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OPEN ACCESS GOVERNMENT

NORTH AMERICA ANALYSIS

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KEEPING PESTS UNDER CONTROL REQUIRES ONGOING RESEARCH

CHRIS BENTLEY, AGRICULTURAL RESEARCH SERVICE – USDA, EXPLAINS WHY RESEARCH MUST CONTINUE TO PROTECT CROPS FROM PESTS AND INSECTS

IN THIS ISSUE

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INTRODUCTION

Welcome to this summer edition of Adjacent Open Access – North America Analysis. In this supplement we highlight several articles from organisations within the U.S and Canada. We focus on topics such as healthcare, the environment and energy, highlighting a couple from each country.

The U.S section starts with an interview with Dr Percy Ivy of the National Cancer Institute (NCI), National Institutes of Health (NIH). The interview outlines the importance of clinical trials within cancer research and the NCI's National Cancer Programme. Gynaecologic health and research is also highlighted in a feature by Lisa Halvorson of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), NIH. Halvorson answers our questions about why gynaecologic health is important and the target areas of research for the institute.

We also shed light on agricultural production in the U.S and the importance of pest control. An article from Chris Bentley at the Agricultural Research Service (ARS), USDA explains why research must continue to protect crops from pests and insects. Other articles from General Fusion and the Canadian Nuclear Association detail the opportunities provided by fusion energy and its potential as an energy source.

In the Canada section, Carrie Bourassa, Scientific Director of the Canadian Institutes for Health Research (CIHR), Institute of Aboriginal People's Health writes about the issue of poor health among Indigenous communities and how research is key to tackling it.

We also look at Cancer research in Canada, with an article from Rob Nuttall and Shawn Chirrey of the Canadian Cancer Society. The article outlines how fighting the disease requires ongoing support for research and screening. We also look at how Health Minister, Jane Philpott aims to improve the lives of Canadians through the governments Health Accord Plan.

Further thought is given to renewable energy sources in Canada. Minister for Natural Resources, Jim Carr, sets out in his article how Canada's clean energy strategy is charting a clear course by accelerating the transition to renewables. The article highlights how Canada is increasingly focused on developing renewable energy resources, as well as oil and gas.

I do hope that you find this North America Analysis thought provoking and useful and as always I welcome any comments you may have. ■

Laura Evans
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OPEN ACCESS GOVERNMENT

Cancer research and training take centre stage in NCI's work

Open Access Government spoke to the US National Cancer Institute's Dr S Percy Ivy about the importance of clinical trials and the agency's role in cancer research and training

The National Cancer Institute (NCI) is one of 27 institutes that make up the National Institutes of Health (NIH). The NCI is the US federal government's primary agency for cancer research and training, and coordinates with the National Cancer Program, which supports research, training, health information dissemination, and other programmes with respect to the cause.

Cancer is a term that everyone worldwide is aware of, with new research suggesting that 1 in 2 people will be diagnosed with cancer in their lifetime. The NCI estimated that in 2016 1,685,210 new cases of cancer would be diagnosed in the US and that 595,690 people would die from the disease. However, the number of people living beyond cancer diagnosis reached nearly 14.5 million in 2014 and is expected to rise to almost 19 million by 2024.

Research is an integral (but not the only) part of the work conducted at the NCI. Research helps to learn more about various forms of cancer and how to treat and prevent the disease. Clinical trials are research that involves people, in order to help find to find new ways to improve treatments and the quality of life for people living with the disease.

Here Editor Laura Evans speaks to Dr S Percy Ivy at the NCI, about the role of clinical trials and how cancer research has evolved over the years.

"Cancer clinical trials are essential for advancing the treatment of patients. These trials are a controlled framework in which selected populations of patients with cancer can be treated in a clinical research setting, based on results of earlier studies," explains Dr Ivy. "Essentially, for patients the goal is to prolong their life and, hopefully, be cured of the disease.

"The trial accomplishes several objectives from a medical and scientific point of view; we hope it changes the standard of care and improves the care and management of cancer patients. Patients are looking for response, slowing of their disease and improvement in their overall quality of life, and in some instances even remission and cure.

"I believe that clinical trials are essential for the advancement of cancer treatment. Networks of clinical investigators allow clinical researchers to evaluate large cohorts of patients, and more efficiently evaluate new treatments together across the country," Dr Ivy adds.

Developing new cancer treatments

The Cancer Therapy Evaluation Programme is one of the many programmes within the NCI and is focused on developing new cancer treatments. The clinical trials are made up of different phases which are used to detect how cancer responds to specific treatments.

As Dr Ivy outlines further: "Within the Cancer Therapy Evaluation Programme there are 2 very large programmes. The first is the Experimental Therapeutics Clinical Trials Network, made up of academic investigators across the US and Canada, who perform early phase clinical trials. The goal of those trials is to determine how to use a drug, what the drug properties are, and how it should be used in humans, as well as developing preliminary information on how the cancer responds to specific therapeutic interventions.

"The other large group in the US is the National Clinical Trials Network," she adds. "This is a group of more than 3,000 investigators who perform much larger randomised phase 2 and phase 3 trials. They are looking for signs of activity, efficacy and survival or response to a treatment or combination treatment that will lead

to a pivotal trial. The goal is to move to phase 3 trials that may result in licensing the treatment for a specific disease indication."

Orphan diseases and rare types of cancer

The NCI is aiming to find treatments for all types of cancer; however, they also focus on rare forms of the disease besides what are known as the big 4 – colon cancer, breast cancer, lung cancer and prostate cancer. The rare forms are ones that are not as actively studied or used in clinical trials by pharmaceutical companies and have less than 200,000 cases per year, although this landscape is changing.

> "I believe that clinical trials are essential for the advancement of cancer treatment. Networks of clinical investigators allow clinical researchers to evaluate large cohorts of patients, and more efficiently evaluate new treatments together across the country."

"Orphan diseases, are defined as affecting fewer than 200,000 cases a year, and have not been as actively studied," says Dr Ivy. "In the past these orphan cancers have been much less attractive targets for pharmaceutical companies, so the NCI has filled this niche as an unmet medical need. Pharma is also changing and starting to work more in niche diseases. As we find that cancers, for example breast cancer, are really made up of a group of biologically distinct diseases that require different treatments, the challenge is to provide effective treatments for all different kinds of cancer and the challenge for pharma is to define a sustainable niche market.

"The goal of the NCI is to provide those treatment opportunities to the U.S public. The US Congress recently passed a bill called the '21st Century Cures Act' that will fund $4.8bn in medical research with approximately $1.8bn cancer related research. This means that we are able to develop synergies between programmes and initiatives that can effectively use that money in service of the public. We will do that collaboratively with researchers, organisations and companies and with our academic co- investigators, with the primary goal to make treatment for cancer widely available and accessible no matter how rare your disease is."

A revolution in cancer research and training

As our knowledge of cancer evolves, new ways to treat the disease are also established. Along with new technology and key innovations, research and clinical trials are able to understand the best treatment for a specific type of cancer. Dr Ivy explains that cancer research is in the middle of a revolution, with new therapies such as precision medicine and immunotherapy coming to the forefront.

"With the exception of immunohistochemistry for PDL1, there are no biomarkers to select patients to receive anti PD-1/PDL-1 immunotherapy," she says. "The tumours that have responded to these so-called checkpoint inhibitors have been those that were treated in the past with other immunotherapy agents, especially melanoma and renal cell carcinoma.

"However, there are areas in immunotherapy treatment that clearly stand out for the favourable response rates that have been seen, including lung cancers and Hodgkin's lymphoma, as well as some rare diseases, such as Merkel cell tumours. However, the utility of the PD-1 biomarker to identify patients who are likely to respond is limited, and more work is needed to develop more robust biomarkers. What is becoming very clear with immunotherapy, as is the case for most effective cancer treatments, is that it needs to be combined with other therapies, including chemotherapy, molecular therapies and radiation therapy.

"Cancer treatment globally will be changing. In addition to the scientific challenges, the high cost of treating cancer patients with immunotherapies and other therapies remain an issue. We must ensure that academic clinical research in the public interest is available widely and not simply to those who can afford it." ■

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Identifying pancreatic cysts that might turn into cancer

There are many challenges associated with identifying potentially cancerous pancreatic cysts. Here, Dr. Annabelle L. Fonseca et al explain

Doctors and patients usually do not know that a problem was even there. It is estimated that millions of people have pancreatic cysts (2% to 13% of the general population in the United States undergoing imaging). Because of the prevalence of these cysts, physicians often see them in patients undergoing diagnostic imaging, but the patients commonly do not have any symptoms from the cyst itself. This usually represents a conundrum for the doctor and patient because the cysts were not expected. The imaging is usually ordered for reasons unrelated to the pancreas (like gallbladder stones or other benign or malignant conditions). The challenge lies with the fact that the vast majority of pancreatic cysts are benign, but a small proportion of cysts can turn into pancreatic cancer, one of the deadliest diseases that afflicts humans.

The common initial reaction: How do I get rid of it?

Currently, the only way to cure pancreatic cysts is with major surgery that may involve removal of part of the stomach and bowel, along with the pancreatic cyst(s). The surgery can be life-altering, and the procedure carries a small risk of death. Even after considering the morbidity and mortality of the surgery, many patients receive too much treatment (also described as over diagnosis) for an otherwise benign condition, largely out of fear that a cancer might be lurking.

Refocusing the question: What are the needles in the haystack?

Techniques to characterise these pancreatic cysts are urgently needed to spare patients with benign cysts from unnecessary surgery and to identify the patients with potentially malignant cysts who need surgery. In our analogy, the haystack represents all the patients with pancreatic cysts. The needles represent the small number of patients who have cysts that may turn into cancer.

There are multiple forms of pancreatic cysts. The most common types that can turn into pancreatic cancer are

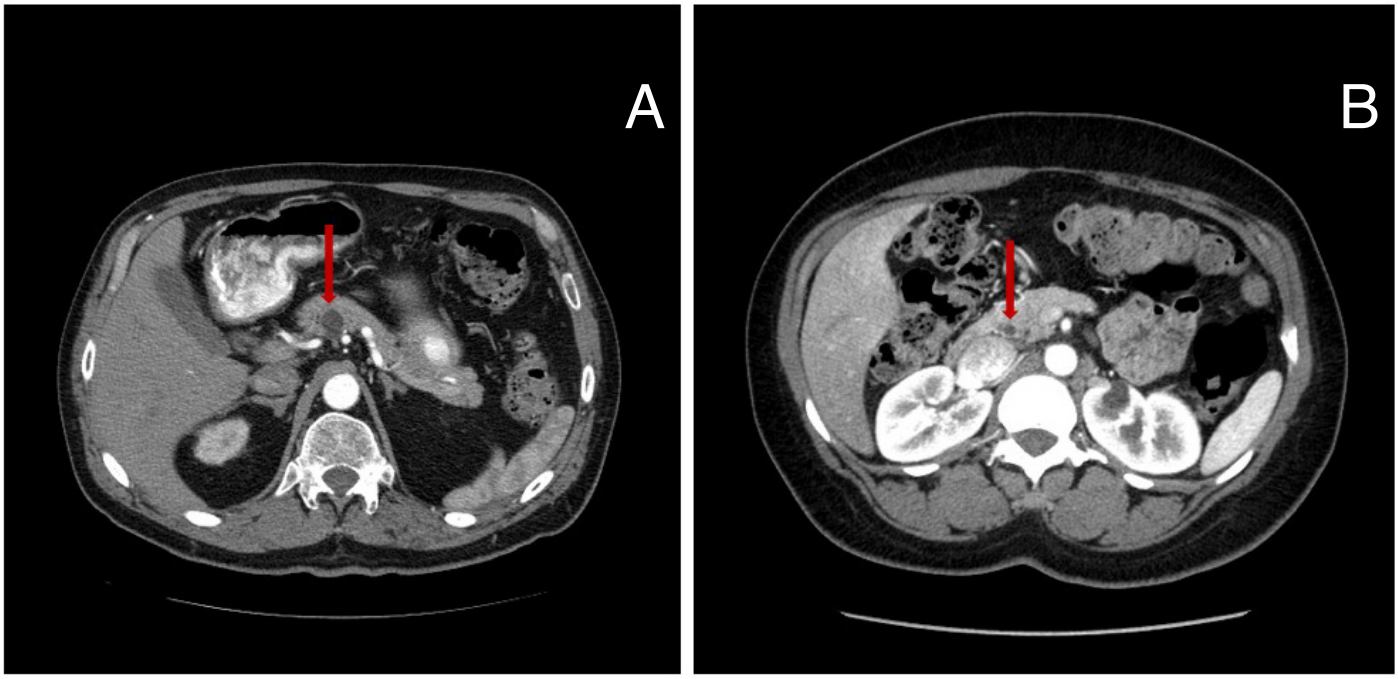

Fig 1: Image A shows an IPMN with low grade dysplasia. Image B shows an IPMN with high grade dysplasia. Both cysts have smooth walls and look generally "benign". The challenge lies in differentiating between these 2 pre-operatively, so that the patient in Image A can be prevented from having a potentially unnecessary operation.

intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs). Studies have shown that surgical removal of IPMNs or MCNs when they have not yet turned into cancer results in 5-year survival rates of 90-100%. Conversely, if any cancer component is found in the cyst after surgery, the survival rate is reduced by half. The current thinking by experts is that benign cysts exhibit a cellular pattern known as low grade dysplasia, and that cysts with a higher likelihood of becoming cancer have high grade dysplasia. Currently, the only reliable method to get the correct diagnosis involves major surgery so that a pathologist can see the entire tissue specimen; a small biopsy is not usually sufficient for an accurate diagnosis. So how do we select patients with pancreatic cysts for surgery?

The current approach: More hay than needles

The current approach to deciding which patients should receive surgery involves the use of consensus guidelines: If a patient meets the criteria, which a group of experts decide on, then the patient is recommended to undergo surgery. This approach does not involve evidence based clinical trials, unfortunately. Although the consensus guidelines have a relatively high sensitivity of around 90% or more (it can detect most cysts with cancer), there is a relatively low specificity of 50-60% (it incorrectly classifies benign cysts as high risk), feeding the over diagnosis problem. How can we accurately identify the high risk pancreatic cysts non-invasively?

A multi-faceted, biophysical approach to the problem

In the next few articles, we will explore the approaches to better identify high risk pancreatic cysts. Our approach involves the use of genetics, proteomics, physics, and math to overcome the current challenges that pancreatic cysts pose to physicians, patients, and the general healthcare system.

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Asbestos exposure can cause significant risks to health

Dr. Christopher P. Weis of the National Institutes of Health, shares with Editor Laura Evans the dangers of long term asbestos exposure

Asbestos is a term used to describe a group of 6 naturally occurring minerals that were mined and commercially marketed for a wide variety of products. Asbestos is just a small subset of dozens of naturally occurring elongated minerals that can cause disease if people come into contact with them on a daily basis. In the U.S exposure to these materials is fast becoming a major health problem. Although the 6 commercial forms of asbestos are regulated in the U.S for occupational exposure, some people argue that those regulations don't go far enough to protect the public because they are outdated.

Open Access Government Editor, Laura Evans spoke to Dr. Christopher. P. Weis, Toxicology Liaison and Senior Science Advisor for the National Institute of Environmental Health Sciences (NIEHS) in Bethesda, MD, about the many health problems asbestos exposure can cause and the importance of raising awareness.

"Commercial asbestos is a silicatious mineral containing magnesium and oxygen that can exist in a variety of mineral forms," explains Weis. "It is made up of long thin fibrous forms of minerals or rock. It's the shape of those minerals, their long, thin nature, along with other physical-chemical characteristics, which causes them to be very poisonous.

"The shape is important because these long particles can make their way deep into the lung by travelling along the laminar flow of the air, as it is breathed in. Since they are made out of rock, they don't dissolve easily, so the lung has a very difficult time removing, dissolving and eliminating them. When the materials that contain asbestos are disturbed or damaged, fibres are released into the air. Once these particles are then breathed in, they can have a devastating impact on a person's health. Although sometimes the health problems do not arise until later in life so it's often hard to tell where the exposure occurred or if it was even asbestos exposure in the first place.

"When someone breathes in asbestos, it causes a series of inflammatory reactions in the lung. When the cells that normally remove particles from the lung cannot remove these elongated mineral particles, they send out signals called cytokines, that trigger inflammation and the formation of reactive oxygen species, which results in fibrosis or scar tissue forming in the lung," Weis says.

"Essentially, when asbestos is breathed in it causes a series of biochemical responses that further aggravate the problem. This can lead to a variety of diseases including asbestosis, lung cancer, and a very lethal and aggressive form of cancer called mesothelioma.

"Importantly and frequently, asbestos may cause non-cancer diseases that progress and become debilitating later in life and that we see a lot of that going on today, in several areas, there seems to be an epidemic of that non-cancerous disease associated with asbestos," he adds.

Problems caused by asbestos exposure

Mesothelioma is an extremely aggressive form of cancer that is almost exclusively related to asbestos exposure - often referred to as Meso. If someone gets Meso it's almost certainly because they were exposed to asbestos. One of the main problems with diagnosis is not always knowing when exposure happened and how, as Weis explains.

"Like most exposures there is a dose-response relationship, the higher the dose the more quickly and more severe the disease. That said, there are many

cases of short term exposure that result in disease later in life, the time between exposure and disease is called a latency period. Exposure can occur today or tomorrow, and they don't see the effects of that exposure for months or years and sometimes even decades, which can be problematic for many reasons.

"It's often difficult for physicians to diagnose the cause of the disease because the patient affected doesn't even remember being exposed in some cases. They may never even know that they were exposed until they are much older and could develop lung cancer or a non-cancer disease that could be lethal."

Asbestos-related diseases from exposure have become a major problem in the U.S. People assume that because the mineral is regulated that the problem is under control, however this couldn't be further from the truth. There are still many ongoing exposures to non-regulated asbestos that can cause debilitating or lethal diseases.

"There is a growing epidemic of asbestos-related disease in the U.S and worldwide that is going on un-addressed," says Weis. "This is because we are still measuring asbestos the same way we did back in the late 1800's. The Environmental Protection Agency, under recent revisions to the Toxic Substances Control Act has proposed regulation of the 6 forms of asbestos using assumptions that came into play decades ago. Unfortunately, regulations have not evolved with our understanding of how the disease has occurred.

"Many elongated mineral forms that occur naturally pose public health hazards," adds Weis. "They just simply have never fallen under any regulatory map in this country and that's unfortunate because the exposure to these non- regulated forms is increasing nation-wide.

"One example of this is a tragedy that occurred in a small mountain town in Montana called Libby. Several hundred people were killed and thousands injured by a form of asbestos that was not regulated. There are also cases of similar exposure that are not as focused as the occurance in Libby, such as the use of asbestos-bearing gravel on roads and for construction materials in California, Nevada, and in the upper United States, for example. The dust from the roads can contaminate vehicles, migrate into homes, and provide a source of ongoing exposure that may last for years."

Raising awareness to the risks of asbestos exposure

Raising awareness of the health problems caused by asbestos exposure is key to ensuring people are aware of the risks. Especially as there is such a close link between exposure and lung disease. Some people will be unaware, for example, that if you smoke and work in places where you are likely to be exposed to asbestos, you run a greater risk of developing lung cancer.

Without people knowing the true damage that asbestos exposure could cause, they are at risk. Weis highlights how the incorrect assumption that asbestos is regulated puts people at risk.

"Awareness is probably one of the most important things, but the only way to really reduce the risk is to break the exposure pathway. For example if there is a residential development in an area known to have asbestos – we have one just south of Washington DC for example – and one is aware of the fact that basements and houses are being built on naturally occurring asbestos, there are many steps that can be taken to minimise or eliminate the exposure. However, without knowing about this problem and without taking the necessary actions to understand what the exposures are, there is really no way to eliminate the exposure and therefore the disease.

"The key thing to remember and think about is that asbestos exposure occurs to a wide variety of elongated minerals outside of the 6 that are regulated. Until we understand that and take active measures to protect public health for the un-regulated forms of asbestos, the health epidemic that is increasing worldwide and in this country will continue," Weis concludes. ■

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Adverse health effects of hazardous asbestos waste

Hazardous asbestos waste causes serious problems in communities in the U.S., Ian A Blair, Penn Superfund Research and Training Program Center details

The community of primary interest to the Penn Superfund Research and Training Program (SRP) Center is surrounded and potentially impacted by the BoRit EPA region 3 Superfund site. The site is located in the Ambler Borough, Upper Dublin and Whitpain townships in Pennsylvania.

