Summer 2019

Developmental Origins of Health and Disease Masterclass Series

A DEVOTION Network initiative

The DEVOTION Network has developed a Developmental Origins of Health & Disease (DOHaD) curriculum, which will be available to all trainees within the Children's Hospital Research Institute of Manitoba (CHRIM). The curriculum will include an overview of the DOHaD concept and its components, epigenetics, bioinformatics, methods, patient engagement, as well as future directions in the field.

The DOHaD Masterclass Series, a component of the curriculum, will feature guest speaker seminars, panel discussions, one-on-one mentoring, and training opportunities. The series is open to faculty, trainees, research technicians, support staff, stakeholders and patient partners. The June 6th Masterclass event was the first of the four-part series featuring invited keynote speaker Dr. Kristin Connor and local guest experts.

Watch the June 6 Masterclass Symposium and upcoming installments of the DOHaD Masterclass Series on the DEVOTION Network website: devotionnetwork.com.

Keynote Address

Dr. Kristin Connor is an Assistant Professor in the Department of Health Sciences at Carleton University. Dr. Connor's research aims to understand how the early life environment (namely nutritional, metabolic, and infectious exposures) influences maternal health and fetal/infant development, leading to chronic disease risk.

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Panel 1: **Read on page 3.**

Dr. Meghan Azad: Assistant professor, CHILD study co-lead, clinical DOHaD researcher

Dr. Meaghan Jones: Assistant professor, epigeneticist, basic science DOHaD researcher

Dr. Alex Singer: Associate professor, family doctor, EMR expert, DOHaD researcher

Panel 2: **Read on page 4.**

Dr. Shyamala Dakshinamurti: Associate professor, neonatologist, biomedical DOHaD researcher

Dr. Robert Schroth: Associate professor, practicing dentist, clinical DOHaD researcher

Dr. Liz Sellers: Associate professor, endocrinologist, clinical DOHaD researcher

The DEVOTION Network accelerates knowledge to action - within the area of maternal and child health - to prevent wellness and prevent chronic disease (focusing on asthma, allergy, diabetes and obesity) for Manitobans.

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KEYNOTE: DOHaD: What we do and don't know, where we want to be, and how we can get there

In her keynote address on June 6 at the DOHaD Masterclass Symposium, Dr. Kristin Connor guided her audience through the essential qualities and foundational evidence of the developmental origins of health and disease (DOHaD) field. One of those essential DOHaD qualities to understand where we are going, we have to know from where we have come.

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Lifecycle- The DOHaD Perspective that Spans Generations
DOHaD perspective examines more than just a lifetime. It includes past and future generations. This is reflected in the key term "life cycle" says Dr. Connor. Another foundational quality is the idea of development programming defined by Dr. Connor as an exposure or stimulus operating at a critical or sensitive period of development that could result in long-term effects on the structure or function of the organism. Most exposures or stimuli are biological factors, but are critically influenced by environmental and social contexts. DOHaD researchers need a perspective spanning generations *and* consideration of the interplay of such exposures.

> "DOHaD is complex, and resesarch takes time. It requires interdisciplinary effort to ensure that every person has the best start to life.- Dr. Connor"

History of DOHaD
This is not a new perspective, says Dr. Connor. Hippocrates (460 BC) could be called the first DOHaD thinker exemplified in his The Nature of the Child and Aristotle's (384 BC) The Golden Mean could be viewed as an early DOHaD text.


Ethel Margaret Burnside

Early epidemiological evidence "showed what happens in our early life may play a role in our later health outcomes". One example of such evidence is the Hertfordshire Records, maintained by Ethel Margaret Burnside (1877-1953). These records helped researchers like David Barker, one of the fathers of DOHaD, determine that low birth weight was related with infant death and to greater risk of dying from coronary heart disease, type 2 diabetes and altered blood lipids. Another foundational body of evidence, the Helsinki Birth Cohort (1924-1933 and 1934-1944), helped researchers determine that size at birth and growth trajectories can influence outcomes later in life and that these factors are the result of something going wrong in a normal process, thus not pathological. Evidence from the Dutch Hunger Winter (1944) and the Great Chinese Famine (1959-1961) showed that external factors can also shape later life outcomes. The meticulous records kept in these periods and beyond helped researchers link the timing of exposures outcomes the offspring would experience as an adult.

