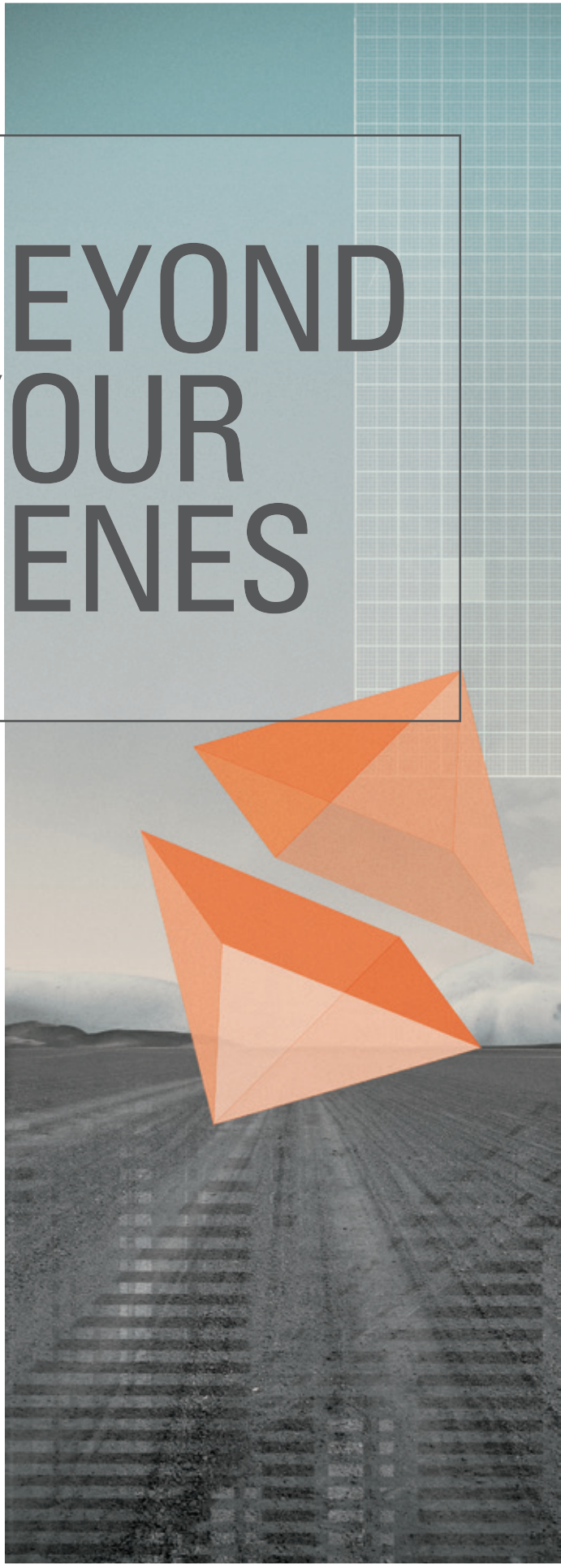
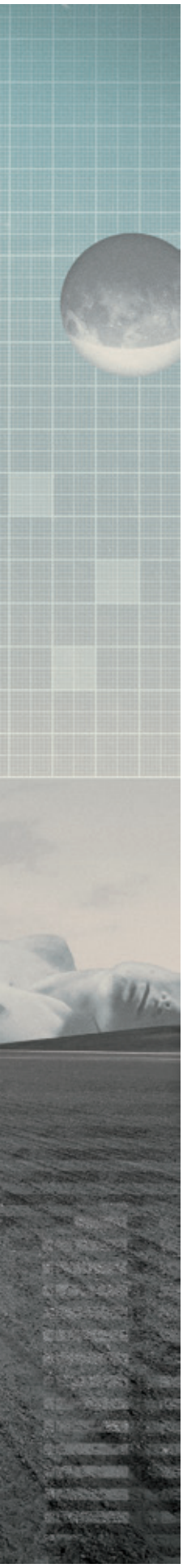
BEYOND YOUR GENES



DR ERIC MARCOTTE, ASSOCIATE DIRECTOR
Canadian Epigenetics, Environment and Health Research Consortium, Canadian Institutes of Health Research

As a Signature Initiative established by the CIHR, in association with multiple national and international partners, CEEHRC provides a fantastic opportunity for the nation's foremost health research stakeholders to achieve more than the sum of their parts. This is particularly important for a multifaceted discipline like epigenetics, and **Dr Eric Marcotte** is enthusiastic about the potential that this burgeoning field has to revolutionise the healthcare landscape in Canada and beyond



How was the Canadian Epigenetics, Environment and Health Research Consortium (CEEHRC) initiated, and how does it operate?