This community has a long history of impact from hazardous asbestos waste. The waste disposal site is proximate to at least 2 very different types of communities: the relatively poor communities of West (predominantly African American) and South (Italian immigrant) Ambler which adjoins the site raising issues of environmental justice. The asbestos fiber used was predominantly chrysotile, which is the fiber considered to be a major cause of mesothelioma in the US.

It is of significant concern that in the Ambler zip code 19002, where the BoRit site is located, a cluster of mesotheliomas has been observed. In 1881, Henry G. Keasbey and Dr Richard Mattison moved their pharmaceutical company to Ambler, known initially for the production of milk of magnesia. Dr Mattison discovered that milk of magnesia (magnesium carbonate) could be combined with asbestos to make pipe insulators and shingles. The Keasbey and Mattison Co. was the leading manufacturer of asbestos textiles and products until it was acquired by England's largest asbestos company, Turner Newhall, Ltd., which manufactured asbestos textiles and products in Ambler from 1934 to 1962. Asbestos-containing waste from the plant was dumped in several surrounding areas, a practice that continued when CertainTeed Corporation and Nicolet Industries took over in 1962. CertainTeed ceased operations in 1974, followed by Nicolet in approximately 1988. Site remediation by the EPA under the Superfund Programme began in 1993. This remediation has involved capping the asbestos piles, adding a soil layer and hydroseeding. However, 3 other contaminated sites, in total about 32 acres and up to 42 feet deep, collectively known as the BoRit Site, and the abandoned plant site itself continue to present an unremediated hazard. The BoRit site was added to the EPA's National Priorities List of the most hazardous waste sites on April 9, 2009, making it eligible for cleanup, using the federal Superfund Programme funding.

- **Can asbestos be remediated?**
- **Is asbestos transported by water?**
- **Why is there a cluster of mesotheliomas among women in Ambler?**
- **Is there a genetic pre-disposition to asbestos-induced mesothelioma?**
- **Can asbestos-induced mesothelioma be prevented?**
- **Is it possible to develop blood tests for asbestos exposure and mesothelioma?**

Figure 1: Six questions posed by BoRit Community Advisory Group to Penn's Center of Excellence in Environmental Toxicology (CEET)

Research to reduce effects of hazardous asbestos in the Penn SRP Centre

Despite clean-up efforts, there is considerable residual community concern about the effectiveness of the remediation and the health effects of potential exposure to chrysotile asbestos. This has led to 6 major concerns being brought to the attention of Penn's Centre of Excellence in Environmental Toxicology (CEET). Dr Trevor Penning as Director of the CEET engaged his long-term collaborator Dr Ian Blair to establish a SRP programme configured around these community concerns (Figure 2).

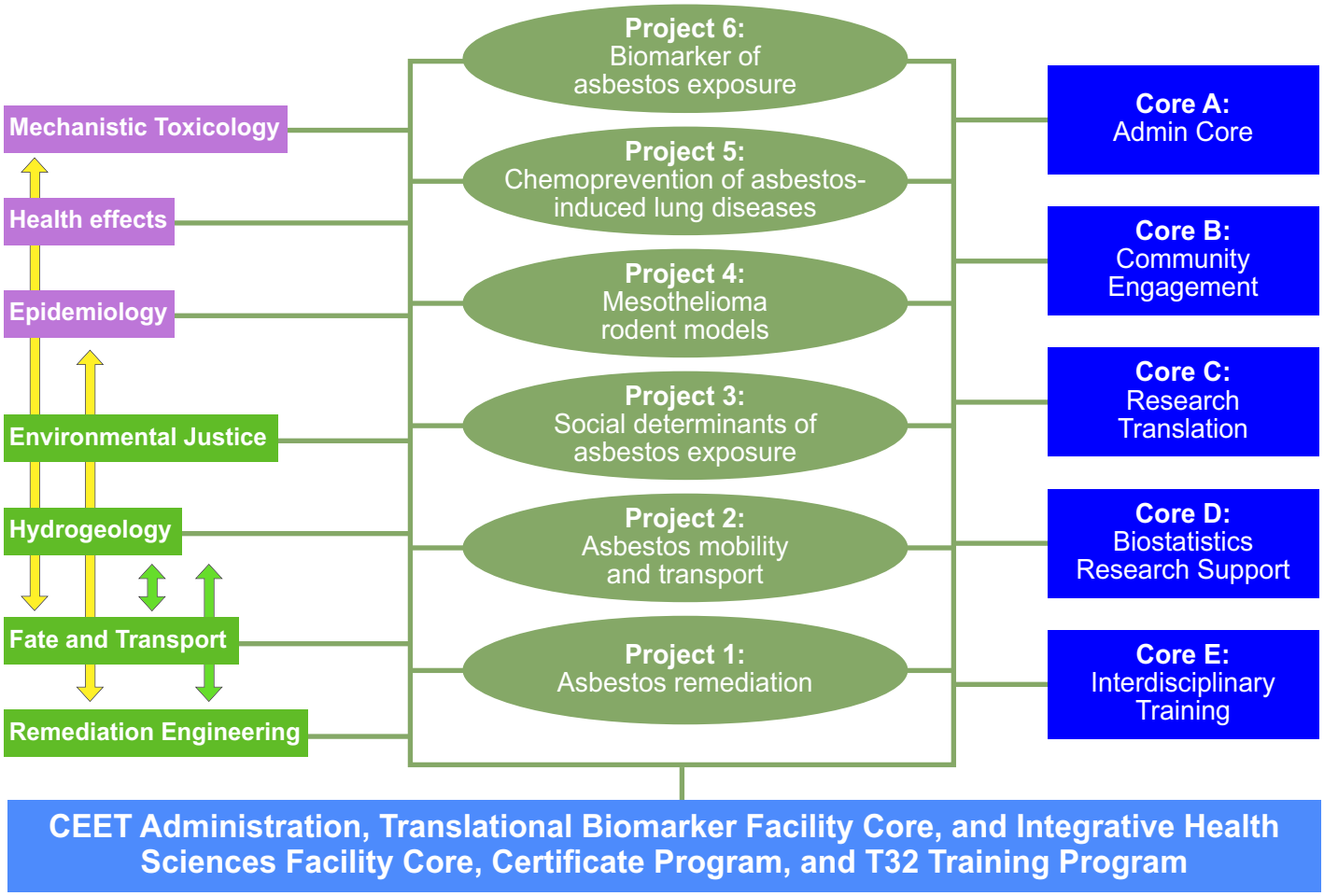

Figure 2: Organization of the Penn SRP Center

Project 1, which is one of the 2 environmental science projects, underpins all the other projects.

Project 2 assesses the physics that govern how asbestos fibers move through and become trapped in soil. The project works closely with **Project 3**, as community exposure to remediated asbestos in Ambler (and other areas) is strongly determined by the transport pathways of asbestos fibers in the environment.

Project 4 will enhance our understanding of the pathogenesis of asbestos-related disease, specifically malignant mesothelioma, using genetically defined mouse models.

Project 5 will develop chemoprevention strategies to prevent mesothelioma.

Project 6 will develop sensitive and specific serum biomarkers of asbestos exposure to assess potential inter-individual risks of developing mesothelioma or lung cancer. The six projects are supported by four conventional Cores as well as the Research Core in Biostatistics.

Relevant Publications

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Cancer immunotherapy: Are we ready to take the next big step?

Dr. Kularatne, vice president of Research and Development at On Target Laboratories highlights cancer immunotherapy as the treatment of next generation to cure cancer

Immunotherapy is starting to play a major role in cancer treatment and it was named as "the breakthrough treatment of the year" in 2013. Cancer immunotherapeutic agents have earned over $60 billion revenues in 2016 and is expected to have a market value of about $80 billion in 2020. Thus, pharmaceutical companies are evaluating new ways to use immunotherapy to treat cancers and develop a wide range of immunotherapeutic drugs for various cancers.

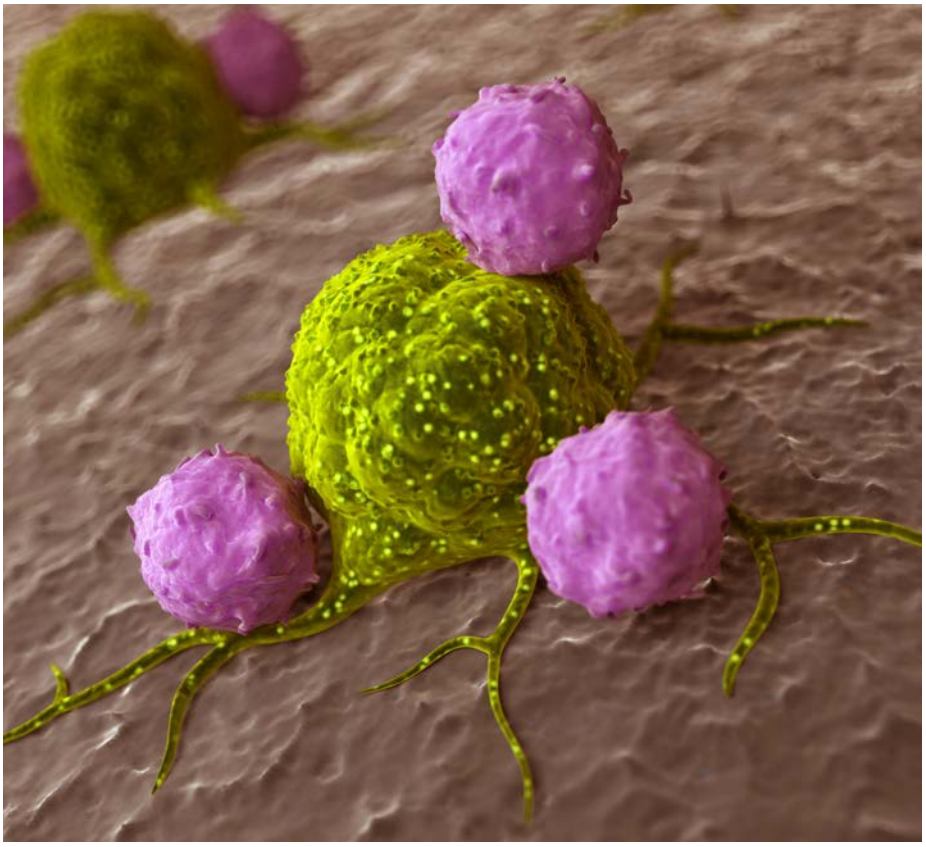
Cancer immunotherapy can be defined as "use of a person's immune system to fight against cancer either by teaching it to work smart or stimulating the immune system by man-made immune components to attack cancer cells". It can also be defined as a "treatment for cancer by inducing, enhancing, or suppressing an immune response". However, the therapeutic outcome of the immunotherapeutic agents highly depends on the type of cancer, type of the immunotherapy, and treatment modality (mono or combination therapy).

Whilst the immune system is supposed to eliminate cancer cells within the body, it is not able to differentiate cancer cells from normal healthy cells. Cancer cells also express CD47 (Cluster of Differentiation 47) as healthy cells do. CD47 is also known as integrin-associated protein (IAP) and it produces a protein named signal-regulatory protein alpha (SIRPα) that sends don't eat me signals to the macrophages, a type immune cells, and do not activate to attack me signals to T-cells, another type of immune cells. On the other hand, if it recognised that the response might not be strong enough to destroy the cancer cells. Moreover, cancer cells recruit immune cells such as tumour-associated macrophages, a subtype of immune cells, which keep the immune system in check and chase away T-cells that come to attack the cancer cells.

Cancer immunotherapeutic agents can mainly be classified into 4 major categories: Monoclonal antibodies, immune checkpoint inhibitors, cancer vaccines, and non-specific immunotherapies.

Monoclonal antibodies in the immunotherapeutic sector can be defined as man-made antibodies that induce antibody-dependent cell mediated cytotoxicity (ADCC), by recruiting immune cells or activating the complement system to attack tumour cells. Recruitment of immune cells can also be accomplished by designing a bispecific antibody that has 2 different monoclonal antibodies with one to recognise biomarker on cancer cells and a second to recognise biomarkers on immune cells. Blincyto (Blinatumomab) is a bispecific antibody that is used to treat acute lymphocytic leukaemia or B-cell lymphoma. It binds to the CD19 protein on B-lymphocytes and to CD3 on T cells. By binding to both of these biomarkers, blinatumomab brings T cells closer to cancer cells and eliciting an immune response to diminishing cancer cells. Blincyto was developed by Micromet and then later acquired by Amgen, which has conducted further clinical development and is predicted to generate sales revenues of over $1.5 billion in 2019.

The second class of immunotherapeutic agents is immune checkpoint inhibitors that take the 'brakes' off the immune system to attack the cancer cells. The immune system has checkpoint proteins, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein (CTLA), that help to keep it from attacking other normal cells in the body. Unfortunately, cancer cells take advantage of these checkpoints to avoid being attacked by the immune system. A joint effort by Bristol-Myers Squibb and Ono Pharmaceutical yield to launch blockbuster PD-1 inhibitor, Opdivo (nivolumab), in Japan for melanoma in 2014 and it expects to generate sales revenues of $4.3 billion in 2019. Keytruda (pembrolizumab), PD-1 inhibitor developed by Merck for melanoma, is predicted to generate sales revenues of $2.9 billion in 2019. Yervoy (ipilimumab) is an example of a monoclonal antibody that activates the immune system by targeting CTLA-4, a protein receptor that down-regulates the immune system. While



Yervoy was developed by James Allison, clinical development of anti-CTLA4 was initiated by Medarex, which was later acquired by Bristol-Myers Squibb. Industry experts have predicted that Yervoy will generate sales revenues of $1.5 billion in 2019.

Cancer vaccines are made from altered cancer cells that have been removed from the patient during surgery, immune cells that have been isolated from the patient's blood, or antigen such as protein, peptide or hapten that have been used to boost immune cells. Cancer vaccines can be used as prevention or therapeutic methods for cancer. In the case of cancer cell vaccines, cells are altered chemically in the lab to ensure they are recognised and attacked by the immune system and then injected back into the patient. On the other hand, isolated immune cells from the patient are exposed to cancer cells, cancer antigens, or chemicals to activate and then injected back into the patient, where they should cause an immune response to cancer cells in the body. Sipuleucel-T (Provenge) is a dendritic cell (a type of immune cells) vaccine manufactured by Dendreon and received FDA approval to treat metastatic prostate cancer in 2010. Provenge generated $303.8 million revenue in 2014.

The fourth category can be classified as non-specific immunotherapeutic modalities that boost the immune system in a general way. Chimeric antigen receptor (CAR) T-cell therapy is promising non-specific immunotherapeutic modality to fight cancer. In this technique, T cells are removed from the patient's blood and genetically engineered in the lab to express CAR. The T cells are then multiplied in a culture dish and infused back into the patient's blood. Theoretically, these T-cells should seek out the cancer cells and launch a precise immune attack against them. Juno Therapeutics, Kite Pharma, Novartis, and Cellectis are conducting clinical trials on CAR-T cell therapies for different types of cancers. While some patients have shown promising results with high remission rates, a large number of patients have experienced untoward toxicities due to non-specific nature of this treatment. It's Obvious that recent deaths in the Juno ROCKET trial are creating uncertainties about CAR-T technology, researchers are currently trying to improve to overcome challenges of current CAR-T cell therapies.

We have to get immune cells ready to battle against cancer cells. To outcompete the intelligence of cancer cells, we have to prepare immune systems well by recognising weakness and strengths of cancer cells. Due to tumour heterogeneity, we have to prepare immune cells differently for each cancer type.

"Every battle is won before it is fought" – Sun Tzu, The Art of War, 400 B.C. That's how I see cancer immunotherapy.

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Gynaecologic research: Improving health for women

Dr. Lisa Halvorson, U.S. National Institutes of Health discusses the importance of gynaecologic research to develop new treatments and keep women healthy

In 2012, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) established the Gynecologic Health and Disease Branch to serve as the epicenter of gynaecologic research at the National Institutes of Health (NIH). Gynaecologic disorders affect women's quality of life in ways distinct from reproduction and infertility and, therefore, require an independent research focus and support. Here, Dr. Lisa Halvorson, Chief of the branch, answers Open Access Government's questions on the importance of gynaecologic health and of research to advance our understanding of gynaecologic disorders.

What is gynaecologic health and why is it important?

Gynaecologic health includes the health, structure, and function of internal organs, including those in the pelvis, and external genitalia that allow for normal menstruation, sexual function, and reproduction without chronic or recurrent pain. Many disorders, although not fatal, can impact gynaecologic health. These include menstrual abnormalities, ovarian cysts, uterine fibroids, endometriosis, and pelvic floor disorders (pelvic organ prolapse, urinary incontinence, and fecal incontinence), to name a few. In addition, there are several gynaecologic pain syndromes, such as chronic pelvic pain, chronic pain in the area around the opening of the vagina (vulvodynia), pain associated with menstrual cycles (dysmenorrhea), and painful sexual intercourse (dyspareunia). Obstetric fistula, defined as a hole in the birth canal, and female genital cutting also are important.

Gynaecologic disorders are fairly common and have far-reaching health and societal impacts. For instance, the most common non-cancerous gynaecologic tumor in women is uterine fibroids, with a lifetime prevalence of 70 to 80%, of which 30% are symptomatic. Another disease, endometriosis, affects approximately 10% of reproductive-age women. Also, it is estimated that several million women in the United States suffer from vulvodynia alone, although the true prevalence of this and other gynaecologic pain syndromes remains unknown. Pelvic floor disorders affect almost 25% of U.S. women between ages 20 and 80 years. As the U.S. population ages, the number of women with pelvic floor disorders is expected to increase substantially. The detrimental health effects of gynaecologic disorders can range from abnormal uterine bleeding, pelvic pain, infertility, and sexual dysfunction to substantial psychosocial illness and limitations in daily activities. The financial burden of these conditions is also very high, with endometriosis and fibroids alone costing the United States billions of dollars every year in health care resources and lost work hours.

How important is research to develop new methods for prevention and diagnosis?

Despite the health and financial burdens of gynaecologic diseases, large gaps remain in our understanding of the key processes contributing to the development and progression of these disorders. Without ongoing

research, the gaps will remain, leaving millions of women without evidence-based prevention methods, diagnosis, or treatment.

What key target areas comprise the focus of research in the NICHD Gynecologic Health and Disease Branch?

Current efforts aim to support research in selected gynaecologic areas that have traditionally been overlooked or underfunded, such as socioeconomic, racial, and ethnic disparities in reproductive health outcomes. Although NICHD funding is allocated for studies of fibroids, endometriosis, pelvic floor disorders, and gynaecologic pain, our goal is to expand our portfolio to address a wider range of problems.

Over the past year, branch research has focused on the following:

- Supporting longitudinal studies to better understand the natural history of gynaecologic disorders, particularly in adolescents, to help identify risk factors, possible prevention strategies, and treatments;
- Fostering partnerships with experts in relevant clinical and basic science fields (e.g., neurobiology, muscle biology, cell biology, and immunology) to enhance knowledge and resource-sharing across disciplines;
- Applying powerful "-omics" approaches (e.g., genomics, epigenomics, and proteomics) to gynaecologic conditions;
- Investigating stem cells as a cause and potential therapy for gynaecologic disorders, from studies of their role in causing such disorders to projects that utilise stem-cell based therapies to treat the disorders;
- Developing new, non-hormonal pharmacologic treatments to improve gynaecologic health;
- Applying novel imaging methods and biomarkers to gynaecologic disorders.

How does your branch support such research and help raise awareness for gynaecologic health?

The NICHD Gynaecologic Health and Disease Branch funds basic, translational, and clinical research to investigate gynaecologic diseases. We also identify research needs and develop grant opportunities to address new or underdeveloped areas of investigation. To ensure that we have our fingers on the pulse of the various fields within gynaecologic health, branch staff participate in national and international meetings and maintain ongoing communication with the scientific community, advocacy organisations, related government agencies, and the general public.

> "Gynaecologic disorders are fairly common and have far-reaching health and societal impacts. For instance, the most common non-cancerous gynaecologic tumor in women is uterine fibroids, with a lifetime prevalence of 70 to 80% of which 30% are symptomatic."

