, and that have helped coordinate national research efforts.
- It is promoting the translation of epigenetic research discoveries into clinical and medical practice. This includes the development of novel molecular tools for diagnostic and therapeutic applications to a wide range of conditions, from cancer to depression.
- It is positioning Canadian researchers, clinicians and policy makers at the forefront of international epigenetics initiatives.

To achieve these goals, CEEHRC has harnessed the power of partnership. The initiative is co-led by the CIHR Institute of Neurosciences, Mental Health and Addiction, the CIHR Institute of Genetics and the CIHR Institute of Cancer Research, in partnership with most of the other CIHR Institutes. CEEHRC also includes a number of external partners, such as Genome Canada, Genome BC, Génome Québec, and le Fonds de recherche du Québec – Santé (FRQS).



### **BUILDING THE WORLD'S EPIGENETIC RESEARCH CAPACITY**

CEEHRC has helped position Canada at the forefront of the International Human Epigenome Consortium (IHEC). This international collective is coordinating researchers around the world to facilitate the sharing of data and prevent duplication of efforts in epigenetics and epigenomics. IHEC members are working to develop human epigenome maps for key cellular states relevant to health and diseases. These maps will serve as an important resource for researchers trying to understand the impact of epigenetic changes on health.

Researchers supported by CEEHRC have already made important contributions to the global efforts to advance epigenomic research. For example, two epigenetics platforms were funded under this initiative: the McGill Epigenomics Mapping Centre and the Centre for Epigenome Mapping Technologies (CEMT) at the BC Cancer Agency.

The two centres needed an efficient way to share their data, so researchers at the McGill facility, led by Dr. Guillaume

Bourque, worked with Compute Canada to develop a data portal capable of managing the large volume of information required to create reference epigenome maps. This portal, originally designed to allow for data coordination between the two Canadian centres, served as a model for the development of the portal used by all of the IHEC members.

“Many countries have recognized the importance of generating reference epigenomics datasets,” says Dr. Bourque. “What the IHEC Data Portal does is to bring these datasets together and facilitate unrestricted access to this valuable resource for all scientists.”

The IHEC Data Portal is still maintained by the researchers at the McGill facility. It is a true example of Canadian ingenuity helping propel forward an entire field of health research, and it is the kind of collaboration and innovation that CEEHRC was designed to promote.

#### **FOR MORE INFORMATION**

Canadian Epigenetics, Environment and Health Research Consortium: <http://www.cihr-irsc.gc.ca/e/43602.html>

CIHR Signature Initiatives: <http://www.cihr-irsc.gc.ca/e/43567.html>

International Human Epigenome Consortium: <http://www.ihec-epigenomes.org/>

IHEC Data Portal: <http://epigenomesportal.ca/ihec/>





Thank you for reading the Spring 2015 issue of *Show me the Evidence*. We hope that you enjoyed learning more about the impact of Canadian health researchers and encourage you to visit CIHR's website, at [www.cihr-irsc.gc.ca](http://www.cihr-irsc.gc.ca), and social media sites, at [www.cihr-irsc.gc.ca/e/42402.html](http://www.cihr-irsc.gc.ca/e/42402.html), to learn about other CIHR-funded success stories.

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