Critical Windows
These famines helped establish an understanding of "critical windows", sensitive period during development where there is phenotypic plasticity. The resultant phenotype is influenced by interactions between the (epi)genome, microbiome and environment as well as the dose and timing of exposure. The critical windows can be leveraged for intervention.

Understand Mechanisms, Design Interventions
Understanding the mechanisms operating in these critical windows is essential for a useful intervention. Dr. Connor shared an example: exposure to glucocorticoids during gestation. If women experience stress during pre-pregnancy or pregnancy, the placental glucocorticoid barrier is compromised at inappropriate times and is associated with higher levels of glucocorticoids in fetal circulation, shorter gestational level, and altered stress responsiveness in the offspring as children and adolescents. A naturally occurring example of this is the Ice Storm (1998) in Quebec, which caused power outages for up to 40 days. Researchers followed the mother-offspring dyads and found that offspring whose mothers experienced the ice storm had averse language and cognitive effects as well as short gestational length and lower birth weight. Objective maternal stress was associated with altered DNO methylation in adolescents and affects immune regulation and metabolic function. Thus, stress prevention intervention may contribute to optimal health.

Future Opportunites and Collaboration
Studies such as these, as well as much of DOHaD research, has looked at single variables in limited contexts through a biomedical lens. There are huge opportunities for advancement such as developing a comprehensive list of exposures, their mechanisms, and how these exposures effect risk trajectories as well as including more diversity in DOHaD research like men and minority populations.

> If DOHaD researchers leverage collaboration with knowledge translation experts, they could streamline DOHaD messaging, help engage policy makers and work to influence clinical practices by engaging directly with people providing care.

One way to take advantage of this opportunity is to collaborate with other disciplines, using a positive, strength-based perspective, rather than a focus on pathology. If DOHaD researchers leverage collaboration with knowledge translation experts, they could streamline DOHaD messaging, help engage policymakers and work to influence clinical practices by engaging directly with people providing care. Working with patient engagement professionals can help ensure DOHaD research addresses areas that important to the public, stakeholders, policymakers, and others. Patient engagement and collaboration with experts in other health fields will add a diversity of perspective. This diversity can help researchers design projects that are complex and multi-dimensional, recognize that an environment or exposure that is suboptimal for one group or person may be neutral or beneficial for another, use a multigenerational lens, and work to understand how and to what extent social determinants of health explain health variance.

DOHaD research stands to gain from intra-field collaboration. Such work could harmonize measures, ensure diverse populations are studied and tackle issues like strengthening animal models to ensure findings are translatable, creating sustainable and effective DOHaD-based interventions, developing tools that help predict resilience and risk beyond adverse events, and influencing policy development.

With multidisciplinary collaboration and a strength-based perspective, DOHaD researchers have opportunities to study big issues, influence policies, impact clinical practice and ultimately, improve the health of Canadian families.

Panel 1: Perspectives on DOHaD

Dr. Singer, Dr. Azad, Dr. Jones

Each researcher discussed their interpretation of DOHaD, lessons learned, and opportunities for DOHaD work in Manitoba.

Dr. Alex Singer

Family Physician, associate professor, DOHaD researcher

Dr. Singer sees family medicine as the clinical home of DOHaD because family physicians care for people throughout their life cycle, through disease origins and the disease itself. He sees the "bench" of Family Medicine research as administrative clinical data. He has done pragmatic clinical trials embedded in clinical care, a promising model research. Dr. Singer sees an opportunity to better understand health outcomes and the spectrums of disease in Manitoba using clinical data. This requires using clinical data to tell a story, rather than just present numbers. However, if we understand clinical data's limitations and modernize the healthcare data systems, clinical data can be harnessed to help us understand DOHaD in Manitoba and can improve the health of Manitobans.