These contacts enable us to distribute information related to research aims, funding opportunities, and study results to better convey the importance of gynaecologic health. The branch also supports research training and career development programs to create a future of excellence in women's health research. In short, the branch serves as a link between the scientific community, the public, health practitioners, and different levels of government with the ultimate goal of advancing gynaecologic research and health. ■

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Uterine fibroids: Where is research heading?

Uterine fibroids represent a prevalent benign gynaecologic problem in the U.S, here Romana A. Nowak of the University of Illinois explains

Uterine leiomyomas (fibroids) represent the most common gynaecological tumours in women. These tumours disrupt the functions of the uterus and can cause excessive uterine bleeding, anaemia, defective implantation, recurrent pregnancy loss, pelvic discomfort and urinary incontinence, as well as possibly mimicking or masking malignant tumours in many U.S. women at some time during their reproductive life. By age 50, nearly 70% of Caucasian women and more than 80% of African-American women bear at least one fibroid and 15 to 30% of these women develop severe symptoms. Uterine fibroids disproportionately affect African-American women, who develop significantly larger fibroids at a higher rate and earlier ages, have more severe symptoms and sustain tumour growth for longer periods compared with Caucasian women.

Approximately 200,000 hysterectomies, 30,000 myomectomies, and thousands of selective uterine artery embolisation's and high-intensity focused ultrasound procedures are performed annually to remove or destroy uterine fibroids with an estimated total annual cost to the U.S of $5.9-34.4 billion. It would not be an exaggeration to state that uterine fibroids represent the most important and prevalent benign gynaecologic problem in the U.S. There is a critical need to identify alternative therapeutic approaches for leiomyomas that do not involve surgical intervention.

Surgery, either hysterectomy or myomectomy, is currently the primary avenue of treatment for leiomyomas, since effective non-surgical treatment options are extremely limited. Uterine artery embolisation is effective only in specific subgroups of patients with small fibroids and is not recommended for patients who intend to become pregnant. Gonadotropin-releasing hormone (GnRH) analogues, which suppress steroid hormones have significant side effects that restrict their use. There is also a high rate of recurrence of leiomyomas once GnRH analogue treatment is discontinued. Success is now being achieved with the use of the selective progesterone modulator ulipristal acetate. Several recent clinical studies have shown that ulipristal treatment was able to control myoma-associated uterine bleeding in over 90% of cases and significantly reduce myoma volume in more than 80% of women. This treatment is considered safe, even at the level of endometrial changes and is viewed as a promising alternative drug therapy.

Uterine fibroids are still misunderstood

Currently available treatments for fibroids are limited due in large part to the fact that the mechanisms regulating the development and growth of these tumours are still not well understood. Many investigators in the field hypothesise that leiomyomas develop in the uterine myometrium as a response to inflammation or injury caused by local hypoxia during menstruation or the presence of bacterial or other pathogens. We and others also hypothesise that dietary intervention, with compounds known to inhibit inflammation-associated pathways, will decrease growth of fibroids leading to decreased size and amelioration of symptoms and this is now a very active area of research.

Several studies from the laboratory of Dr. Al-Hendy and colleagues have supported the use of vitamin D as a dietary intervention for leiomyomas. His group reported that the vitamin D receptor activator, paracalcitol, inhibited leiomyoma tumour formation in a rat model and that vitamin D also inhibited proliferation and collagen production in cultured human leiomyoma cells. Dr. Al-Hendy has also shown that green tea extract, given orally to women with fibroids, caused a reduction in fibroid volume and symptoms. Green tea is a natural product, commonly used as a nutritional supplement for multiple purposes. Epigallocatechin gallate, the major catechin in green tea, exhibits several useful biological effects, including anti-inflammatory, antiproliferative, and antioxidant effects. Studies carried out in animal models

have tested the potential benefits of adding lycopene to the diet to slow the growth of fibroid tumours.

Lycopene is a major carotenoid present in tomatoes and has been shown to be a powerful antioxidant. The results show that treatment with lycopene reduced the size and incidence of leiomyomas in quail by approximately 45-52%. Recently our lab has characterised oviductal leiomyomas that occur spontaneously in hens as they age, as a relatively inexpensive, naturally occurring animal model for fibroids. We now have preliminary data showing that hens fed a flaxseed diet showed a decrease in the size of the fibroids compared to hens fed the normal corn-based diet. Thus, dietary intervention for treatment of symptomatic fibroids has great potential but there is a critical need for larger scale dietary trials in naturally occurring animal models as well as in women.

Fibroid tumours represent many genotypes and somatic mutations and are also strongly influenced by epigenetic factors including inflammation, ethnicity, parity, metabolism and diet, and hormonal environment. Several physiological pathways have been implicated in the development of leiomyomas. However, genetic mutation is strongly thought to be the root cause of leiomyomas. Approximately 40% of leiomyomas have non-random chromosomal abnormalities. These cytogenetic abnormalities likely reflect general genomic instability, however mutations in leiomyomas that may underlie such genomic instabilities are only beginning to be understood. Mutations in a small number of genes including fumarate hydratase (FH), the high mobility group AT-hook 2 (HMGA2) gene, tuberin (TSC2) and mediator complex subunit 12 (MED12) have been implicated in the initiation of these tumours. Several studies have now been published demonstrating that MED12 mutations are present in 56-73% of uterine fibroids. Polymorphisms in genes such as CYP17 and cathechol-O-methyltransferase, have also been associated with a higher risk of developing leiomyomas. Recent studies have indicated a role for miRNAs in that many miRNAs including miR-21, miR-363, miR-490, and miR-137 have been shown to be differentially expressed in leiomyomas. As new therapies are developed, the heterogeneity of this disease becomes therapeutically relevant, and a broader knowledge of its genetic basis is vital for tailoring specific therapies to patients. Identification of previously unknown genes whose altered expression and function may contribute to the initiation and growth of fibroid tumours will lead to better therapeutic treatments.

In contrast to other areas of tumour biology, the number of published studies reporting whole-genome or whole-exome deep sequencing of leiomyomas is relatively few. These studies have confirmed the high prevalence of MED12 mutations in leiomyomas and have also confirmed aberrations in HMGA2 and TSC2. However, the populations studied appear to have limited diversity, and the data sets from most of these papers are not freely available to the scientific community, leaving a significant gap in our understanding of the genetic and molecular underpinnings of this disease. Thus there is a critical need to provide better insight into leiomyoma biology through the identification of previously unknown genes whose altered expression and function may contribute to the initiation and growth of leiomyoma tumours. This includes investigating the potential role of viruses in leiomyoma pathology, by using RNAseq methods to detect actively transcribed viral genes.

> "By age 50, nearly 70% of Caucasian women and more than 80% of African-American women bear at least one fibroid and 15 to 30% of these women develop severe symptoms."

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) has established the Gynaecologic Health and Disease Branch whose focus is on gynaecological diseases and women's reproductive health. One of the priority areas for NICHD is uterine fibroids and there have recently been funding announcements for proposals focusing on gene sequencing studies and on new therapeutic approaches to treat fibroids. The next 3-5 years will likely lead to major advances in the treatment of uterine fibroids as a result of these studies.

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Early learning and behaviour research at the US NICHD

Research on early learning and behaviour translates into effective interventions and care, Dr James A Griffin of the NICHD at the US National Institutes of Health

The National Institute of Child Health and Human Development, at the National Institutes for Health (NIH), was established with support of Congress, to study the 'complex process of human development from conception to old age'. Here, Dr James Griffin, Deputy Chief, Child Development & Behavior Branch, at the NICHD answers Open Access Government's questions with regards to early learning research and the impact this can have on a child's development.

How does research help us to further understand child development and the importance of this?

Research funded by the Child Development and Behavior Branch (CDBB) within the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), helps us to understand and make sense of child development in all its complexities. Basic research helps us to understand the complex relationship between genetic and environmental factors as they interact to shape brain development and early learning and behaviour. This basic research, in turn, helps to inform translational research that addresses topics ranging from how to promote optimal health and development over time to how to create and implement interventions addressing the needs of children at-risk for language and learning delays and behavioural difficulties.

How does the NICHD support research in child development, particularly in early learning?

The Early Learning and School Readiness Research Program within CDBB funds a range of research studies seeking to understand the influences that come together to support or hinder early childhood development and how they impact early learning opportunities and affect a child's ability to make the successful transition to school. Studies supported include: descriptive studies of how early care environments (home, family and centre-based child care) are associated with later school achievement and adjustment; intervention studies in paediatric primary care settings that examine the impact of early developmental interventions during well baby/child visits on parent and child behaviors (e.g., increased parent reading to the child, decreases in problem child behaviours); and preschool intervention studies that attempt to boost school readiness skills, including early language, pre-literacy, early numeracy, and self-regulation, social-emotional and social skills prior to entering kindergarten.

> "Several studies that have followed children from disadvantaged backgrounds who received a preschool intervention continue to show positive effects on academic performance and behaviour well into adulthood."

How important is early learning for a child's development?

Early learning is both the result of and shapes the overall development of a child. Parents, siblings and other family members, and caretakers are an infant's first teachers, and interaction with them provides essential learning opportunities, as well as influencing the physical health and safety of an infant. Infants learn how to interact with the world from these early experiences, developing early gestures and vocalisations leading to language, and the capacity to better regulate their own emotions and behaviour. Lack of appropriate stimulation (unresponsive caretakers, lack of reciprocal language exchanges, unmet physical and emotional needs) can result in less developed early language and learning skills and difficulties regulating their own impulses and behaviours. Such deficits will make it

more difficult to interact with family members and peers and may make it difficult for a child to transition to a school environment.

How does early learning impact children later in life?

Several studies that have followed children from disadvantaged backgrounds who received a preschool intervention continue to show positive effects on academic performance and behaviour well into adulthood. These interventions commonly employed a stimulating preschool environment coupled with home outreach focused on parent skill training and support. The current hypothesis is that these interventions, above and beyond enhancing immediate school readiness skills, produced long-term effects by promoting children's early executive function (EF) skills. These skills, developed in the first three years of brain development and then again in late adolescence, help children to regulate their own behaviours by teaching them impulse control, the ability to shift and focus their attention, and other abilities necessary for both learning and social interactions. These EF skills likely help children in their transition to school, providing them with an increased ability to learn in school, make friends, and engage in fewer problematic and disruptive behaviours. The cumulative effect increases the likelihood of a positive outcome in adulthood, relative to peers raised in the same disadvantaged environments who did not receive a preschool intervention.

How does research help to figure out the best ways for parents and caregivers to help children develop early skills?

NICHD has funded research ranging from observational studies of parenting behaviours in home and laboratory settings to intervention studies that attempt to teach early parenting skills. Both types of studies have resulted in recommendations regarding: talking and reading with children from infancy onward; how to interact with them to promote their early language skills and promote curiosity about the world around them; providing a secure attachment relationship that provides a safe base from which a child can explore the world from infancy onwards; and sensitive support from dependence to independence and a greater capacity for self-regulation and social exploration with peers.

How can areas such as home life/the environment/economic stability impact a child's early development?

NICHD has supported a range of studies examining how stability in home life, family income, and neighbourhood conditions etc. impact children's early development. Fluctuations in income and neighbourhood conditions are often beyond the control of parents, but early sources of stress for infants and young children often can be changed once parents understand how such stress negatively impacts their children's development and capacity to learn. Examples of home environment stressors include constant loud music, television or computer sounds that may make it difficult for a young child to focus their attention or which disrupt their sleep, lack of space for a child to safely move about and play, and lack of safe and age-appropriate toys and household items for the child to manipulate and play with. Chronic exposure to stressors may negatively impact a child's development of executive function and school readiness skills. ■

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Umbilical cord blood: A life enhancer for all babies

Judith Mercer and Debra-Erickson Owens have found positive changes after a short delay in cord clamping, indicating the benefits of umbilical cord blood

When cord clamping is delayed at birth (DCC), an infant receives a placental transfusion and benefits from a 30% increase in blood volume and a 50% increase in red cell volume, resulting in increased iron stores over the first 6 months of life. Red blood cells hold 80% of the iron in our bodies, making this added volume of red blood cells responsible for the observed increase in iron stores. Thus, DCC results in less iron deficiency in early infancy.

Iron deficiency in infancy has been shown to adversely affect cognitive, motor, socio-emotional, and behavioural development. These first 6 months of life coincide with the most critical period of brain growth and myelin development, during which most of the brain's eloquent neural pathways are established and refined. Iron is an essential component of myelination which is critical for normal brain development and function.

Mercer and Erickson-Owens decided to take the current research a step further and look at the effect of DCC on brain development and myelination over the first 2 years of life in infants receiving either DCC, or immediate cord clamping (ICC) at birth. They wondered if the higher iron stores from DCC would result in greater brain myelin content at 4 months of age.

Significant positive change in brain myelination

Myelin is a fatty white substance that is wrapped around nerve cells in the brain to form an insulating layer and creates the white matter in our brains. Myelinated white matter is a corner-stone of human neurodevelopment, establishing and maintaining efficient communication pathways across specialised neuronal systems. Iron plays an essential role in the formation of the cells responsible for producing

myelin. Animal studies clearly link low levels of brain myelin with iron deficiency and neurodevelopmental impairment. Also, abnormal myelination underlies a variety of childhood developmental disorders, including conditions such as dyslexia and autism, thus making it a key area of study. Through their research, Mercer and Erickson-Owens hope to fill the knowledge gap on the effects of cord clamping time, at this critical and dynamic period of infant neurodevelopment.

"We chose to do this study because a high percentage of babies world-wide are anaemic or iron deficient (ID) by 6 to 9 months of age. Cord blood is an excellent source of iron and is readily available to every infant via placental transfusion at the time of birth. Anaemia and ID in infancy are also associated with decreased cognitive abilities, and behavioural problems. And, there is good evidence for the safety and benefits of DCC."

After receiving US National Institutes of Health funding, Mercer and Erickson-Owens were joined by Dr Sean Deoni to launch their latest study known as the 'Infant Brain Study'. Deoni brought expertise in using MRI scanning to examine myelin and normal brain development in infants and children. Normal healthy women delivering at term with healthy foetuses were recruited and randomised to either ICC (within 20 seconds) or DCC (5 or more minutes). [If the provider felt that they could not delay cord clamping, they were instructed to milk the cord 3 to 5 times – a safe alternative to DCC]. At 4 months of age, blood samples were collected and MRI quantitative myelin scans were done with accompanying developmental assessments (within one week of scanning). Currently these researchers are reporting the study's 4-month MRI scan results and are awaiting the 12 and 24-month results to be finished later this year.

Most of the MRI scans were conducted in the evening so infants could be scanned during natural sleep. Mothers put infants to sleep in a comfortable room and they were then placed on the scanner table and inserted into the MRI scanner. Several techniques – ear covers, special headphones, slowing the scanner, and noise insulation – were used to reduce noise. The imaging times ranged from 20 to 30 minutes. Parents were invited stay in the MRI room or wait outside. If the child woke, mothers attempted to get them back to sleep and the scan was restarted.

Haemoglobin higher after delayed clamping

There were no significant differences between the mothers or infants in each group – an important finding in any clinical trial. Drainage of the placental blood showed that infants who had ICC left about 30% more blood in the placenta. Blood levels of haemoglobin were higher in those infants who received DCC, without any adverse effects. Ferritin levels (a proxy for iron stores) at 4 months of age were higher in the DCC infants, as expected.

There was significantly more myelin content in several areas of the brain in the infants with DCC, compared to those with ICC. Differences occurred in the earliest myelinating brain regions such as the cerebellum, the internal capsules, and the motor cortex. As the infants were just 4 months old at the time of scanning and these are the brain areas that are rapidly myelinating during this stage of development, DCC appears to have a significant impact on myelination across the brain. Thus, placental transfusion (DCC & milking) facilitates the transfer of residual placental blood without adverse effects and supports increased brain myelination at 4 months of age.

This study, in its fifth year, will be completed in December 2017. Currently, Mercer and Erickson-Owens are awaiting the results of the MRI scans of brain myelin content and parallel developmental testing at 12 and 24-months. They expect differences at 2 years of age when data on young infants is more robust. A Swedish study that reported no differences in development at one year for children who had DCC or ICC at birth, found significantly better outcomes at 4 years in fine motor skills and social-emotional functioning.

Dr Mercer began her research examining DCC for preterm infants as they have the most serious life-threatening problems. In 2006, she reported less bleeding in the brains of infants who had only a brief delay in cord clamping (30 to 45 seconds), compared to infants who had immediate cord clamping. Her work has been replicated by others and these findings are the major reason DCC is being adopted at the time of birth of premature infants. Erickson-Owens joined her in 2005 and added her research which examined umbilical cord milking in term infants. Her study showed that milking the cord at caesarean section was safe and resulted in

better haematocrit levels at 2 days of age – a marker of better iron levels later in infancy.

Umbilical cord blood and stem cells

In the future, these researchers plan to explore stem cells in umbilical cord blood. Stem cells augment the infant's own healing system in ways that may benefit the child not only in infancy but over his lifetime. Umbilical cord blood contains many millions of stem cells that help to protect the infant. If the cord is cut right away, the infant will leave about 80 millilitres of blood, containing approximately 1 billion nucleated cells behind in the placenta. However, both human and animals studies demonstrate the immense healing power of stem cells.

Human umbilical cord blood stem cells, used for transplants in human diseases, are remarkably successful in promoting healing. In the United States and Japan, scientists are extracting stem cells after birth and placing them back into the bodies of infants afflicted with a life threatening condition known as hypoxic-ischemic-encephalopathy. They have had some success in reducing mortality. Mercer and Erickson-Owens believe these precious stem cells should be allowed to transfuse into every infant's body at the time of birth and that they might help prevent or lessen the severity of this devastating disease. There is, however, a dilemma. The infants who may need their stem cells the most often receive ICC. Current neonatal resuscitation policies demand ICC so that infants can be quickly moved to warming tables, denying a placental transfusion to the very babies who may benefit the most.

To address this problem, scientists in the UK and the US are conducting research on resuscitating infants near the mother with the umbilical cord intact to allow the placental transfusion to continue. In order to examine whether obtaining cord blood at birth would help these infants, a team from Virginia is conducting a large trial in which they will resuscitate preterm infants without clamping the cord. If successful, this will encourage transitioning of all infants with an intact cord.

Umbilical cord blood donation is not the answer

But shouldn't parents be altruistic and donate their infant's umbilical cord blood? In 2017, experts still do not know how to prevent most newborn diseases, such as cerebral palsy, hypoxic-ischemic-encephalopathy, and persistent pulmonary hypertension. While some treatments such as head cooling for encephalopathy have improved outcomes, still over half the infants who develop this condition are

either permanently disabled or die in their first 2 years of life.

Mercer and Erickson-Owens do not support cord blood donation at this time except in rare cases such as blood for a sibling in need. Instead, they urge scientists to continue to learn how to make the umbilical cord stem cells proliferate or expand in the laboratory so they can be used for transplantation. Some modest success has resulted in reproducing stem cells but they are not yet as potent when transplanted as the stem cells from cord blood. The race to find the perfect medium continues. Even after a long delay in cord clamping, there is still a small amount of blood remaining in the placenta, which could provide many stems cells via successful expansion techniques. Meanwhile, scientists have identified stem cells in the umbilical cord tissue itself, in amniotic fluid, and in the placenta. All of the sources are under intense study to develop them as alternatives to cord blood stem cells.

It is true that the usual obstetrical practice of ICC, a practice lacking evidence-based support, denies an infant up to 50% of its iron rich red blood cells and stem cells. The birth setting can influence the timing of cord clamping. Historically, obstetricians delayed cord clamping in hospital. However, in the middle of the last century there was a major shift to ICC. The shift in practice led to institutional policies and the adoption of ICC which we now know does not benefit the infant's well-being. Many midwives have used DCC throughout history, often in birth centres and home birth settings, but institutional policies often prevent this practice.

Mercer and Erickson Owens are passionate about umbilical cord clamping and present their work nationally and internationally. Their ongoing research supports the idea that DCC (or milking) is a low tech, no cost approach that is valuable for all infants of all gestational ages across the globe.

"Our knowledge about the value of cord blood for infants is akin to what we knew about colostrum fifty years ago when most people thought it did not matter and could be discarded! Now we know of its great value to newborns. All babies can benefit from a placental transfusion."

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What do we know about cognitive development in infancy?