The Consortium is one of the Canadian Institutes of Health Research (CIHR)'s Signature Initiatives – a group of operations that aims to capitalise on Canada's strengths, or to stimulate progress in priority areas of health research where the opportunities for translational impact are great. In this case, the overall goal when the initiative was first conceived was to help better position Canada for the rapid translation of epigenetic discoveries into practical health benefits.

The process we go through when developing these initiatives at the CIHR is extremely detailed. We have institutes that are aligned along themes of common research interests and thematic areas, and bring together large research communities as well as partners and stakeholders. Within the broader strategic goals of CIHR, each institute develops its own set of strategic priorities and plans and, in the process, identifies areas of potential overlap with other institutes. We look at cross-cutting areas between institutes to see if there is potential for major impact. Eventually, we roll these up into large internal business cases that outline why each focus area should be a priority for the agency.

Once we have arrived at this stage, we tend to have involved many, if not most, branches of CIHR, its institutes, a good number of external partners, and the research community. So when we are ready to launch these initiatives, they have already been under both internal and external scrutiny, and we have a well-articulated sense of what we are trying to achieve. In the case of CEEHRC, the CIHR Institute of Neurosciences, Mental Health and Addiction (INMHA) was a real driver in the creation of the initiative, in close collaboration with the CIHR Institute of Genetics (IG). These CIHR institutes organised a number of consultative workshops with the broader research community and funding partners, and ultimately led the design of the goals and structure of CEEHRC.

We are aiming to do something that could not be accomplished by our main investigator-initiated discovery grant approach. Each partner that comes into this initiative is contributing a portion of the total. The reason this is attractive to the partners is that they have all self-identified this as a potential priority area, and by putting a little bit of money in they get to leverage that with what other partners are doing. Therefore, there is a significant return on investment, and we can accomplish what could not be accomplished by individual standalone programmes.

Are there any challenges that arise from the multidisciplinary nature of epigenetic research? How are these dealt with?

Something we are trying to encourage in our multidisciplinary teams is bringing together people from different backgrounds. In epigenetics you have people who bring in the basic science of epigenomic mechanisms and sequencing experience; others who bring expertise in a particular disease or health mechanism; and still others with a more clinical focus who are bringing in patient samples and diagnosis. You might even have people who have a broader focus and are trying to bring in cohorts or an epidemiological perspective. That's a lot to integrate.

We've decided to let groups self-assemble, tell us what their biggest challenges are, and then we try and support them to be aligned with the

CEEHRC fact file

LEADERS

- Institute of Neurosciences, Mental Health and Addiction (INMHA)
- Institute of Genetics (IG)
- Institute of Cancer Research (ICR)

CANADIAN PARTNERS

- Genome Canada
- Genome BC
- Genome Québec
- Fonds de recherche du Québec – Santé (FRQS)
- Other CIHR institutes

INTERNATIONAL PARTNERS

- Japan Science and Technology Agency (JST)
- French National Research Agency (ANR)
- German Federal Ministry of Education and Research (BMBF)

OBJECTIVES

1. Provide leadership on international coordination activities, like the International Human Epigenome Consortium (IHEC)
2. Support innovative research linking epigenetic marks to key questions related to human health and disease, including environment-gene interactions
3. Create an effective national network, with optimised access to critical infrastructure and sharing of technological developments and discoveries
4. Develop bioinformatics resources for epigenomic data sets, with links to parallel functional studies in human health
5. Increase research capacity in Canada for identifying epigenomic marks and relating them to human health, disease and environment-gene interactions

theme of translating epigenetic discoveries for health benefits. We try to put the mechanisms in place to support multidisciplinary research for those who are voluntarily self-assembling.