> "An important lesson for DOHaD researchers- What is the story you're trying to tell people? Knowledge translation boils down letting the data tell a story, using the data to provide the message." - Dr. Singer

Dr. Meaghan Jones

Assistant Professor, epigenetist, DOHaD researcher

Dr. Jones is looking at windows and risks of exposures that are biologically embedded through interaction with the genome and epigenome. Changes in the environment shift the epigenome and change your risk trajectory. Opportunities for DOHaD growth include developing the tools and collaborations to look at epigenetic mechanistic relationships and develop interventions and changes to clinical care that contribute to better health for Manitobans.

> "Important to DOHaD is this idea of a window of opportunity in early development when an environmental exposure is *biologically embedded*...The mechanism behind biological embedding is epigenitic in nature." - Dr. Jones

Dr. Meghan Azad

Assistant Professor, DOHaD researcher

Dr. Azad's understanding of DOHaD research in based in fetal health, the microbiome, and epigenetics. Her focus in on the first 1000 days, begining at conception. As the co-lead of the CHILD cohort longitudinal study in Manitoba, Dr Azad has learned that DOHaD research requires high quality, multidisciplinary longitudinal studies and retention in those studies is essential. Retention is made easier by family engagement, excellent staff, and good funding. What's exciting is that there are many opportunities to shift the degree of risk for healthier outcomes. To develop these interventions, we need to understand the mechanisms and external factors that contibute to DOHaD.

> "[Microbial cells] have important roles in keeping us healthy... Can we change our mircobiomes and can these changes happen as early as the preconception period?" - Dr. Azad

L to R: Drs. Meaghan Jones, Meghan Azad, Alex Singer.

Panel 2: Perspectives on DOHaD

Dr. Schroth, Dr. Sellers, Dr. Dakshinamurti

Each researcher discussed their interpretation of DOHaD, lessons learned, and opportunities for DOHaD work in Manitoba.

Dr. Bob Schroth

Dentist, associate professor, DOHaD researcher

When people question Dr. Schroth's place in DOHaD, he reminds them that outcomes for health and disease aren't necessarily decades down the road, they can be in early childhood and the developmental origins of strong oral health begin before conception with maternal health. This area of healthcare is a perfect place for risk assessment and early prevention and intervention from a DOHaD persepective, particularily around prenatal and maternal health and infant feeding. Exploring the oral microbiome is another opportunity for oral health research from a DOHad perspective. DOHaD work will be strengthened by multidisciplinary collaboration and cohort studies with strong, validated measures.

> "We need to multidisciplinary and partner with others....Are there shared disease outcomes that could be studies together with joint shared cohorts?" - Dr. Schroth

Dr. Shyamala Dakshinamurti

Neonatologist, associate professor, DOHaD researcher

Dr. Dakshinamurti struggles to identify as a DOHaD researcher because her research, catastrophic neonatal illness, particularly hypoxia and persistent pulmonary hypertension of the newborn (PPHN), doesn't always fit in traditional perceptions of DOHaD. Her participants are the sickest children and experience high mortality. They're difficult to study and thus animal models are often used, but with limited generalizability. If this research is to grow in Manitoba, a translational approach using more appropriate animal models and population studies must be adopted and will result in more useable findings.

> "If you are looking for what makes the greatest impact on DOHaD, I think we do have to open our eyes to the vanishing population that doesn't have a voice." - Dr. Dakshinamurti

Dr. Liz Sellers

Endocrinologist, associate professor, DOHaD researcher

For Dr. Sellers, the Next Generation cohort study is a wonderful example of DOHaD research. NextGen looks at the offspring, from conception onward, of mothers and fathers who have youth-onset type 2 diabetes (T2D). Of all 268 offspring, 14% have T2D. Of those who are aged 10+, 37% have T2D. Of those 15+, 58% have T2D. Now, Next Gen collects data from women before they're pregnant to inform interventional and mechanistic studies. There is an opportunity to study the whole lifecycle and intergenerational effects of T2D with all the perspectives available to us, including community members, social sciences, and biological sciences.

> "We need to look at the lifecourse with all the expertise we bring... We need to look at the individual and family level, the community level and the systems level."- Dr. Seller

L to R: Drs. Shymala Dakshinamurti, Bob Schroth, and Liz Sellers