Research into cognitive development in infancy has thrived over recent years, but there's still a lot we don't know, as UCLA Professor Scott P Johnson writes

Our research focuses on the origins of knowledge in humans. The past several decades have witnessed a blossoming in research on perceptual and cognitive development in infancy, and a view has emerged that infants take in far more information, and are more aware of their surroundings, than we often give them credit for.

By the end of the first year after birth, infants seem to know many of the basics of the world around them: Objects tend to behave in certain ways (e.g., they persist when they are hidden), people interact with each other using language and gesture, and moving around and handling objects are good ways of obtaining more knowledge.

Despite these advances, fundamental questions remain concerning how this state of knowledge comes to be. The UCLA Baby Lab explores these questions with preferential looking and eye tracking paradigms, as well as connectionist modelling of developmental phenomena. Because the focus is on origins, we are less interested in participating in traditional "nature vs. nurture" debates (though we do it anyway), than in understanding and elucidating precise developmental mechanisms: Endogenous prenatal or postnatal organisation; the role of experience in shaping responses to recurring patterns; contributions of perceptual (i.e., low-level) skills to cognitive (i.e., high-level) functions; and the context of the family and wider social environment. The question of origins of knowledge lies at the intersection of developmental psychology, social psychology, vision science, cognitive science, and developmental neurobiology.

Cognitive development in infancy

Many "smart" mechanisms emerge from simple mechanisms, given the right environment. Infants are born with rudimentary perceptual and learning skills and a handful of reflexes, but there is little evidence that "knowledge" is available to neonates, beyond the ability to acquire information quickly and retain it over short intervals.

Within several months, however, the situation is radically different. The goal of our research is to explain developmental phenomena, first by describe age-related changes in visual perception and early learning abilities, and then by revealing the mechanisms responsible for these changes. We distil a question to its fundamental essence, see how and when infants respond to the simplest possible version of a cognitive challenge, and from there, develop new theory.

We devote a lot of time and energy to new methodological advances, such as computer-controlled experiments and eye movement recordings in infants. Computer-controlled experiments give us precise management of stimulus generation and presentation.

Recording eye movements is technically challenging but the resulting data are incomparable in their precision, and, I believe, bring us as closely as possible to what infants are thinking. We also use imaging techniques such as fMRI and EEG (functional magnetic resonance imaging and electroencephalography) in studies of cortical correlates of perception and learning, and computational models of perception.

Our research programme currently involves studies of infant social attention and infant statistical learning.

Infant social attention

The means by which humans acquire and represent knowledge of other people is fundamental to social and cognitive science, and a central question asked by developmental psychologists concerns how infants learn so much in so little time in the absence of explicit instruction. The rapidity and apparent ease with which infants and young children understand and produce speech, recognise faces, and interpret others' mental states, for example, have led to suggestions that innate cognitive mechanisms provide some knowledge in each of these social domains.

Yet such views may risk neglecting the potential roles of perception, attention, learning, and experience in guiding social development. Recent theoretical proposals that account for such skills, such as social-orienting models, hold tremendous promise for elucidating the nature and origins of human social cognition. Central to these models is the possibility that social attention in infancy serves to identify targets that afford social relationships which in turn promote normative brain and behavioural development. This cycle acts like a positive feedback loop, affecting subsequent social development. Social attention, therefore, is the initial "gateway" through which the social environment is engaged.

Social attention develops in context, and a central research question is whether differences in social context – for example, language background or racial composition of the family – yield specific "downstream" consequences for categorisation, just as social categories, once formed, have consequences for impressions, attitudes, stereotypes, and prejudice. A series of studies currently underway examines infants' ability to discriminate or categorise various properties such as gender and emotion from face and body stimuli. We recently discovered visual preferences for minority faces (African-American and Hispanic) vs. White faces in Hispanic and White 11-month-old infants, a finding that may bear important implications for the origins of social cognition and social categories.

Infant statistical learning

"Statistical learning" refers to the ability to detect associations among items such as visual stimuli or words, eventually leading to grouping and detection of coherence among items and the acquisition of sophisticated knowledge structures, such as words and sentences. That is, statistical computation mechanisms may contribute to early language acquisition by segmenting the speech stream into units.

Statistical learning exists broadly across sensory modalities. Certain animal species have been found to learn statistically structured speech streams, and human infants can parse streams of musical tones based on statistical probabilities and detect statistical information in sequences of discrete, looming shapes. These results imply a domain-general statistical learning device that is available early and operates across modalities, across time and space, and across species, suggesting that statistical learning might be a predisposed, general associative mechanism. This hypothesis is supported by reports of statistical learning of visual and linguistic sequences in newborns, constituting evidence for sensitivity to statistical information at birth in at least two modalities.

However, more recently, research in the UCLA Baby Lab has revealed striking limits in infants' visual statistical learning, and revealed some of the fundamental perceptual mechanisms underlying learning performance. Current evidence suggests that statistical learning actually consists of the gradual accrual of "chunks" of structure, not specific computations. Alternatively, statistical computations might contribute the first steps in pattern learning, to be superseded by a chunking mechanism that does not retain statistical information.

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Out of sight: Low vision is a National Eye Institute priority

Low vision can be a blight on the lives of those it affects, which is why it's a National Eye Institute priority, as Dr Cheri Wiggs told Open Access Government

Around 4.2 million people in America are visually impaired, which is expected to increase to 7.2 million in 2030. Of those 7.2 million in 2030, 5 million will have what is known as low vision. Low vision is an impairment characterised by partial sight that cannot be corrected or treated by wearing glasses, contact lenses or through surgery. With people living longer it has now become a major public health concern in America.

Having low vision can have a devastating impact on someone's life. The impact on day-to-day activities can leave people feeling depressed and anxious. Low vision sufferers may struggle to carry out everyday tasks, such as reading, shopping, cooking, driving and even matching up clothes when getting dressed. Although the majority of people who suffer from low vision are said to be 65 years and older, younger people and even children can also suffer from this health issue.

There are a wide range of causes of low vision, from eye diseases, cataracts to glaucoma. Health problems such as diabetes can also lead to low vision developing. The National Eye Institute (NEI) in America, part of the National Institutes of Health (NIH), supports research and other programmes, relating to visual disorders including low vision.

Causes of low vision issues

Dr Cheri Wiggs, Program Director for the Low Vision and Blindness Rehabilitation Programme at the NEI, speaks to Editor Laura Evans about the importance of raising awareness for people with low vision and how advances in science have helped over the years.

"The majority of low vision issues are caused by eye diseases and/or injury, but brain damage can also lead to visual impairment", explains Dr Wiggs.

"There has been more attention recently on cortical blindness, or cortical visual impairment. This is where people can still see, but they have difficulty interpreting that visual information. Some people have double or tunnel vision, or their vision is extremely blurred. This can be caused by traumatic brain injury, and we are seeing a lot of people that come back from combat and complain about these visual issues after a situation with an IED.

"Cortical visual impairment can also be caused by insults to the brain at birth. Vision loss due to neurological damage to the brain affects both children and adults," adds Dr Wiggs.

Age-related macular degeneration

As the majority of people with low vision are over the age of 65, this could become a bigger problem due to ageing populations. One of the most common causes of low vision is age-related macular degeneration. However, there are a few studies being done to ascertain how to prevent low vision in later life.

"There have been a few studies on vitamin regimens to keep these eye health problems at bay." says Dr Wiggs.

"In particular, a clinical trial examined whether taking antioxidants and zinc would reduce the risk of developing advanced age-related macular degeneration (AMD). The results showed that the dietary supplements, while not a cure for AMD, could help at risk older people keep their remaining vision.

"However, it is also integral to ensure that the public are aware of the importance of regular eye examinations that include looking at the retina. Because if you can catch it early you may be able to start some therapy that can at least decrease the probability that it will advance.

"The biggest problem is how low vision can impact day to day life," adds Dr Wiggs. "It really does impact people's quality of life and their independence. People who have low vision are at an increased risk of falls, which means fractures, time spent in bed and limited mobility for a number of reasons. If part of your vision is absent then its difficult manoeuvring around, including driving but even just walking. People with low vision are at an increased risk for depression, and it can also complicate the management of other health issues."

Understanding the mechanisms behind low vision

Research is integral in order to better understand the mechanisms behind the problem and to develop therapies and rehabilitation that are tailored to help people who have low vision cope with everyday living. As science has evolved, technology is key to this area and has led the way to develop a number of assistive devices that help people with low vision carry out everyday tasks, such as reading.

"Part of the mission of the National Eye Institute (NEI) is to address the special health requirements of the visually impaired," Dr Wiggs says. "We have encouraged collaborations between vision scientists and people from both engineering and computer science backgrounds to help develop creative strategies to address some of the issues faced by people with low vision."

As well as assistive devices, rehabilitation plays a major role in helping people to adapt and maintain their current lifestyle. It can help them to feel more confident and comfortable with their vision loss, by teaching them how to move safely around the home, continue to read, cook and do other activities, and find resources, adaptive devices, and support. Rehabilitation is something that the National Eye Institute supports. The low vision and blindness rehabilitation programme at the NEI aims to develop further understanding about those already living with low vision.

"In addition to the applied translational work that develops assistive devices and rehabilitation strategies, NEI also supports basic science on the impact of vision loss," explains Dr Wiggs.

"For example, neuroscience research indicates that the brain reorganises functionally after losing sensory inputs; for instance, areas of the brain used for processing visual information get recruited for other functions, such as touch. The long-term impact of visual impairments on brain structures and functions remain unclear and could be very useful for informing rehabilitation efforts," she adds.

"We have a lot of behavioural studies which we also support that target the types of changes you see in crucial activities, such as navigation, driving, reading strategies, and movement in people who are losing their vision. So, even though that's more on the basic science side, it's always with the understanding that information can inform whatever rehabilitation strategies you might develop."

February was Low Vision Awareness Month at the NEI with the aim of raising awareness for people living with low vision, as well as their family and friends. ■

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Innovative device for cataract surgery in sight

In 1950, the British ophthalmologist Sir Harold Ridley performed the world's first implantation of an artificial intraocular lens (IOL) to restore a patient's vision after cataract surgery. This innovation rose from his observation of WWII pilots, who suffered eye injuries in which acrylic pieces from shattered cockpit windows lodged within their eyes.

The realisation that artificial IOLs can replace the diseased lens removed during cataract surgery, has arguably been one of the medical technologies that have benefited the greatest number of patients worldwide. Today, IOL innovation continues at a rapid pace, and many believe that a quantum leap in IOL performance may be just around the corner and bring rejuvenated, perfect vision to an ageing population.

One hurdle, however, is the delicate capsule that surrounds the lens. In cataracts, the normally optically clear lens becomes cloudy and, if left untreated, it can result in blindness. During surgery, an opening is made by the surgeon using forceps in the paper-thin capsule bag that encases the lens. This capsulotomy procedure allows the physician to remove the diseased lens through the capsulotomy opening, while preserving the bag to hold the IOL.

Performing the perfect capsulotomy

Capsulotomy is one of the most difficult steps of surgery, and a perfectly round, accurately sized and well-centred capsulotomy is required for optimal patient visual outcome. This is well-recognised for advanced multifocal IOLs currently on the market, whose performance is significantly degraded if misaligned. New IOLs under development place an even greater premium on a perfect capsulotomy, as they either stretch the capsulotomy opening to its limits or depend completely on the centration of the capsulotomy position for IOL alignment on the visual axis.

While some physicians are well-practised in capsulotomy, others are not and may struggle with technique. All agree, however, that making consistently perfect capsulotomies by hand is difficult. Five years ago, femtosecond laser systems were introduced for automated capsulotomies. While effective in making accurate capsulotomies, the femtolaser equipment suffers from its considerable financial outlay that requires the physician to pass on significant costs to the patient and also limit technology accessibility to the majority of surgeons and patients. In addition, the femtolaser adds time to each surgery, interrupts patient flow and operating theatre throughput, making this technology less attractive to surgical practices. Lastly, the medical literature indicates a higher capsule tear rate and other complications after femtolaser capsulotomy. The adoption of femtosecond lasers for cataract surgery has slowed significantly since its introduction.

The realisation of upcoming IOL innovations may instead hinge on Zepto, a disposable automated capsulotomy device about to enter the market (Mynosys Inc. Fremont, California, USA). (Zepto is the metric unit of measurement 1 million times smaller than femto). Zepto comes as a handpiece attached to a small control console. The handpiece's tip comprises of a soft, clear silicone suction cup that houses a nitinol super elastic capsulotomy ring, which compresses to enter a small corneal incision and re-expands within the eye to its native circular shape. Suction is applied through the cup to oppose the bottom edge of the capsulotomy ring to the capsule surface, trapping a very thin layer of water. A 4-millisecond pulse train causes a quick phase transition of the water molecules into vapour, and the accompanying volume expansion results in the cutting effect, which occurs simultaneously everywhere along the circular capsulotomy path. The tip is then withdrawn and the surgeon continues with the remainder of the cataract surgery.

Reaching for Zepto

Zepto requires no change to the steps of cataract surgery or patient flow. Instead of forceps, the surgeon simply reaches for Zepto to obtain quick, consistent, perfectly circular capsulotomies of the desired size (~5.2mm diameter). To date, Zepto has been used in over 200 cases worldwide with consistently excellent results. Patient follow-ups 8 months after surgery have shown stable capsulotomies with well-centred IOLs.

Test data and surgical experience have highlighted a number of unique

and noteworthy Zepto capabilities. Biomechanical testing showed the Zepto capsulotomy edge to be much stronger and more tolerant of stretching than from the manual method or by femtolaser, due in part to an innovative capsule collagen re-modelling effect that results in a slight upturn of the capsulotomy edge. This upturning provides a rounded capsulotomy edge that presents the undisturbed undersurface of the capsule as the functional edge encountered during surgery. Zepto therefore potentially provides a greater surgical safety margin. Importantly, Zepto's resilient capsulotomy edge is also critical for the safe implantation of the upcoming generation of larger IOLs, designed to change shape in response to the eye focusing at different distances.

Zepto's product design and mechanism of action also help the surgeon avoid potential complications. The use of suction stabilises the lens during capsulotomy and eliminates stretching the delicate zonular tissues that is inherent in the manual capsule tearing method. This significantly benefits patients with weakened zonules from disease or trauma. As Zepto's capsulotomy action also occurs simultaneously everywhere along a circular path, Zepto can be used to instantaneously relieve pressure underneath the capsule in advanced cataracts, and the potential for explosive capsule rupture is eliminated. Thus, patients with these and other co-morbidities benefit when complicated surgery becomes easy with Zepto in the surgeon's hands.

Zepto is the only technology that allows the surgeon to place the capsulotomy intraoperatively precisely on the patient's visual axis. The eye's complex anatomy exists to ensure that images are focused along the visual axis onto the fovea, the retinal area with the highest visual acuity. In today's surgery, despite available imaging technologies, surgeons are – at best – still guessing at the location of the visual axis when performing capsulotomy. Surgeons are already aware of this limitation for multifocal IOLs that require proper centration. The same limitation presents itself even more acutely for new IOLs that are anchored to the capsulotomy edge. Surgeons can interact with patients looking through the transparent Zepto suction cup and use Purkinje reflections to align the capsulotomy on the patient's visual axis. Zepto will be a real game changer as visually-centred capsulotomies are increasingly used to specify effective lens position.

ZACS

These advantages and unique capabilities of Zepto have engendered much interest in the concept of Zepto assisted cataract surgery (ZACS), as a potential new gold standard in cataract surgery. With ZACS, physicians can offer their patients not only a dimensionally perfect capsulotomy, but also one that has added safety. Complicated cataract cases will become routine while providing patients with the best possible results regarding IOL performance and stability. ZACS, for the first time, allow surgeons to precisely locate the capsulotomy on the patient's functional visual axis. This ability to tailor capsulotomies to the specific patient's ocular anatomy promises to be a new paradigm of personalised cataract surgery with optimised visual outcome.

As an easy-to-use tool that automates the most demanding step in cataract surgery, Zepto and ZACS offer something for every surgeon. For the surgeon less confident in capsulotomy, it offers quick and perfect results. For surgeons contemplating offering premium IOLs to their patients, it offers capsulotomy quality along with personalised visual centration, to support practice expansion. For the high volume practitioner, Zepto and ZACS offer safety, consistency and efficiency in both simple and complex cases, while at the same time ensuring premium outcomes for patients via visual centration.

Zepto is expected by physician leaders to significantly impact cataract surgery, not only by being a highly versatile clinical tool, but also by being a low cost disposable tool that is easy to learn and integrate into routine cataract surgery. Of note, Zepto can be placed easily into phacoemulsification machines, and is commercially attractive not only as a standalone device, but also as a platform product that can be offered together with premium IOLs, viscoelastics, and cataract surgical packs. Be prepared to see Zepto and ZACS broadly disseminated and potentially become a new gold standard in the years to come.

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Keeping pests under control requires ongoing research

Chris Bentley, Agricultural Research Service – U.S. Department of Agriculture, explains why research must continue to protect crops from pests and insects

Agricultural production in the U.S. and around the world is under constant attack. One of many enemies standing at the gate: thousands of different insect species. Left unchecked, they compete for the food we eat and represent threats that could decimate our natural, agricultural, and urban landscapes. If not for today's pest control measures, insects would ruin many of the crops grown in the U.S.

Scientific research has provided a palette of measures and strategies to help farmers and ranchers, as well as gardeners, homeowners, and the general public, control these insect pests. Many of these innovative tools and techniques are the direct result of the U.S. Department of Agriculture's (USDA) Agricultural Research Service (ARS).

Thanks to ARS scientists, many large-scale insect-related problems – like screwworm infestations of livestock – are no longer on America's "need-to-worry-about" list. If not for the sterile-male insect release technique pioneered by ARS researchers Drs. Edward F. Knipling and Raymond C. Bushland more than 6 decades ago, the flesh-eating screwworm would have decimated U.S. livestock production – just as it does today for many of our Central and South American neighbours.

Unfortunately, science can't rest on past successes. That's because insects continue to invade, which researchers often learn about by comparing specimens to those maintained in the hundreds of ARS scientific collections. These collections provide a definitive resources for agricultural research to include the identification of invasive insects. Pests also evolve and are quite adept at developing countermeasures to overcome control methods designed for them. In turn, that requires ARS scientists to find newer and better approaches for controlling insects, a few of which are mentioned here.

Image: © Steve Ausmus

Clown-colored harlequin bugs are no joke – H3ARS scientists developed a synthetic version of a harlequin bug pheromone to lure the bugs to traps

Don't let the harlequin bug's red and black clown suit fool you. There is nothing funny about the way this pest can destroy a whole field of broccoli, Brussels sprouts, cauliflower, and other vegetables popular with urban and organic growers, as well as conventional farmers. ARS researchers are supercharging harlequin bug control.

It all involves a synthetic version of the insect's own aggregation pheromone to use as a lure to either trap the bug directly or make so-called "trap crops" work efficiently. Pheromones are chemicals that trigger social responses in others of the same species. In this case, when a male harlequin bug finds food, he releases a pheromone to alert others to gather and feast – much like ringing a dinner bell.

When researchers tested a synthetic version of the pheromone on plants under conditions similar to farm fields, harlequin bugs – old and young, male and female – came crawling and flying from many yards away.

The technique allows growers to make trap crops – a lower-value alternative grown to lure pests away from higher-value crops – even more attractive.

Protecting cotton from stink bugs

Forget for a minute about the invasive brown marmorated stink bug that has become such a common pest in homes, backyards, and farms in recent years. Cotton growers in the U.S. are concerned about native stink bugs that have attacked cotton and other crops for decades.

ARS scientists have found environmentally friendly alternatives to insecticides for the 3 native stink bugs – namely, green (Chinavia hilaris), southern green (Nezara viridula), and brown (Euschistus servus) stink bugs – that continue to threaten U.S. cotton.

Thanks to ARS research, growers are now planting trap crops such as grain sorghum to lure stink bugs away from cotton. They're using pheromone-baited traps to capture and kill stink bugs, and are planting nectar-producing plants – such as milkweed and buckwheat – to feed the stink bugs' native enemy, a parasitoid wasp.

Applying beneficial nematodes to peach trees

Peach growers are facing a formidable insect foe: the lesser Peachtree borer, a native insect first reported in 1868 in Pennsylvania. ARS scientists have developed sustainable and cost-effective ways to combat this destructive pest.