We have very explicitly tried to incorporate many of the lessons learnt in an early CIHR Strategic Initiative that was dedicated to supporting multidisciplinary research – the Regenerative Medicine and Nanomedicine initiative. One thing we did with CEEHRC was develop and launch a coordinated set of funding opportunities with different goals – and targeting different audiences – over a well-defined time course. This allowed many of the individual components to be put into place early. It is a question of not just expressing the ultimate vision, or the final goal you wish to achieve, but also providing the practical steps that will build one upon the other to actually reach that point.

Can you outline your role within the Consortium, and how your career path led you to your current position?

My research background is in neuropharmacology, and I worked for several years as a biotechnology analyst. I was recruited to CIHR to develop and lead an early strategic initiative programme focused on multidisciplinary research, because of my genuine interest in trying to find ways of better supporting scientists who are looking to integrate disciplines. It's easy for each institute to focus on their own activities and priority areas, but to work collaboratively requires someone who can move back and forth between them. When I was hired, they thought I was well-placed to relate to those other institutes and show that it was not just a neuroscience-dominated initiative.

At present, I have a significant role in helping the CEEHRC initiative develop, in my position as Associate Director of both INMHA and IG. But once all the defined funding opportunities are launched and funded, I expect the installed researcher capacity will take that forward. An example of this comes from our efforts as part of the International Human Epigenome Consortium (IHEC). CIHR – through the CEEHRC initiative – is a founding member of IHEC, and I currently serve as Chair of the IHEC Executive Committee. Ultimately, IHEC will have a much greater collective impact than any one of its member projects.

Why is the study of epigenetics particularly important for better understanding the causes of complex diseases such as cancer, diabetes, addiction and asthma?

I believe complex disease is one of the areas where the potential impact of epigenetics research is the greatest. These diseases are typically multifactorial, and likely the result of complex processes, including both genetic and environmental contributions. We have long been aware that there is a strong role for environmental factors in the development and expression of many complex diseases – even those with a known genetic predisposition.

In the years since the completion of the Human Genome Project, genome-wide association studies (GWAS) have become a very powerful tool for identifying specific genetic loci associated with human disease. While important insights have been gained for complex diseases, the underlying mechanisms and basis for many of these disorders remains frustratingly unclear. A broader perspective incorporating environmental influences in the control of gene expression is definitely needed at this point in time. There are a number of research groups looking to expand GWAS approaches with environmental or epidemiological data. Significantly, most of the GWAS disease-associated single nucleotide polymorphisms (SNPs) that have been identified come from outside the direct gene-coding regions – suggesting a key role for regulatory or functional control of gene expression.

Epigenetics provides a potential mechanism for understanding the interplay of the environment with the genome, and I think it is a particularly compelling model for how environmental influences during early development can have lifelong effects on human health (and perhaps even across generations).

CEEHRC recognises that epigenetics as a discipline poses many challenges; what are the major issues ahead, and how is the Consortium striving to address them?

Work in epigenetics is a little fragmented, with people often looking at it through a narrow lens. What we are trying to do is better integrate all the different areas, to understand if there are common underlying mechanisms that are broadly applicable.

There are certainly challenges when it comes to performing comprehensive epigenomic studies; they require access to state-of-the-art genomic sequencing technologies, and experience with rapidly developing approaches and methodologies. This is why one of the first funding opportunities launched by CEEHRC was our National Platform programme, where we sought to repurpose existing genomic sequence expertise and infrastructure for epigenomic purposes. Of critical importance in this undertaking was the support of the leading genomic centres themselves, and the funding agencies that invested in their infrastructure and operation (especially Genome Canada and the other members of the genome enterprise across Canada). There are also technological and methodological challenges in performing epigenomic analyses that can be limiting in certain fields. Neuroscience is a good example where it is difficult to obtain sufficient human tissue; this is where general attempts to reduce the amount of material required can have important practical benefits in facilitating research.