Enter Steinernema carpocapsae, a tiny beneficial roundworm (or nematode) that can protect peach and other stone fruit trees by attacking borer pests. They are "beneficial" in that they control insect pests in an environmentally friendly way. But the sun's ultraviolet rays and heat can dry and kill the roundworms after they've been applied. To survive the sun's rays and do their job, these nematodes need protection.

ARS entomologists developed a way to protect the nematodes by using the type of "fire gel" that prevents the spread of fire in residential and commercial structures. In tests, they first sprayed nematodes onto tree limbs infested with lesser Peachtree borers and then applied the fire gel over them.

An initial drawback to that approach was overcome when one application (containing both nematode and protective gel) was developed. The treatment has proven as effective as the standard chemical approach

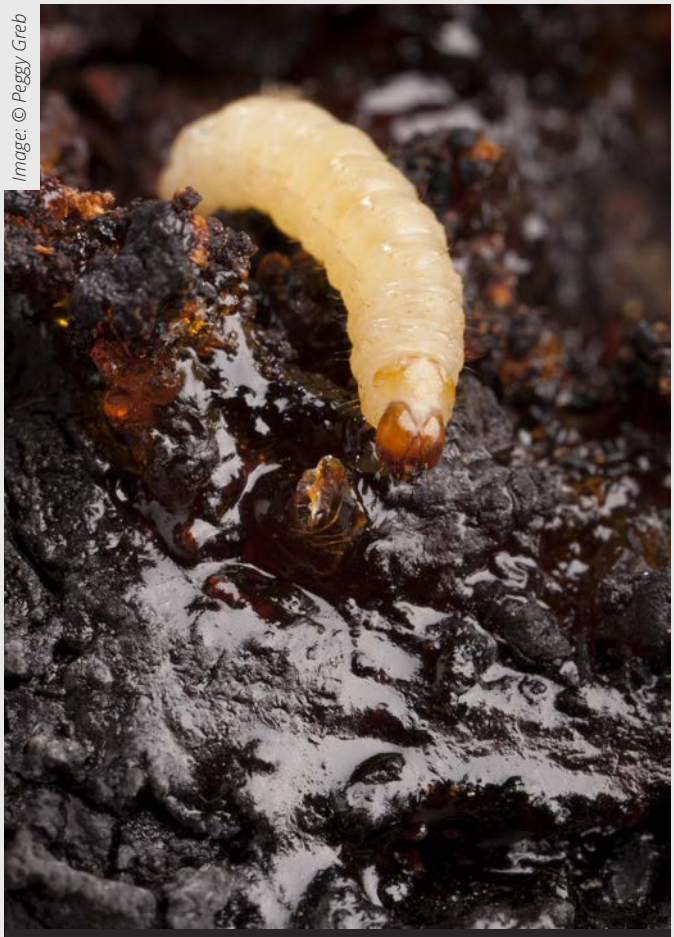

Image: © Peggy Greb

A lesser peachtree borer larva on a damaged peach tree

to combating the problem. These are but a few examples of the many ways ARS researchers across the country are working to stay one step ahead of insects – all while tackling other issues that affect the productivity and wellbeing of our agricultural and natural resources.

As the sterile-male insect release technique mentioned earlier illustrates, a good piece of innovation can go a long, long way. This will become especially important as the world population swells to an estimated 8.5 billion by 2030. Fortunately, the spirit of scientific and technological excellence of ARS pioneers like Dr. Knipling and Dr. Bushland continues to burn brightly in today's ARS researchers. ■

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Cotton Incorporated Incorporates Supply Ch

Cotton Incorporated is the U.S. based not-for-profit research and promotion company serving the global cotton supply chain

Cotton Incorporated

Cotton Incorporated is the research and marketing company for U.S. cotton growers and importers. Established in 1970 as a not-for-profit company, our mission is to increase the demand for and profitability of cotton. The company meets this straightforward mission by identifying efficiency and best practices' opportunities along each link of the global cotton supply chain, and through global marketing efforts aimed at consumer and trade audiences.

As a company dedicated to providing research and intelligence to the global cotton industry, Cotton Incorporated has offices in strategic textile centers around the world: Hong Kong, Mexico City, New York, Osaka and Shanghai, with the World Headquarters based in Cary, North Carolina. The Cary facility is a state-of-the-art research center that initiates or oversees innovations in agricultural practices, fiber processing and analyses, textile chemistry, spinning, weaving, and fabric engineering; and provides in-depth crop, market and consumer marketing analyses to stakeholders. The company also creates and disseminates seasonal surface and color trend directions, and is aggressively researching commercial product uses for the entire cotton plant.

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Fusion energy: Unlocking the zero-emission grid

The opportunities provided by fusion should not be overlooked. Here, Michael Delage, of General Fusion Inc. explains the potential of the energy source

A cornerstone of any realistic path to overcoming climate change is developing sources of energy that are emission-free, on-demand and economically viable. Such sources would sustain the world's growing population and broaden the opportunity for economic prosperity. The need for these sources is urgent: global electricity demand is forecast to increase by 69% in the next 20 years, and while renewables are growing rapidly, the majority of this demand nonetheless looks set to be fulfilled by fossil fuels.[1]

The clean energy grid will need a mix of generating technologies to supply the diverse needs of consumers. When it comes to sectors with high energy intensity, such as industry or dense urban areas, fusion energy is a very attractive option. Fusion has the potential to provide clean, safe and on-demand power worldwide. It also has the potential to demonstrate the best energy payback ratio (EPR) and lowest carbon life cycle footprint of any source, making it a powerful tool to tackle climate change.

Fusion: a national priority

The potential of fusion has long been recognised by the scientific community. Over 30 years of investment by governments in research and development has brought tremendous scientific advancements, and a number of countries now consider further development of fusion to be a national priority.

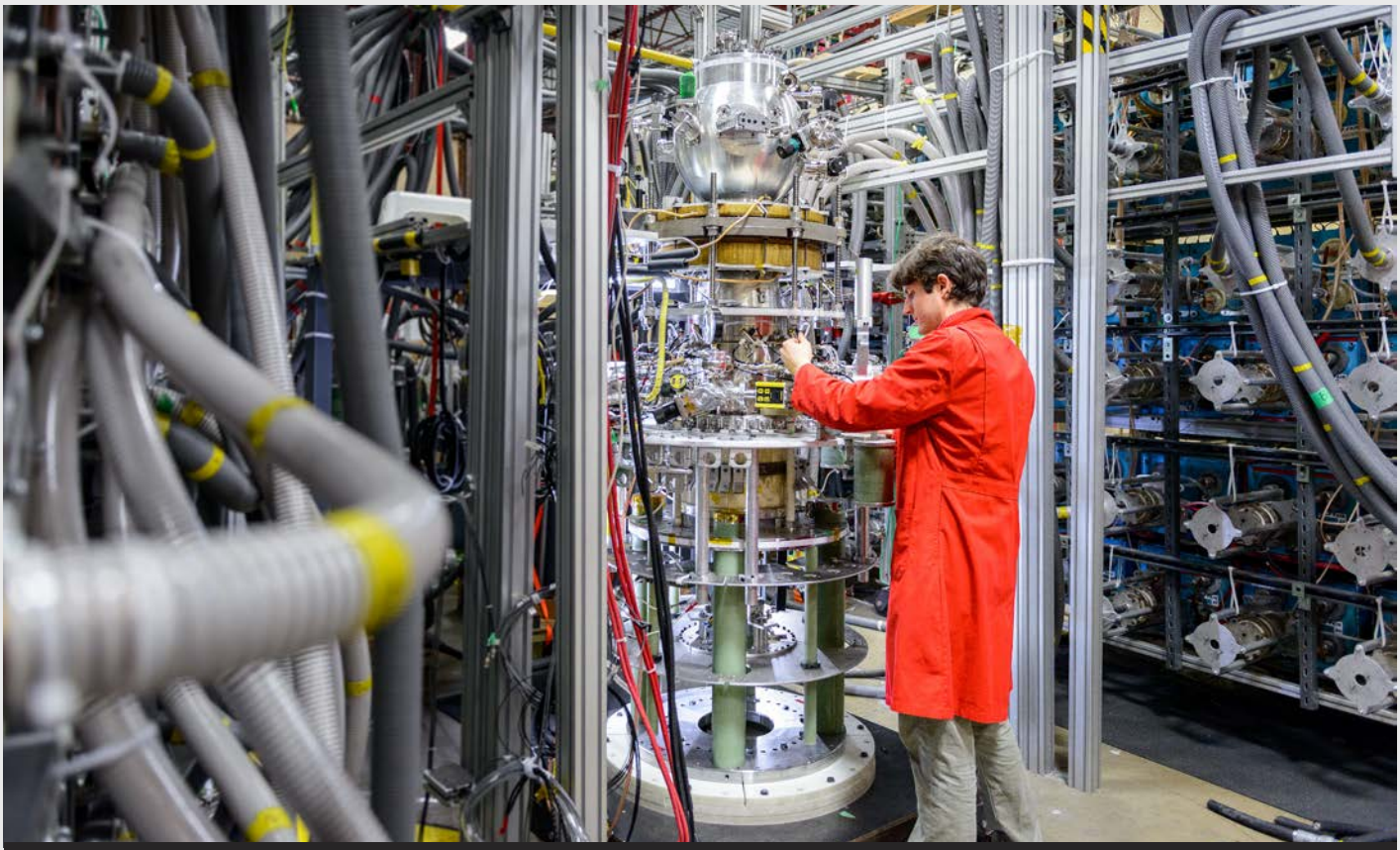
In addition to their involvement in the 35-nation ITER fusion project, China also plans to train 2,000 new fusion scientists by the end of this decade, and South Korea is investing heavily in the field.[2, 3] These projects are demonstrating the scientific understanding that is enabling fusion to move from lab experiments to applied engineering projects.

Now is an innovative time in fusion, both in government and the private sector. New ideas are springing up: proposals for fusion system designs that are more practical to implement, at lower capital cost, and which will lead us to commercially viable power plants sooner than the earlier concepts.

This renewed wave of enthusiasm is the result of a combination of factors. The scientific knowledge gained through decades of research has provided us with an excellent understanding of the principles underpinning fusion. Fields such as plasma physics, key to achieving the extreme temperatures needed to fuse the hydrogen nuclei fuel, have been intensively studied and the parameter space we must work within has been established.

In parallel, substantial technological advances have taken place in fields complementary to fusion. Computing power and electronics, simulation, and materials science have progressed dramatically since the early days of fusion research in the 1960's. Previously only feasible on the most powerful of national laboratory supercomputers, simulation of the behaviour of fusion plasmas is now possible on commercially available cloud computing platforms.

These advances provoked a vanguard of private fusion companies such as General Fusion, Tri Alpha Energy and Lockheed Martin to enter the space, capitalising on new technologies to push forward the development of innovative new approaches. With parallels to the emergence of companies such as Blue Origin and SpaceX in the aerospace industry, serious private sector investors are funding sophisticated efforts to pursue practical solutions with the goal of advancing the timeline for a commercial solution to fusion by decades.



Private companies such as General Fusion (pictured here) are drawing on 30 years of research in fusion to develop new approaches focused on commercial power plants

Backed by venture capital, these firms are developing new, power plant-focused approaches at a pace not previously seen. In the coming years we will see the first demonstration prototypes emerge, which will marshal the energy industry to drive fusion's commersialisation.

These advances come not a moment too soon. The latest figures show that while the deployment of clean energy infrastructure is growing rapidly, it is being outpaced by the staggering level of new demand. Some perspective: In 2015, China alone was responsible for 40% of global renewable power growth, but that represented only half of the country's electricity demand increase[4].

Much as we see a mix of technologies supplying our energy needs today, de-carbonising the world's electrical networks will require a new mix of generating technologies incorporating distributed renewables, large scale storage, and high output, on-demand sources. Energy companies, corporate partners and governments around the world are recognising the ability of fusion to make a significant contribution to this mix, and are investing to unlock the full potential of the zero-emission grid. ■

1 US Energy Information Agency, May 11, 2016. International Energy Outlook 2016. Figures 5-1 & 5-3

2 University of Science and Technology China Newsroom, March 24, 2011. National Design Panel for Magnetic Confinement Fusion Reactors Established at USTC

3 Nature, January 21, 2013. South Korea makes billion-dollar bet on fusion power.

4 International Energy Agency Newsroom, October 25, 2016. IEA raises its five-year renewable growth forecast as 2015 marks record year.

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Fusion energy could be the future of power production

Neil Alexander for the Canadian Nuclear Association shares why society should be looking to fusion energy to power homes and businesses in the future

Modern society loves energy. Whether it is lighting our offices, heating our homes or delivering our goods, it all takes energy.

But delivering the energy we need is becoming a problem. Fossil fuels have been the backbone of our development but we now realise burning fossil fuels is unsustainable and we must wean ourselves off them as soon as possible. There are alternatives but each comes with its own advantages, disadvantages and limitations. Nuclear fission has been delivering cost-effective power for decades but has barriers to entry that can restrict its application. Renewables, such as wind and solar have a large physical footprint, but are often not close to where the energy is needed and are intermittent. Biomass locks up large quantities of land, is hard to transport and still leads to the release of greenhouse gases. Lots of new energy models have been tried but none have been an unqualified success and none can be freely and sustainably replicated. Fusion could change that.

> "It may well have taken time to get where we are today but with few constraints on deployment and a massive demand for what it delivers, fusion could easily be the next great step in mankind's development. And it may come sooner than you think."

Fusion as a source of energy

Fusion would be a high-density energy source entirely under mankind's control with an affordable, easily available fuel. It could be easily replicated in almost any jurisdiction and doesn't have environment damaging carbon emissions.

That is why economic fusion is the holy grail of the energy industry.

When matter condensed out of energy after the big bang, an electron combined with a proton to form our simplest element, hydrogen. That is why it is by far the most common element in our universe.

But it is not the lowest energy atom. That title belongs to Iron 56. If the repulsive forces that keep light nuclei apart can be overcome they will fuse and give out energy, and lots of it.

This is where the energy of the Sun comes from. Every day when the Sun rises we are reminded that fusion works.

The issue of creating power from fusion is then, not one of its fundamental science, but rather one of engineering, materials science and control. The Sun uses its massive gravity to confine the fuel and the energy produced just dissipates into space. Controlled fusion, here on earth, requires us to find another way to contain fuel at a hundred million degrees Celsius and then to collect the energy and convert it into something useful. The Sun is self-sustaining. We begin with a cold fuel that we need to heat before the reaction can start by putting massive amounts of energy very quickly into a very small target.

Mankind has risen to the challenge, imagining many ways in which this might be done and then proving that it can. Historically the experiments have been large, as magnetic confinement has been used to hold a hot plasma (a state of matter where electrons have been stripped from the atoms) or powerful lasers have been used to create shock waves in solid fuel pellets. Notable experimental facilities include the Joint European Torus (JET) in the UK, National Ignition Facility (NIF) in the U.S. or more recently the Wendelstein 7-X

Modern society loves energy but delivering that energy is becoming a problem

stellarator in Germany. Thirty-five countries have come together to support the next phase of the Tokamak development known as the International Thermonuclear Experimental Reactor (ITER) in France. Construction of this large and complex facility will take some time and is expected to cost in excess of $20billion.

It has been a hard slog for fusion as it has had to overcome many challenges at the very edges of our knowledge and capability. Without the benefit of the Sun's gravity the temperatures needed for ignition are 6 times higher than the Sun's core and at the moment, Tritium and Deuterium (isotopes of hydrogen) have to be used rather than much more available hydrogen itself. The fusion process kicks out a lot of radiation and the materials used must be able to tolerate that radiation.

At times people have joked that commercial fusion power was 30 years away when it was first considered and it is still 30 years away. But there is powerful evidence to suggest that technologies develop exponentially and that fusion is now lifting off that initial flat part of the curve so that from here on in progress could accelerate away. Certainly, this can be seen in the announcements of technological progress on the big projects, but just as importantly it can be seen in the surge of spin-off commercial concepts such as Vancouver's General Fusion or First Light Fusion in the UK. Even ex Google executives are getting in on the game, with Mike Cassidy recently announcing the creation of Apollo Fusion.

It may well have taken time to get where we are today but with few constraints on deployment and a massive demand for what it delivers, fusion could easily be the next great step in mankind's development. And it may come sooner than you think.

Dr. Alexander is also a Principal Consultant at Bucephalus Consulting, and was one of the signatories to Fusion – 2030, a roadmap for reinstating Canada's Nuclear Fusion Research program. ■

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Helping Indigenous communities become healthier

Carrie Bourassa, Scientific Director, CIHR-IAPH discusses the issue of poor health among Indigenous communities and says research is the key to tackling it

The Canadian Institutes of Health Research-Institute of Aboriginal Peoples' Health (CIHR-IAPH) is one of the 13 founding institutes of CIHR, established in 2000. My recent appointment as the latest Scientific Director of the CIHR-IAPH allows me the chance to consider our mandate and our opportunities to bolster the self-determination of Indigenous communities to become healthier Nations, groups and individuals. As researchers, we are committed to working with the priorities Indigenous communities see for themselves in order to advance their progress in becoming healthier communities.

The IAPH fosters the advancement of a national health research agenda to promote and improve the health of First Nations, Inuit and Métis Peoples in Canada through research, knowledge translation and capacity building. The Institute's pursuit of research excellence is enhanced by our respect for community research priorities and Indigenous knowledge, values and cultures. Our goal is to contribute to the improvement of the health and wellbeing of Indigenous people in every part of Canada. We will stimulate health research with and for Indigenous communities, build a community of Indigenous researchers who can engage in "two-eyed seeing" research (conducted using Indigenous research paradigms side by side with other paradigms such as those involving Western epistemologies), form research partnerships with organisations in Canada and abroad, involve Indigenous communities respectfully in every project undertaken, and create new knowledge.

Addressing the issue of poor health

Canada's recent Truth and Reconciliation Commission (TRC) presented all Canadians with 94 Calls to Action. Some of these are calls to the government to address the issue of the poor health of Indigenous Peoples in Canada. The TRC calls upon governments to acknowledge that the current state of Indigenous health is a direct result of previous Canadian government policies, including Aboriginal residential schools, and to recognise and implement the healthcare rights of Indigenous people as identified in international law, constitutional law, and under the Treaties. Other calls to action include having the federal government identify measurable goals to determine the gaps and to report on progress toward closing those gaps in health outcomes between Indigenous and non-Indigenous Peoples, increasing the number of Indigenous healthcare professionals, and compelling those who can effect change within the Canadian healthcare system to recognise the value of Indigenous healing practices and to make them available when treating Indigenous clients.

Good research can inform good policy and practice and thereby help to achieve good results for people in need. Good research into Indigenous health requires us to see the Indigenous communities we want to work with as partners in Indigenous health research from the early stage of setting research priorities right through to reporting on our research in a way that is accessible, meaningful and, therefore, useful to Indigenous communities. We must be guided by the

Dr. Janet McElhaney, Dr. Jennifer Walker and Dr. Carrie Bourassa

Indigenous communities that are our research partners. These communities are not subjects of research; they are active participants in the entire research enterprise. Indigenous communities have protocols for sharing knowledge, and researchers must learn and respect these protocols when undertaking research.

Building research capacity

An important part of the CIHR-IAPH mission is to build research capacity in the First Nations, Inuit and Métis communities. We will do this by mentoring, supporting, and encouraging a new generation of Indigenous people to become health researchers and to create new knowledge that will improve the health and wellbeing of Indigenous communities. We will also help to negotiate partnerships and alliances between Indigenous communities and non-Indigenous health research organisations and institutes at the local, regional, national and international levels.

It is central to our mission and our values that, in creating new knowledge to benefit Indigenous peoples, the CIHR-IAPH supports health research that respects Indigenous cultures. Part of our task is to make sure that this is how all CIHR-funded health research is conducted and to act as a resource for all of the other CIHR institutes, to ensure that all researchers understand the Indigenous perspectives on the issues they are researching and include the Indigenous perspectives in their work.

The challenges to helping to create healthier Indigenous Peoples and communities are large, but the benefits of doing good research in a way that respects and contributes to Indigenous communities and actively involves Indigenous communities in the research project make the effort worthwhile. I look forward to seeing what we can accomplish with Indigenous communities in my years as Scientific Director. ■

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Ensuring health equity for Canadian indigenous populations

Professor Pierre S. Haddad shares the challenges of overcoming health inequality for Canadian indigenous populations and highlights solutions to the issue

Canada's Indigenous population is composed of First Nation (FN), Inuit and Métis peoples. They often suffer from a greater burden of disease, notably chronic (e.g. diabetes[1,2]) and infectious ones (e.g. tuberculosis[3]), than the rest of the non-Indigenous Canadian population.

Part of the health problems faced by Canadian Indigenous populations stems from the cultural disconnect that exists between the health care and services offered by public sanitary organisations, on the one hand, and the worldview of several Indigenous peoples, on the other[4]. Thus, North American Indigenous populations are deeply connected to the Earth and nature. Their health is therefore intuitively more holistic and interconnected with their communities and their environment. Consequently, health care and the response to disease also call to a more holistic approach.

Aside from being morally and socially reprehensible, the health inequities afflicting Indigenous Canadians put a significant burden on the Canadian health care system. Apart from high health care costs related to the severity of afflictions, considerable travel and living costs are required by individuals residing in more remote areas, who must be transferred to major centers in order to receive appropriate care.

As will be argued in the next sections, Indigenous traditional medicine represents a valuable avenue to explore in order to reduce the burden of health inequities, the cultural disconnect of modern therapeutics, and the high economic cost of Indigenous health care.

Indigenous traditional knowledge and traditional medicine: Valuable opportunities for improved indigenous health

Indigenous traditional knowledge (TK) in general, and traditional medicine (TM) in particular, has shown remarkable resiliency in most Canadian Indigenous communities[5], even though its transfer to younger generations is currently critically threatened. Indigenous TM is a science that is rooted in so-called "Natural Laws" and involves a close contact with nature, as well as a deep understanding of its elements and their uses for human health and wellbeing. It is also a common misconception to consider Indigenous TK and TM as static or retrograde. TM is a true science and as such evolves continuously. Elders are notably well aware of the precariousness of TK and TM, while they also fully understand the urgent need to help their fellow community members dealing with chronic or infectious diseases.

It is therefore both timely and pertinent to consider Indigenous TM as a feasible and, strangely enough, innovative means to reduce health inequities throughout Canadian Indigenous populations. Firstly, Indigenous TM has proven to be safe and efficient, both in historical and contemporary terms[6]. Secondly, Indigenous TM is very culturally connected. It is thus plausible that Indigenous people will comply better with treatments originating from their own culture than they do with "modern" medicine. It must also be stressed that Indigenous TM is a holistic paradigm whereby not only the physical part of the diseased individual is encouraged to participate in the healing process (for instance, by taking a traditional medicinal plant preparation), but also the mental, emotional and spiritual parts.

"Aside from being morally and socially reprehensible, the health inequities afflicting Indigenous Canadians put a significant burden on the Canadian health care system. Apart from high health care costs related to the severity of afflictions, considerable travel and living costs are required by individuals residing in more remote areas, who must be transferred to major centers in order to receive appropriate care."

Including Indigenous TM in health care also carries great potential to reduce the economic burden of health inequities. Indeed, through the use of local human and natural resources, the cost of therapeutic regimens can be reduced. This holds true even if Indigenous people continue using both contemporary pharmaceutical treatments and TM. Indeed, it is conceivable that

combining TM with modern drugs may reduce the dose and length of treatment required with pharmaceuticals. If Indigenous TM can mitigate, even partially, the impact of several chronic or infectious diseases, a greater fraction of the population will remain healthy or will develop less severe forms of chronic diseases and their complications. This in turn should diminish the number of Indigenous patients that need to be sent to large urban centers to be treated.

Lastly, Indigenous elders or knowledge holders will get recognition and could potentially derive a non-negligible income from their practice. Of course, this raises the question of the "professional" framework within which Indigenous TM will need to be practiced, but this issue is beyond the scope of the present discussion. Given that Indigenous TM should be delivered in a safe, efficient and ethical way, additional wealth could be generated from its practice and related activities (for instance, collecting medicinal plants and preparing traditional remedies). The consequence should also involve a reduction of poverty, one of the major social determinants of Indigenous health.

Challenges and solutions

Turning to Indigenous TM to reduce health inequities comprises a fair share of challenges. Major ones are: 1) Historical devaluation of Indigenous TM, with ensuing skepticism from the medical establishment; 2) Mistrust by several Indigenous peoples of the established order, with associated concrete fear of misappropriation of TK and TM and biopiracy; 3) Potentially harmful herb-drug interactions; and 4) The development of appropriate models to include Indigenous TM into current healthcare systems.

Many call for the integration of Indigenous TM in Indigenous health care. However, the word "integration" raises some profound questions in many FN, Inuit and Métis minds. Indeed, integration may lead to a form of assimilation or subordination that many Indigenous people fear. Given the power imbalance between the established government-run medical system and the parallel practice of Indigenous TM, such fears are legitimate.

Although these challenges can appear quite daunting, a number of fruitful endeavors have nevertheless seen the light in Canada and abroad, whereby Indigenous TM is being used safely and efficiently alongside modern health care. The key issues related to successful outcomes in such projects include the following: 1) Indigenous and non-Indigenous stakeholders must be engaged in truly equitable and empowering partnerships; 2) The agenda must be set by and for Indigenous communities; 3) Partnerships need to be based on mutual trust, mutual respect and mutual appreciation; and 4) Cultural brokers need to be involved to ensure proper knowledge transfer and exchange.

In short, Indigenous TK and TM are viable tools to consider for the reduction of health inequities afflicting Indigenous populations, notably in terms of chronic and infectious diseases. Because of the cultural and paradigm gaps that exist between current health care approaches and Indigenous TM, it is highly recommended that partnerships be developed among stakeholders and that these include culturally competent partners.

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Health Accord: Healthcare for all

Open Access Government highlights how Health Minister, Jane Philpott aims to improve the lives of all Canadians through their new Health Accord Plan

In September 2016, Canada's Health Minister, The Honourable Jane Philpott, revealed plans for Canada's new Health Accord Plan to the CANADA 2020 Health Summit. The Summit was in partnership with the Canadian Medical Association, aimed to open debate and discover solutions to help Canadians lead better and healthier lives – particularly for the more elderly population of the country.

In the opening of her speech, she stated that, "Already, Canada is one of the world's highest spenders on healthcare and yet we are not achieving the kind of results Canadians need and deserve."

This is evident from in the CMA National Report Card 2016, where only 37% of Canadians assigned a letter grade of A to the "overall quality of health care services available".

Philpott went on to outline the Federation's "shared priorities for health", which include homecare, pharmaceuticals, mental health, and improved healthcare for the Indigenous population. Overall, the Federal Government's priorities for healthcare spending align with aspects of the healthcare system that Canadian citizens prioritised in the National Report Card.

Homecare

One of the key priorities for the Health Accord is improving investment for homecare. The Minister outlined how in Canada $10 billion, around 5% of total health spending is spent on home and community care.

"That's a lot of money, but it's probably not enough, especially since our population is aging and burdened by increasing rates of chronic disease," Philpott stated.

Philpott went on to say, "Today, some 15% of hospital beds are occupied by patients, who might be better off at home or in long-term care. This has a huge financial impact. For example, in Ontario, basic homecare costs $42 a day, compared to a minimum of $840 a day in a hospital.

"More importantly, it's not the best way to care for them – we know the hospital it not where they want to be, unless it's absolutely necessary. We have a golden opportunity to put in place robust systems of services and supports that will address these gaps."

Not only was Philpott's argument for better investment, she also stressed the importance of putting more resources into homecare, so that patients, carers, and families have more support and "don't burn out".

Mental Health

The National Report Card stated that 83% of Canadians placed mental health services within the top funding considerations. This emphasis on mental health is no surprise when the Canadian Centre for Association and Mental Health (CAMH) found that by the time Canadian's reach the age of 40, half have, or have had, experiences of mental illness. Furthermore, a third of people who had reported mental health issues in the past year said that their needs had not been met.

At the Health Summit, Philpott added mental health to her priorities as part of the Health Accord Plan to improve healthcare across the country. She highlighted mental health as something that needs to be discussed openly between families and even communities.

The Minister said, "For too long, mental illness was something to be hidden, something to be ashamed of. Today, we talk about it somewhat more openly in our families and in our communities, and that is a good thing.

"But as the full extent of the burden of mental illness in Canada becomes clear, it's become obvious that our systems are not well-equipped to heal the trauma caused by mental illness."

She also admitted that while "doctors and other front line workers do their best", they "often don't have adequate training".

However, she did mention plans to "build systems where mental health services are widely available and supportive".

Indigenous populations

Canadians placed better healthcare for the Indigenous populations below many other healthcare improvements, with only 64% of people believing it to be an important area of funding.

However, Philpott clearly stated that this was an important issue for the Government. She argued that challenges within the healthcare system are "magnified many times over for Indigenous peoples in Canada".

Evidence for this includes the 2017 life expectancy statistics that found that life expectancy among the total Canadian population is 79 years for men and 83 years for women. However, for the Indigenous populations, the projected life expectancy is much lower, 64 years for men and 73 years for women.

Philpott summarises this gap in healthcare by saying "If you are an Indigenous, your life expectancy is up to a decade shorter than for other Canadians. Your rates of diabetes are 3 times that of the national average. In First Nations, rates of tuberculosis are 33 times that of other Canadians. For Inuit, the rates of tuberculosis are 375 times higher than those for non-Indigenous Canadians".

In her speech at the Health Summit, Philpott ended by emphasising the "need to adapt to new ideas" and renew Canada's "approach to health policy", concluding with the message that "by working together, Canada can be a world leader to ensure our ultimate collective goal, that is, health for all".

The full speech from the Minister at the Canada 2020 Health Summit can be found here. ■

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Using Positron Emission Mammography to detect breast cancer

Dr Alla Reznik, Canada Research Chair in Physics of Medical Imaging, explains how Positron Emission Mammography is effective when detecting breast cancer

Breast cancer accounts for approximately 26% of all cancers diagnosed today. One in 8 women are expected to be diagnosed with breast cancer in their lifetimes. According to the National Cancer Institute, in 2016 there were 246,660 new cases and 40,450 deaths from breast cancer in the U.S alone. Like other cancers, breast cancer is most successfully treated if the disease is diagnosed early. In addition to better health outcomes, there are economic benefits to accurate screening and early diagnosis of the disease. It is estimated that the cost of treating early stage breast cancer is about $12,000, while late stage treatment costs start at around $150,000.

Common practice for breast cancer screening is x-ray mammography for women over 50. Unfortunately, for too many women, x-ray mammography is too ambiguous to detect their disease in time for effective treatment. The problem is that the specificity of mammography suffers from its difficulty in distinguishing between benign and malignant masses: dense breast tissue appears similar to cancer on x-ray mammograms, leading to inconclusive imaging results. Patients with suspicious mammograms are prone to either unnecessary biopsies or late identification of serious disease. Of the women that are screened with mammography, roughly 18% have a suspicious but inconclusive finding and a third of these are sent for biopsy. Roughly 75% of biopsies prompted by mammography come back negative and in the U.S alone these account for 1.5 million unnecessary biopsies that could be prevented with more cancer-specific diagnostic imaging. The situation is the most urgent for women with a known high and intermediate lifetime risk for breast cancer. High-risk patients have to be screened at a significantly younger age than average risk women. Younger high-risk women tend to have denser breast tissue which does not produce accurate images when scanned using x-ray mammography.

The inconclusive nature of breast cancer detection with either mammography or its combination with MRI means that a large cohort of women (especially, high-risk patients) cannot rely on imaging to start disease treatment at the early stage. These women are forced to contemplate prophylactic mastectomy because the predictive power of current imaging is so poor.

Early detection

Radialis Medical Corporation, a joint venture (spin-off) of the Thunder Bay Regional Health Research Institute (TBRHRI) and Lakehead University, Ontario, Canada, addresses this important unmet patient's need. Radialis is manufacturing an advanced Positron Emission Mammography (PEM) system for molecular (or functional) imaging of breast cancer. PEM detects small cancerous breast lesions based on their increased glucose metabolism and in such its imaging performance is inherently independent on breast tissue density.

The core technology of the PEM system was developed in Dr. Alla Reznik's research laboratory at Lakehead University and TBRHRI. Radialis PEM employs 2 planar high-resolution detector heads placed on both sides of gently steadied breast (Figure 1). Each detector head contains a large field-of-view (17cm x 22cm) gamma-photon sensor based on the novel type of solid-state (silicon) high-gain detection technology. During image acquisition, detectors fully cover the entire breast that allows for improved sensitivity capable of significant radiation dose reduction (by the factor of 4) in comparison with commercially available scanners.

Another advantage of Radialis's design is its slim detector head and minimised "dead area" (the distance between the imaging part of the detector and its housing). This comparatively small step allows for significant clinical benefits since it tremendously improves visualisation of deep chest lesions, provides more options for detector heads positioning around the patient breast and access to lymph nodes to evaluate its possible metastatic involvement.

The assembly and imaging performance evaluating of Radilis's PEM are

underway. Initial results with phantoms mimicking breast lesions of different sizes demonstrate that tumours as small as 1.2mm in size will be detectable in a clinical setting. The ultra-high resolution achieved combined with a large field-of-view detector design enables high-resolution, low-dose molecular breast imaging. Additionally, large area stationary solid-state sensor design means that there will be less radiation that will escape Radialis's device.

In addition to improved early breast cancer detection for a large cohort of patients, the use of PEM for screening of the high risk population will allow for significant improvement in patients' compliance for frequent tests. Indeed, at the current stage of mammographic detector technology, extreme breast compression is applied. The associated pain and anxiety is so strong that a large number of patient refuse mammography after their first experience. In contrast, PEM only requires breast immobilisation rather than compression and hence completely eliminates pain. This has the potential to significantly improve compliance and the effectiveness of cancer detection.

Overall, once implemented in clinical practice, Radialis's PEM technology can be used as (1) an adjuvant technique for breast cancer detection, and (2) an integral part of the surveillance protocol of women at high and intermediate lifetime risk of breast cancer. In addition, the technological advances used will reduce manufacturing cost for PEM devices facilitating their widespread clinical usage, thus positively influencing people health.

Dr Alla Reznik

Dr Alla Reznik is a Canada Research Chair in Physics of Molecular Imaging and an Associate Professor in the Physics Department, Faculty of Science and Environmental Studies, Lakehead University. She is also affiliated as a Senior Scientist in the Thunder Bay Regional Health Research Institute (TBRHRI). Dr. Reznik has completed her PhD in solid-state physics at the Technion- Israel Institute of Technology. After several years as a Senior Physicist at the GE Medical Systems she decided to return to academia and accepted a Research Associate position at the University of Toronto, Canada. In 2008 she was appointed a Canada Research Chair in Physics of Molecular Imaging and in 2013 re-appointed as a Canada Research Chair in Physics of Medical Imaging. She is a specialist in photoconductive materials and technologies for radiation medical imaging. The focus of her work is on solid-state technology for organ-specific Positron Emission Tomography (PET). The goal is an improvement in resolution and sensitivity over commercially available PET imagers. Another focus of her work is on advanced low-dose direct conversion x-ray imaging detectors based on novel x-ray-to-charge transducers. Reznik group's PET research has led to the launch of Radialis Medical – the first joint Lakehead – TBRHRI spin-off-company, which will produce a commercial version of the technology for breast cancer detection.

Radialis™ Medical

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Fighting against breast cancer in Canada

Canadian Cancer Society's Dr Rob Nuttall and Shawn Chirrey explain how fighting against breast cancer requires ongoing support for research and screening

In 2016, an estimated 26,000 Canadian women and 230 Canadian men were diagnosed with breast cancer. Breast cancer occurs when cells change and no longer grow or behave normally. A Canadian woman has a 1 in 9 chance of getting breast cancer during her lifetime.

Research in Canada and across the world has managed to boost survival rates from 70% in the early 1970s to 87% today. Thanks to this research and advances in screening, today we know more about how to diagnose and treat breast cancer than we ever have.

> "Thanks to organised screening programmes, research, improved treatment options and prevention recommendation we now have more breast cancer survivors than ever. We're grateful to now be able to turn more attention to survivorship and how we support women who are able to live their lives thanks to research."

What increases my risk of getting breast cancer?

In general, about half of all cancers can be prevented by not smoking, exercising and maintaining a healthy body weight. The same goes for breast cancer – if you're able to lead a healthier lifestyle, then your chances of getting breast cancer will go down.

While the risk of breast cancer increases with age, a personal or family history of breast cancer may further increase your risk. Additionally, studies have shown that women with inherited BRCA1 or BRCA2 gene mutations have up to an 80% chance of developing breast cancer in their lifetime. Women with these inherited mutations also have a higher risk of developing breast cancer at a younger age (usually before menopause) than other women.

Drinking alcohol also increases a woman's risk for breast cancer. Even low levels of alcohol consumption (just over 1 drink per day) can increase a woman's risk. The risk increases with the amount of alcohol consumed. One possible reason for this is that alcohol is thought to cause higher levels of estrogen. Other factors that can increase a woman's risk of breast cancer include obesity and hormone replacement therapy.

Are there tests for breast cancer?

In Canada, there are breast cancer screening programmes in each province and most territories. For women at average risk for developing breast cancer, mammogram screening is most effective every 2 years, between the ages of 50 and 74. It's important to note that breast cancer risk varies from woman to woman, so you should make a point of discussing your personal risk with your doctor. If you have family members who have had breast cancer, or you carry a certain gene mutation, then you may be recommended to start breast cancer screening earlier and more often. If you have high breast density (75% or greater) you may be asked to screen annually.

Breast cancer screening is done via a mammography. A screening mammogram is used to look for breast cancer in women who don't have any symptoms of the disease. It may be done in a clinic, screening centre or mobile screening mammography unit. During a mammogram, a plastic plate will be slowly pressed down to flatten your breast and hold it in place for a few seconds while two images of each breast are taken. You will feel some pressure on your breast during the x-ray.

Like most screening tests, there are benefits and limitations to mammography. Scientific evidence tells us that regular mammography screening leads to fewer deaths in women with breast cancer. This is because it

helps finding breast cancer when it is smaller and more treatable, which increases the chances of survival. Limitations of mammography include having false positives, false negatives, or finding cancers that may never cause any symptoms (over-diagnosis).

If you want to learn whether a mammogram is right for you, then we encourage you to use our screening-decision aid tool called My Breasts, My Test. Launched last year, the tool will help you understand what factors to consider and help you to ask questions of your healthcare provider.

Supporting more survivors than ever before

Thanks to organised screening programmes, research, improved treatment options and prevention recommendation we now have more breast cancer survivors than ever. We're grateful to now be able to turn more attention to survivorship and how we support women who are able to live their lives thanks to research.

Since merging with the Canadian Breast Cancer Foundation earlier this year, CCS is better equipped than ever to fund more research, prevent more diagnoses and support more Canadians affected by breast cancer.

For those in Canada, if you'd like to speak with someone about yours or a loved one's breast cancer diagnosis, you can visit www.cbcf.org/support to speak with a CCS representative, or call 1-888-939-3333 to speak with someone from CCS's Cancer Information Service. ■

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Viruses and cancer: Integrating large-scale data to identify unique gene signatures

Cancer is a terrible disease that touches the lives of millions of individuals every year. With cancer being the second leading cause of death in adults, most people have lost a parent, a loved one, or a friend to cancer. The most recent statistics from the American Cancer Society estimate that roughly 40% of people will develop cancer in their lifetime. Cancer is a disease that originates in our cells. Our bodies are made up of millions of cells, grouped together to form tissues and organs such as the lungs, the pancreas, the liver. Our genes order our cells to grow, function, reproduce and eventually die. Normally, our cells obey these rules and we remain healthy. But sometimes things go wrong, causing the cells to multiply uncontrollably, forming lumps or tumours, and spreading through the bloodstream to other parts of the body (metastases). With the recent advances in medical research, many of these can now be better diagnosed and treated. Although significant progress has been made in treating many cancers over the past 25 years, a number of cancers such as pancreatic and brain cancers, continue to have high case fatality rates after diagnosis thereby creating havoc in that person's life as well as their loved ones.