These needs reflect the various funding opportunity streams launched by CEEHRC. We have funded dedicated technology development opportunities, research capacity building and multidisciplinary team-based approaches to translate basic science research findings to health. Together, we can produce a much greater impact than an equivalent number of standalone projects

With the environment having such a significant impact on human health, is there a need for more collaboration with organisations responsible for environmental management?

Absolutely. We have engaged with a number of organisations who have a broader interest in applying epigenetic discoveries. Last year, for example, we convened a Best Brains Exchange with Health Canada to explore integrating epigenetic effects of food and environmental contaminants into risk assessments. It is very much on the minds of the CEEHRC co-lead CIHR institutes: how best to build on what we have created, and truly integrate the environmental component.

In Canada, have there been any recent breakthroughs in epigenetic research on the aetiology, treatment and prevention of chronic diseases?

This is certainly an area of great interest to many of the CEEHRC partners – especially INMHA, which has funded a number of pivotal findings in recent years in the area of suicide and epigenetics of mental health, as well as neurodevelopmental conditions. A very large programme has just been announced for the Canadian Consortium on Neurodegeneration in Aging – several teams have an epigenetic focus. CIHR is leading this initiative through its Institute of Aging and INMHA. Neuroscience is by no means the only area of Canadian epigenetic expertise – cancer and metabolic disorders also come to mind as areas in which I think Canada is particularly strong. Finally, however, I think it is important to emphasise that these findings often occur within the broader context of international partnerships.

The future of epigenetics

While Dr Eric Marcotte maintains that he is excited about all the possibilities that the field of epigenetics holds, here he summarises some of the areas that show the most immediate promise in terms of healthcare applications

CANCER

"Our understanding of the role of epigenetic marks in various cancer states continues to develop rapidly, and the area of 'cancer stem cells' (or more accurately, tumour-initiating cells) is one where epigenetics could play a very important role. This will likely take the form of better biomarkers and diagnostics – not only predictive of disease, but also treatment response. I think the potential is there to help identify the most efficacious targeted therapies for epigenetically-distinct cancer subtypes in the near future."

BIOMARKERS AND PERSONALISED MEDICINE

"More generally, I expect there will be an even greater impact in the development of appropriate biomarkers for common and chronic diseases. The early detection of predictive factors for chronic/complex diseases will be particularly useful in cases where there are currently no effective treatments. Epigenetics is therefore likely to play a pivotal role in the development of new personalised medicine approaches going forward."

DRUG AND TOXICITY SCREENING

"I can foresee how it is possible for epigenetics to be examined as part of the regulatory evaluation and assessment of new drugs and treatments – as well as for impacts on the environment. As our knowledge of epigenetic regulatory factors grows, epigenetic assays could potentially serve as more specific or accurate screens of biological effect than those that are currently performed (eg. potentially more relevant and specific than general genotoxicity screens for new compounds)."

HUMAN DEVELOPMENT AND BRAIN HEALTH

"Finally, I have also been struck by how strongly the epigenetic concept has been embraced by those studying early life events and the developmental origins of disease. The implications for neuroscience, mental health and addiction are potentially profound, and this is certainly an area of research strength in Canada. I know the CIHR Institute of Human Development, Child and Youth Health, along with the Institute of Gender and Health, are planning to launch a new Developmental Origins of Health and Disease (DOHaD) funding opportunity in January 2015."

International Human Epigenome Consortium

One of the key drivers underlying the initiation of the Canadian Epigenetics, Environment and Health Research Consortium (CEEHRC) was the growing interest in establishing an International Human Epigenome Consortium (IHEC). By building on a number of established initiatives from around the world – including much of Europe, the US, Korea and Japan – IHEC coordinates reference epigenome mapping and characterisation worldwide, implements the highest assay and data quality standards, facilitates data analysis, and provides free access to the epigenomes produced. It also serves to produce a 'gold standard' for assays, techniques and approaches; and massively increases opportunities for collaborative scientific impact.

CEEHRC's IHEC Data Portal has recently been launched, and offers an incredible resource for the epigenomics research community. Current plans in development promise to further enhance its value.

www.epigenomesportal.ca/ihec/
www.ihec-epigenomes.org

http://bit.ly/1tIGh4a