Viruses and cancer

It is nearly impossible to identify what causes a cancer in any individual, because most cancers have multiple possible causes. There are numerous causes and risk factors for cancer such as genetic mutations, hormonal changes, immune dysfunctions, tobacco use, alcohol use, obesity, dietary factors, physical inactivity, environmental polluants, and radiations. One of the most fascinating cause of cancer that is often overlooked is infection by viruses. Indeed, human viruses play an important role in cancer. Around the world, cancer-inducing viruses are estimated to cause 15 to 20 percent of all cancers in humans. With the advent of new technologies allowing genetic identification, it is very likely that this number will continue to increase. Although only a small proportion of virus-infected individuals develop cancers, the total burden of infection-associated cancer is very large, with an estimated 2 million new cases of virally-induced cancer worldwide each year. To date, Epstein-Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV), human papillomaviruses (HPV), Merkel cell polyomavirus (MCPV), hepatitis B virus (HBV), hepatitis C virus (HCV) and Human T-cell Lymphotropic virus type 1 (HTLV-1) have been classified as cancer-inducing infectious agents. Cancer-inducing viruses are implicated in many types of human cancer such as liver cancer (hepatitis B and C viruses), cervical cancer (HPV), Burkitt's lymphoma and nasopharyngeal carcinoma (EBV), leukemia (HTLV-1), stomach cancer (EBV), skin cancer (MCPV), and Kaposi's sarcoma (KSHV). Over the past fifty years there has also been considerable interest in determining whether a virus may play an important causative role in other types of cancer, such as breast cancer, but no consensus has been definitely reached.

How do viruses cause cancer?

Viruses typically initiate cancer by altering the expression of the genes in the cells that they infect or by integrating their genetic materials in key regions of our DNA. They can also induce inflammation or produce viral proteins which will eventually lead the infected cells to start multiplying uncontrollably. The process by which a virus can cause cancer is complex and requires multiple steps in addition to virus infection. Therefore, the latency period (from viral infection to the appearance of the virus-positive tumor) can be many years. Cancer-causing viruses frequently maintain chronic infections in which there is absence or little production of viral particles. However, in many cases, the exact mechanisms by which these viruses cause cancer remain largely unexplored.

During viral infections, the expression of cellular genes is subjected to alterations that are induced by both viral and antiviral mechanisms. Interestingly, cancer cells also harbor modifications in the expression of their genes. It is therefore not surprising that many laboratories are entering

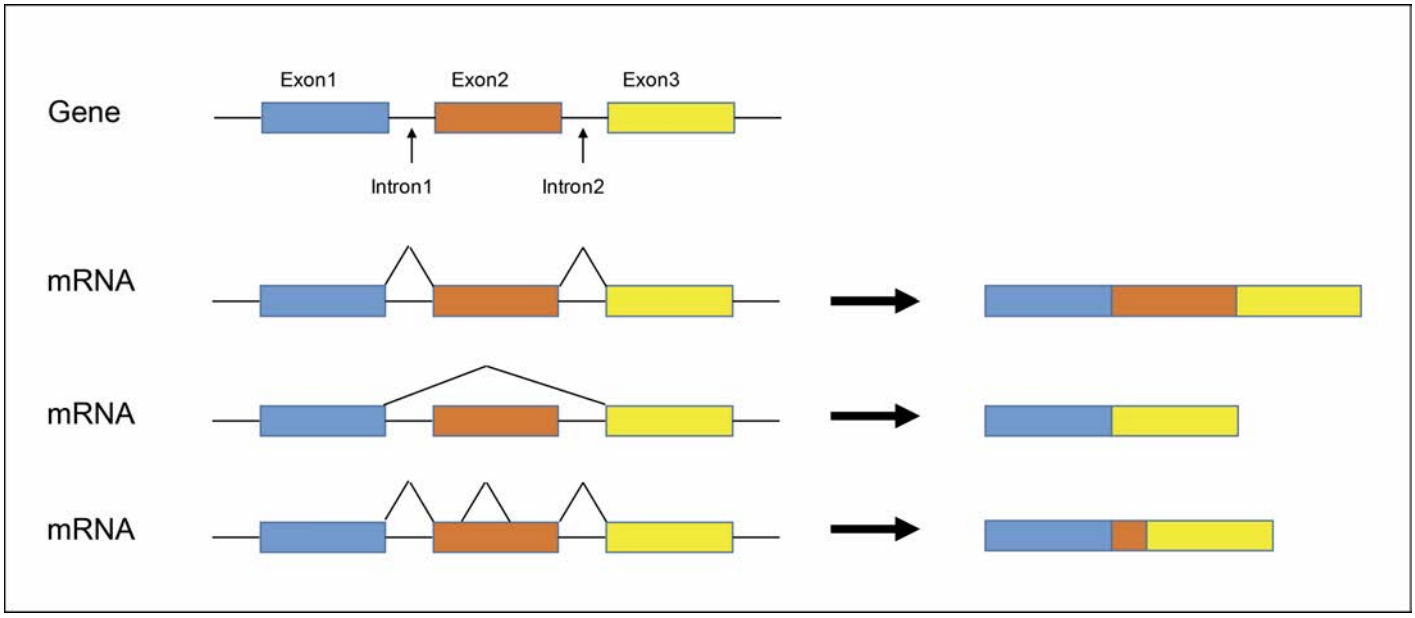

Fig. 1: Alternative RNA splicing. Alternative splicing is a regulated process during gene expression that results in a single gene coding for multiple proteins. In this process, particular exons of a gene may be included within or excluded from the final mRNA produced from that gene. Consequently the proteins translated from alternatively spliced mRNAs will contain differences in their amino acid sequence and, often, in their biological functions. Only a few examples of alternative splicing are presented

the personalised medicine era by focusing their studies on identifying unique genetic signatures which allow scientists to distinguish between very similar cancers. For instance, infection by EBV is associated with at least 10% of all cases of stomach cancer. Nearly 80,000 patients worldwide are estimated to develop EBV-associated gastric carcinoma (EBVaGC) annually. Interestingly, EBVaGC has unique morphological, genetic, and phenotypic features, compared to EBV-negative gastric cancer tissues, and treatment is therefore different for these two similar types of cancer. Correctly and rapidly identifying these types of cancer is therefore crucial for the effective treatment of patients with stomach cancer.

Alternative RNA splicing and cancer

Traditional profiling of global gene expression has resulted in several sets of biomarkers capable of detecting cancer subtypes. However, most expression profiling techniques have focused on changes in the levels of gene expression and have simply ignore changes in the transcript architecture resulting from a molecular mechanism called alternative splicing. Our genetic information is stored in genes, located in DNA in the nucleus of cells. This information is transcribed from DNA into a messenger RNA (mRNA) template by a process called transcription. These mRNAs are then coverted into proteins by a process called translation. However, before the mRNA can be translated into proteins, non-coding portions of the mRNA sequence, called introns, must be removed and protein-coding parts, called exons, joined together by a mechanism called RNA splicing to produce a mature mRNA. Scientists quickly discovered alternative patterns of mRNA splicing that produced different mature mRNAs containing various combinations of exons from a single precursor mRNA. Recent studies indicate that almost every human gene can produce different combinations (or isoforms) through alternative splicing. Indeed, the vast majority of gene products (~90%) use alternative splicing (Figure 1). In humans, alternative splicing plays a central role in protein diversity by generating multiple and functionally diverse protein isoforms. In the last few years the contribution of alternative splicing to human diseases, particularly in cancer, has been widely recognised. It is now evident that the unbalanced expression of splicing variants or the failure to properly express the correct isoforms is part of the biology of cancer cells.

Genome-wide approaches are starting to reveal that tumorigenesis, the process by which cells become

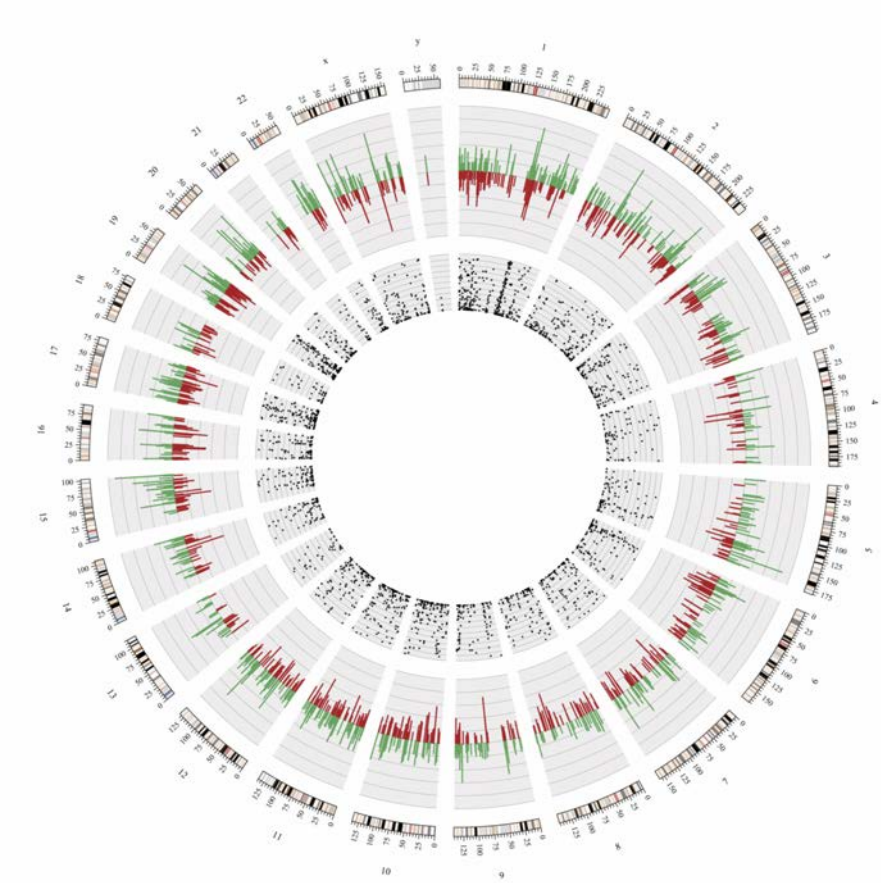

Fig. 2: Global profiling of alternative splicing event modifications in gastric cancer. Alternative splicing event modifications in gastric cancer tissues are presented. The circular representation of the human genome is shown. The localisation of significant alternative splicing events is shown by a histogram where each bars represent an alternative splicing event that is modified between normal and cancer tissues. Positive differences are represented in green whereas negative differnces are represented in red. The inner circle represents the statistically significance of each spliced genes where the outer dots show statistical p-value of 0.05 and the inner dots represent a p-value of 0.0001

cancerous, often involves large-scale alterations in alternative splicing. Such approaches have been valuable in providing insight into the regulation of splicing in cancer, and have revealed to be useful in the classification of tumors. In fact, alternative splicing events can now be used as specific biomarkers, as was recently shown in the case of breast cancer tissues. In the case of prostate cancer, it has been shown that alternative splicing signatures derived from microarray-based profiling are more reliable for diagnostic purposes than are signatures derived from mRNA expression profiling. Frequently the function of the alternative splicing isoform is unknown, but it appears that maintaining a subtle balance between splicing variants is vital to cellular function and dynamics. However, one major challenge still resides in a better molecular understanding of splicing programs which are found in different types of cancer.

Can viruses modify the alternative splicing program of infected cells?

During the past year, my research group has been actively investigating the ability of viruses to modify the alternative splicing program of infected cells. The study of alternative splicing in mRNAs encoded by cellular genes during infection by human viruses remains sparse. Only a few specific examples of cellular mRNAs for which alternative splicing is modified upon viral infection had been previously identified. We relied on a technique called RNA sequencing (or RNA-seq) to provide a comprehensive portrait of global changes in the RNA splicing signatures that occur in cells following infection with a human virus. This technology uses the capabilities of next-generation sequencing to reveal a snapshot of all the mRNAs from a cell at a given moment, thereby providing the ability to look at changes in alternative splicing and gene expression. We designed a simple experiment where we infected cells with a model virus (called reovirus) and looked at all the cellular mRNAs following infection. This initial study allowed us to identify modifications in the alternative splicing patterns of 240 cellular mRNAs. Interestingly, these modifications seemed to occur on mRNAs which encode for proteins with important roles in viral infection/immunity. Among the transcripts for which alternative splicing was significantly affected upon viral infection, many splicing events we documented affect important protein domains. This led us to hypothesise

that viruses might target specific cellular mRNAs in order escape cellular immunity.

We next investigated alterations to the global RNA splicing landscape of cellular genes in the context of a virus-induced cancer. We chose gastric cancer as a model since two distinct types of gastric cancer can be easily identified: EBV-negative, and EBV-positive associated gastric cancer. Using high-throughput RNA sequencing from 295 primary gastric adenocarcinomas, we identified alterations in the AS patterns of more than 1700 genes (Figure 2). Interestingly, the vast majority of these genes encode for proteins with are known to be important for the development of cancers (such as tumor suppressor genes, transcription factors, and kinases). This study also allowed us to identify unique gene signatures for which alternative splicing is misregulated in EBV-negative, and EBV-positive associated gastric cancer. Analysis of the alternative splicing landscape revealed numerous gastric cancer–specific markers, which significantly increases the number of potential biomarkers that can currently be identified by standard expression profiling alone. We also showed that a specific protein from EBV, called EBNA1, interacts with cellular splicing factors and modifies the alternative splicing profile of cellular genes. The currently available gastric cancer markers available today mainly detect advanced gastric cancer, for which only palliative treatment is available. The current identification of unique signatures for genes in which alternative splicing is misregulated in the different types of gastric cancer clearly constitutes a step toward the identification of other useful gastric cancer-specific markers.

The future?

Cancer has been around for a very long time being mentioned in papyri dating to around 1500 BCE. However, the global cancer burden is growing at an alarming pace. It is estimated that in 2030, about 22 million new cancer cases and 13 million cancer deaths will occur, simply due to the growth and aging of the population. The future burden may be further increased by the adoption of behaviors and lifestyles frequently associated with economic development and urbanisation such as smoking, exposure to polluants, and physical inactivity. Fortunately, there has never been a better time for researchers to work on finding a cure for cancer. With so many new technologies and the advent of personalised medicine, medical decisions and practices will likely transform the way we fight this disease. A number of challenges will surely arise in this new era, including intellectual property rights, patient privacy and confidentiality as well as regulatory oversight. Alternative splicing profiling of tumors, such as we and others are currently performing, is one of the multiple genomic approaches currently being used to better diagnose and treat cancer patients. Interestingly, strategies to modulate alternative splicing by splice-switching oligonucleotides in order to correct aberrant alternative splicing events are currently being developed. It is therefore tempting to speculate that such a strategy could be applied to many different cancers, including cancers induced by viruses. Our identification of extensive changes in the cellular alternative splicing landscape in gastric cancer likely represents a first step toward the development of such anticancerous agents.

Profile

Pr Martin Bisaillon is an expert in Biochemistry and viral enzymes. He obtained a PhD in Microbiology and Immunology at the Université de Montréal in 1999. He then completed his post-doctoral training at the Sloan- Kettering Institute in New York City before directing a research team in the pharmaceutical industry aimedat developing antiviral agents. He is currently Chair of the Biochemistry Department at the Université de Sherbrooke.

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An ounce of prevention, a pound of cure: What makes successful obesity policies?

Philip Sherman, Mary-Jo Makarchuk and Keeley Rose at the Canadian Institutes of Health Research, highlight the need for research to inform successful obesity policies

Obesity is a chronic condition in which excess body fat is associated with impaired health. Rates of obesity have risen in Canada over the last 2 decades[1]; it is estimated that 1 in 4 Canadian adults and 1 in 7 Canadian children are now obese[2]. Rates of obesity vary by geographical area and in specific populations, such as in Indigenous Peoples[1, 3].

Concern about obesity rates is not limited to Canada. Worldwide obesity rates have been rising globally since 1980, with an estimated 600 million people globally estimated to now be obese[4]. Although obesity is generally associated with higher income countries, rates of obesity are also increasing in low and middle income countries[4]. Recognising the impact of rising obesity rates around the world, in April 2016 the UN General Assembly declared a Decade of Action on Nutrition (2016-2025), calling for the reversal of rising trends in overweight and obesity and reducing the burden of diet-related, non-communicable diseases across all age groups[5].

Obesity is a risk factor for the development of chronic diseases such as stroke, heart disease, type 2 diabetes, osteoarthritis, and cancer,[2, 4] which have the potential to negate health advances that have contributed to increased life expectancy over the last century. In addition, those with obesity face physical and emotional consequences of stigma and discrimination associated with their body weight[6]. In Canada, the significant economic costs of obesity include direct costs such as the costs to treat obesity-related health conditions, and indirect costs such as workplace absenteeism, disability, and premature mortality[1, 2].

It is recognised that multiple factors – including biological, behavioural, and societal factors – contribute to obesity. As a result, interventions at multiple levels

(including individual, organisational and community levels) will be required to address the challenges of obesity[1, 7]. Additional research is needed to support this multi-tiered approach, with focus on understanding the underlying causes of obesity and developing more effective preventative strategies and treatment interventions. For example, numerous animal studies suggest a role for the gut microbiome in obesity, but more work needs to be done to establish the role of microbiome in human obesity and determine whether microbiome-based interventions can be used to either prevent or treat obesity. Evidence to inform the development of effective population health interventions is also greatly needed, particularly evidence to inform effective interventions that target health inequities.

Translating research into policy

The Canadian Institutes of Health Research (CIHR), the Government of Canada's health research investment agency, supports health research across 4 health research themes (biomedical, clinical, health services, and population health research). Obesity has been a strategic focus of the CIHR Institute of Nutrition Metabolism and Diabetes (INMD) since 2001[8]. As a result of targeted investments in research, Canada is now inter-

nationally recognised for producing excellent and highly impactful research in the field of obesity[9]. To support the development of evidence to inform policy and treatment, CIHR will continue to fund research on obesity and healthy body weight and to mobilise knowledge for effective preventive and therapeutic interventions and public health policies.

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The Government of Canada is taking actions to address the challenges of obesity in Canada, including initiatives related to nutrition. For example, in October 2016, the Honourable Jane Philpott, Canada's Minister of Health, launched the Healthy Eating Strategy for Canada that contains elements to support the maintenance of healthy body weight, including the revision of Canada's dietary guidance, improving food labelling, and restricting the marketing of unhealthy food and beverages to children. In addition, CIHR and Health Canada, have partnered to support research on dietary sugars and health outcomes, as well as population level approaches that could contribute to reduced consumption of sugars. ■

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www.cihr-irsc.gc.ca/e/12043.html
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Optimising the menstrual cycle: Fact not fiction

Researchers at the Human Performance Laboratory are separating the fact from the fiction when it comes to optimising the menstrual cycle of female athletes

Athletes, coaches, and sport physiologists know that the menstrual cycle can impact athletic performance, positively and negatively, despite limited research. In the mid-80s, female athletes were overlooked for research studies because of the challenges and complexity of measuring hormones. I wanted to investigate biomarkers associated with overtraining in rowers, specifically females. An important research component would be understanding how hormonal responses impact the metabolic stress of exercise. My graduate supervisor, however, said it would be too difficult and costly to measure the many factors affecting menstrual cycle characteristics.

Menstrual 'cycle'

A quick review highlights that the idealised model of cycle length is 28 days. In the follicular phase, days 1-13, the pituitary gland stimulates egg development through estrogen production. After the egg is released the ovary produces the hormone progesterone to ready the uterine lining for implantation. Days 13-15 are the ovulatory phase. The luteal phase, days 16-28, is dominated by progesterone and follows post ovulation. Ovulatory disturbances include cycles where no egg is released, (anovulation) or shorter or longer follicular and luteal phases. Throughout the cycle, the luteinising hormone (LH) is secreted and controlled by the hypothalamic-pituitary-ovarian (HPO) axis. Energy balance factors associated with caloric intake, low body fat and weight restriction, influence the ability of the HPO-axis to withstand the stress brought on by exercise (Loucks & Horvath, 1985). Subsequently, a negative energy balance results in ovulatory disturbances including amenorrhea (periods are absent), which often associated with the Female Athlete Triad.

The female athlete 'triad'

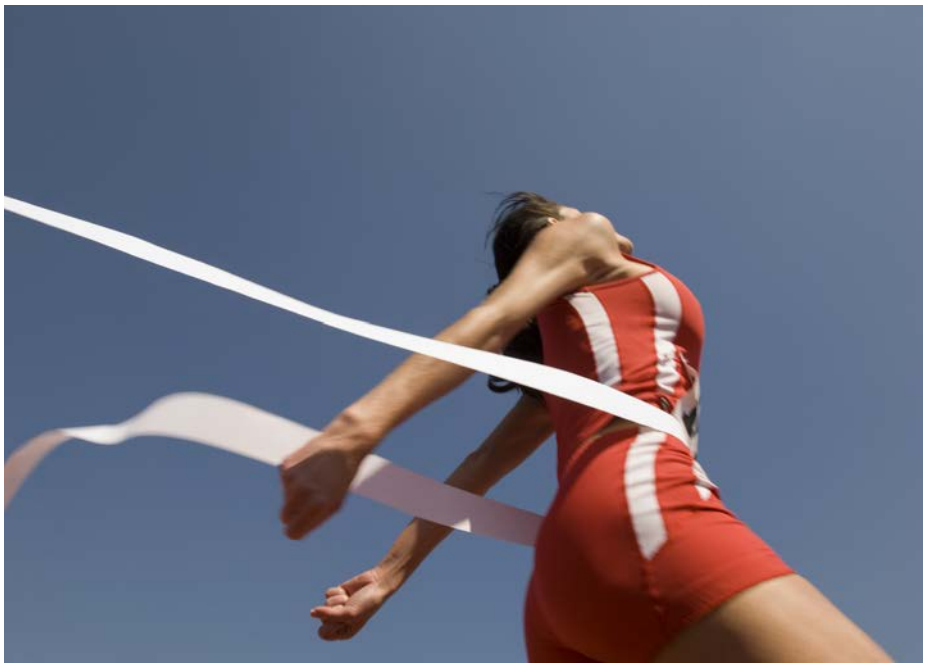
The triad is a combination of energy deficiency, ovulatory disturbances, and bone loss (osteoporosis) or bone weakening (osteopenia). Triad research in the early 90s was focused on athletes participating in aesthetic (gymnastics, figure skating, and ballet) and endurance sports (cross country skiing and running). At the time, I was the sport physiologist for the national ice hockey team. We investigated energy expenditure and the metabolic-hormonal profiles of elite ice hockey players (HG) and non-athlete but active university students (CG) (MacDonald & Doyle-Baker, 2000, 2001). We measured luteal phase length using basal body temperature (BBT). This method coupled with keeping a menstrual cycle diary was too time intensive for the HG, with only a 28% completion rate versus 70% with the CG. Our data suggested that although HG and CG were in a chronic state of negative energy balance, they did not exhibit a loss of body weight or percent body fat, commonly associated with disordered eating practices and the triad. But they did have varying cycle lengths.

'Cycle' length

The mean cycle length for both groups was within the defined range of a typical length, 21-36 days (Munster et al., 1992). The maximum cycle length of both groups, however was suggestive of the occurrence of oligomenorrhea, i.e. greater than 36 days. Similarly, the minimum cycle length was indicative of polymenorrhea, i.e. less than 21 days, but was only observed in the HG. Both groups were classified as having short luteal phases (less than 10 days), with the mean luteal phase length for the CG slightly less than that of the HG. Anovulation occurred in 50% of HG and 43% of CG cycles. Overall, the HG group exhibited slightly longer cycle lengths when compared with the CG. These results loosely supported Loucks and Thuma's seminal research to show that low energy availability, not necessarily the stress of exercise or athletic involvement, was the factor responsible for altering the LH pulsatility in exercising women (2003).

Energy availability

We continued to ponder the idea of energy availability in the menstrual cycle from a substrate utilisation and fuel perspective for a decade before embarking on more research. Estrogen is well known to reduce carbohydrate oxidation and increase free fatty acid



availability, and progesterone promotes protein catabolism. Therefore, hormone fluctuations high or low during the menstrual cycle may influence: 1) endurance and high intensity exercise performance and 2) the trainability of muscle strength and increase in muscle mass. Hormones also play a role in fluid regulation measured by blood plasma volume (hematocrit). When hormones are high, estrogen and progesterone may contribute to a decreasing plasma volume resulting in blood viscosity changes (hemoglobin). Based on the above, we hypothesised that in a 4-week training study aerobic fat oxidation would be improved during the luteal phase when compared to the follicular phase (Minichiello et al., 2016).

Training study

Recreationally trained eumenorrheic (menstruating) cyclists (n=8, 46.0 ±5.1 years) were recruited in Calgary Alberta. Weekly performance testing was accompanied by 'day of cycle', urine colour selection, body composition, hematocrit and hemoglobin measures. To mimic training intensities two workloads below ventilatory (anaerobic) threshold were used maximizing fat burning (approximately 60% VO_{2max}) and two mean max power (MMP) tests (6 and 60 second) were used for power output measures. Fat oxidation mean results were significantly different ($p<0.05$) over the four weeks specifically between week 1 and 4 and week 3 and 4. The six second MMP test showed no significant difference with means of 747.25 watts, 718.00 watts, 751.88 watts, and 715.63 watts for weeks one through 4 respectively. Although inconsistencies occurred throughout the 4-weeks, these findings suggest a trend towards improved fat burning during the luteal versus the follicular phase. More training studies with larger numbers are needed to fully understand the effect of menstruation on sport performance determinants such as fat oxidation and power output.

Menstruation and sport performance

The combined research and anecdotal evidence I have heard as a sport physiologist identifies that the menstrual cycle effect on sport performance is not science fiction. After three decades of menstrual cycle research there is no clear consensus but agreement exists that substrate availability and fluctuating hormone levels play an important role particularly in endurance performance (Abdollahpor et al., 2013; Oosthuyse and Bosch, 2010). There is complexity in measurement, which is influenced by individual variability, a fact identified in the 80s by my supervisor. Verification difficulties in hormones and cycle length have been lessened with cost effective mobile device apps that chart BBT and urine based ovulation tests. Despite these advances the underrepresentation of females in sport research related to the perceived barrier in menstruation, unfortunately still exists (Costello et al. 2014).

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Clear trajectory for Canada's clean energy strategy

By accelerating the transition to renewables, Canada's clean energy strategy is charting a clear course, as Natural Resources Minister Jim Carr sets out here

When most people think of Canada's energy resources, they are likely to think about our vast stores of oil and gas. What they might not realise is that Canada is increasingly focused on developing our renewable energy resources as well.

As the world undergoes a historic transition to cleaner forms of energy, countries are positioning themselves to capitalise in a clean growth century. They're realising that climate action is now a competitive advantage. The environment and the economy are now two complementary elements of a single engine of innovation.

Canada's strategy is to leverage the fossil fuel resources we have today to deliver clean-energy solutions for tomorrow. This means making significant new investments in clean energy technology, accelerating its adoption at home and exporting it abroad.

We already have one of the cleanest electricity mixes in the world. Approximately 80% of our electricity comes from non-greenhouse gas emitting sources, primarily hydro (59%) but also nuclear, solar, wind energy, and biomass.

A first for solar heating

Recently, we announced plans to accelerate the phase out of coal-fired power from our electricity mix, which will significantly improve the air quality and the health of Canadians. This initiative will move Canada closer to 90% from non-emitting sources by 2030.

Canadians have already seen exciting developments in clean energy. Last winter, for instance, a community just south of Calgary – the Drake Landing Solar Community – became the first community in the world to meet its heating requirements entirely through solar energy.

Jim Carr, Minister of Natural Resources

Our government is working to accelerate the transition to renewable energy by investing in the research and development of innovative clean energy technologies, energy efficiency programs, alternative transportation infrastructure, and electricity infrastructure interties that promote electricity cooperation across our vast nation.

Smart grid technologies

Since 2001, our renewable energy programs have supported almost 5.4 gigawatts (GW) of new renewable electricity capacity and reduced greenhouse gas emissions in the electricity sector.

Our investments will support the development of clean technologies to increase the supply of renewable energy from sources such as solar and wind energy, as well as that of new and emerging sources, including wave, in-stream tidal, geothermal and biomass. Further, the use of smart grid technologies and grid connections will provide off-grid communities, such as those in the north, with cleaner energy.

Based on existing federal, provincial and territorial policies and initiatives, the International Energy Agency estimates that Canada's renewable capacity is expected to grow by around 13 GW over 2015-2021, led by wind energy (7 GW) and solar (2.7 GW). An additional 2.4 GW

of hydroelectric capacity could also come on line by 2021.

Progress on Canada's clean energy strategy

We are proud of the progress we've made, but there's still much more to do. Climate change is among the great challenges of our time, and we must make investments that reflect this reality. That's why we're investing an unprecedented $180 billion in infrastructure. This includes green infrastructure investments of $5 billion announced in the Budget 2016 and a commitment to provide an additional $21.9 billion over the next decade. These investments will help support greenhouse gas emission reductions; enable climate change adaptation and resilience; and, help communities have clean air and safe water.

We're investing in new low-carbon and renewable power projects; expanding smart grids to make more efficient use of existing power supplies; and, deploying infrastructure for alternative transportation fuels, including re-charging/re-fuelling stations for electric and alternative fuelled vehicles. In order to meet our emissions reduction target and grow the economy, we have also adopted the Pan-Canadian Framework for Clean Growth and Climate Change – a plan which includes a pan-Canadian approach to pricing carbon pollution, and measures to achieve reductions across all sectors of the economy.

While the transition to a lower-carbon economy may be long, its trajectory is clear. Canada is determined to seize the opportunities presented by the new clean energy economy by acting decisively and investing wisely, and creating jobs and opportunities for generations to come. ■

Jim Carr
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Sustainability through technology: The power of N

Popularism and bumper sticker science should not stop us tackling sustainability through technology, argues Ingenuity Lab Director Carlo Montemagno

Ingenuity Lab is a unique organisation, designed and created to solve many of the grand challenges facing a modern world. Ingenuity Lab is a research organisation that focuses on the development and deployment of effective solutions to seemingly intractable challenges.

It works using a formal connect-and-develop process which involves building teams from members of government, industry, and academia. Central to this process is problem identification and the visualisation of the ideal solution. Often the identified problem is not the problem, but a symptom. Symptoms tend to be obvious, but quite often provide little insight into the most effective solution. With the recent intense discussion surrounding the newly imposed carbon tax in Canada, I think that it is time to extract ourselves from the emotion of the issue surrounding climate change, examine the impact of humanity on our environment, and identify the salient challenges needed to ensure global sustainability.

The unassailable fact is that the Earth's climate is changing. But the Earth's climate has been changing since its creation. The Earth's atmosphere, governed by complex, non-linear physical processes is easily perturbed. Changes in solar radiation, volcanic activity, deforestation, construction of cities and roads, large-scale irrigation and, yes, the release of CO_2 into the atmosphere, can all impact the Earth's climate. The challenge is teasing out the climate variations caused by natural phenomena which we cannot manage from the impacts caused by anthropomorphic activities.

Firstly, we need to understand the impact of human activity versus natural processes on the climate. Then, isolate the impact of different human activities to further identify the effect that each activity has on the environment, especially when many of the activities occur simultaneously. For example, the change in albedo – the amount of solar energy absorbed/reflected – caused by the expansion of population centres is usually accompanied by an increase in CO_2 emissions. Which of the two impacts is more important? Are their collective impacts additive or multiplicative? There are many questions yet unanswered. If we cannot clearly define and quantify the "cause", how can we craft an effective solution?

Disagreeing with Malthus

The bottom line is that human activity has impacted the Earth's environment since our society transitioned from hunter-gatherers. In 1798, Thomas Malthus postulated that humans were quickly going to exceed the carrying capacity of the Earth and that the positive population checks of starvation, disease, and war were necessary. He also dismissed the idea that technological advances in agriculture would provide the solution to the Earth's resource limits. I hear echoes of Malthus in much of the dialogue surrounding climate change. While no one is proposing eugenic behaviour for addressing man's impact on the environment, there is a distinct tenor in the dialogue that humankind must accept a lower quality of life and reduced opportunity for future generations. There is also the implied truth that the human race cannot address the challenges associated with man's impact on the environment through advances in technology. I soundly reject both premises.

When I was growing up one of my favorite TV shows was Get Smart. I always waited for the moment in the show when Maxwell Smart would use his shoe phone. It was hilarious because most people perceived it as ridiculous. The concept of portable communication was outlandish. Nine years ago when Apple introduced the iPhone, it revolutionised global communication. In just 30 years, the technologies of science fiction fantasy transformed the way we engage in commerce, deliver healthcare, and interact as people. It effectively shrunk the world, making the Earth a single village where virtually every voice can be heard.

Popularism politics and bumper sticker science

Unfortunately, not every voice should be heard at the same volume. The cult of personality has enabled individuals without the requisite gravitas to seed popularism politics and bumper sticker

science. By feeding personal prejudices, rational discussion has been kicked to the curb and has been replaced by intensely polarised emotion. Culturally, Canadians have an intense connection to the environment. I believe that it is fair to say that the wonder of nature is strongly woven into the fabric of Canadian society. This is why Canadians feel compelled to lead the charge against global warming and why Canada has acted to impose a significant tax on the use of carbon. The question that many are asking, both inside and outside of Canada is, is this an effective path for addressing the global warming challenge?

Canada is currently responsible for releasing approximately 1.6% of all of the global CO_2 emissions. The European Union, China, India, Russia, Japan, and the United States are collectively responsible for releasing over 70% of the global CO_2 emissions. It is doubtful that even a 50% reduction of Canadian CO_2 emissions would have any material impact on global warming. To have any real effect on global warming, CO_2 emission reductions must occur in concert with all six of the major emitters. Even with over 10 years of significant effort, it has not been possible to achieve a meaningful coordinated global response to CO_2 emissions. Acting in isolation will only stress the Canadian economy and place an unnecessary burden on Canadians without achieving the desired goal of reducing man's impact on global warming. There is a better path forward.

We must recognise that humankind has impacted and will continue to impact the Earth. It is our responsibility to access the Earth's bounty in a sustainable way. Our ultimate goal should be to consume each of Earth's resources within cyclic processes to maximise the utility of all of the resources that we harvest. The economic reusing of resources would ensure their continued availability for future generations. Achieving this vision can only be accomplished through technological innovation.

Examining the challenge of CO_2 emissions you find opportunity. Let's flip our perspective; instead of labeling CO_2 as a waste product we should recognise it as a valuable raw material. Carbon is the foundation, the building block of all living organisms. At the very core of the global ecosystem, nature uses the Sun's energy to assemble all living organisms from CO_2. Visioning the solution to CO_2 atmospheric emissions, suppose we can generically insert our industrial processes within the web of nature's carbon cycle. We take the CO_2 which would normally be emitted into the atmosphere, such as from an electrical power generating plant, and instead, using light, repurpose the CO_2 into valuable products. Effectively we insert the carbon that would have been wasted and transform it into the fabric of our society. Ingenuity Lab is currently commercialising this new technology.

Using the power of N – inspiration from nature to guide the manipulation of matter using nanotechnology to build networks – Ingenuity Lab succeeded in replicating the natural process of carbon assembly and translated it into an industrial process. The process required learning how to convert light into the various chemical fuels of life and the ability to cheaply fabricate nano-compartmented systems to assemble an artificial metabolism that fixes and transforms CO_2 into valuable products. While not the total solution to the global climate warming challenge, it does pull back the curtain to display the possible. It shows that the potential for technological achievement is boundless.

Advancing sustainability through technology

We must consider the past technological achievements of modern man as governments assess the optimum strategy for addressing global sustainability challenges. These achievements speak loudly about the human potential for creative innovation. Canada needs to occupy the position of a leading global steward of the environment, but must achieve it as a champion of sustainability through technology. It is the path forward.

Set the stage for a bright future for coming generations by embracing the potential of the possible, as well as understanding that technological achievement can drive market forces that lead to a more sustainable world. World leaders need to focus on providing an environment that supports the crafting of solutions to the global warming challenge and not at regulatory instruments as the primary weapon of choice. This strategy will accelerate economic and societal prosperity and has a much higher likelihood of long-term success. Canada, believe in the inventiveness and creativity of your citizenry. Provide the needed environment, and the people will deliver. The future belongs to the bold.

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POLAR: Investigating the issues Arctic communities face

Polar Knowledge Canada, a new federal organisation, brings together indigenous and scientific expertise to look at the issues Arctic communities face today

Polar Knowledge Canada (POLAR) is primed to set Canada at the forefront of the search for new knowledge of the Polar Regions. Based in Nunavut, the new federal organisation emphasises bringing together indigenous and scientific expertise to create that knowledge – and helping transform it into action on some of the urgent issues that Arctic communities face.

To Inuit and northern First Nations peoples, whose knowledge of the Arctic is built on centuries of experience and close observation, the Arctic is an intimate and familiar home. Scientists consider the Arctic one of the least studied and understood regions on the planet. Both groups are concerned at the significant changes they see occurring there. Whether in terms of sea ice, permafrost, or wildlife, the impacts are being felt today in northern communities – and also in distant corners of the globe, as the Arctic is connected to the rest of the planet via atmospheric and ocean currents.

Learning and sharing opportunities

The purpose of Polar Knowledge Canada is to create new knowledge that decision makers in northern and southern Canada can use to improve economic opportunities, environmental stewardship and quality of life for Northerners and all Canadians. Its headquarters, once construction is completed, will be at the Canadian High Arctic Research Station (CHARS) campus in Cambridge Bay, western Nunavut. With its state-of-the-art laboratories and generous public space, the unique facility is designed to welcome Cambridge Bay residents while ensuring that visiting researchers, educators, and students – from PhD level all the way down to elementary school – have ample opportunity to learn, and share information and perspectives.

POLAR's current research programme is focusing on 4 areas: (1) alternative and renewable energy for the north; (2) increasing baseline information to prepare for northern sustainability; (3) predicting impacts of changing ice, permafrost and snow conditions and how they affect shipping, infrastructure, and communities; and (4) improving design, construction and maintenance of northern built infrastructure. These will be revisited in 2019, and every 5 years thereafter. This regular reassessment and renewal will allow POLAR to adapt to changing research needs, and remain at the forefront of knowledge creation that matters in the Arctic.

One project that POLAR is supporting, SmartICE, brings together the expertise of Inuit hunters and ice scientists to make ice travel safer. SmartICE, which started in Nunatsiavut and has expanded to Pond Inlet, Nunavut, is installing thickness sensors in the ice along routes in places that hunters have identified as potentially unsafe. The measurements are sent to a website where they can be retrieved locally, in Pond Inlet's case by ice expert Andrew Arreak. Sensors have also been mounted on a qamutiik (sled), in order to take measurements while travelling. The technology is reliable and easy to operate, and can be passed from one community to the next.

Another key focus is helping northern communities move away from dependence on fossil fuels for electricity and heat. In the Northwest Territories, this means support for a community-led wood-pellet district heating project in Whati, and 2 community solar power demonstration projects in Inuvik. In Sanikiluaq, Nunavut, a wind monitoring tower will provide data for potential future wind power developments in the community.

Gaps in our Arctic understanding

The size, remoteness, and complexity of the Arctic means that despite decades of excellent research,

The main research building of the Canadian High Arctic Research Station campus in Cambridge Bay, Nunavut, during the midwinter darkness

there are still plenty of gaps in scientific understanding of the region. Those 3 factors also make Arctic research very costly. POLAR intends to create a world class hub for science and technology research in Canada's Arctic, with partnerships an integral part of its success.

"Most Arctic science is only possible because researchers work together, combining their resources," says David Scott, president of Polar Knowledge Canada. "And we've heard from research organisations from around the world who are keen on collaborating with Canadian researchers. They're excited about the possibilities that the CHARS research campus and our programme offer."

One of those is the US National Aeronautics and Space Administration (NASA). NASA's Arctic Boreal Vulnerability Experiment is using on-the-ground scientific teams, satellites, and aircraft to monitor and study environments in the arctic and boreal regions of western Canada and Alaska, which are changing rapidly because of a warming climate.

"We are trying to gain a better understanding of how these northern ecosystems function, how they might alter under a changing climate and what that means for both northerners and the planet as a whole," says Mike Gill, Senior Science Officer with POLAR. "This will help answer such questions as: Will there be caribou available to harvest? How will the global carbon budget be altered under a warming Arctic and the potential release of methane? Will natural disturbances, such as fire, become an increasing threat?"

Answering these questions affects northerners directly, says Scott, and so it makes sense that northerners be involved in research at all levels. "We're looking to a future where more northerners are in the driver's seat," says Scott, "asking the questions, developing and doing research projects – and finding the answers they need." ■

Polar Knowledge Canada
www.canada.ca/en/polar-knowledge/index.html
www.twitter.com/POLARCanada

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