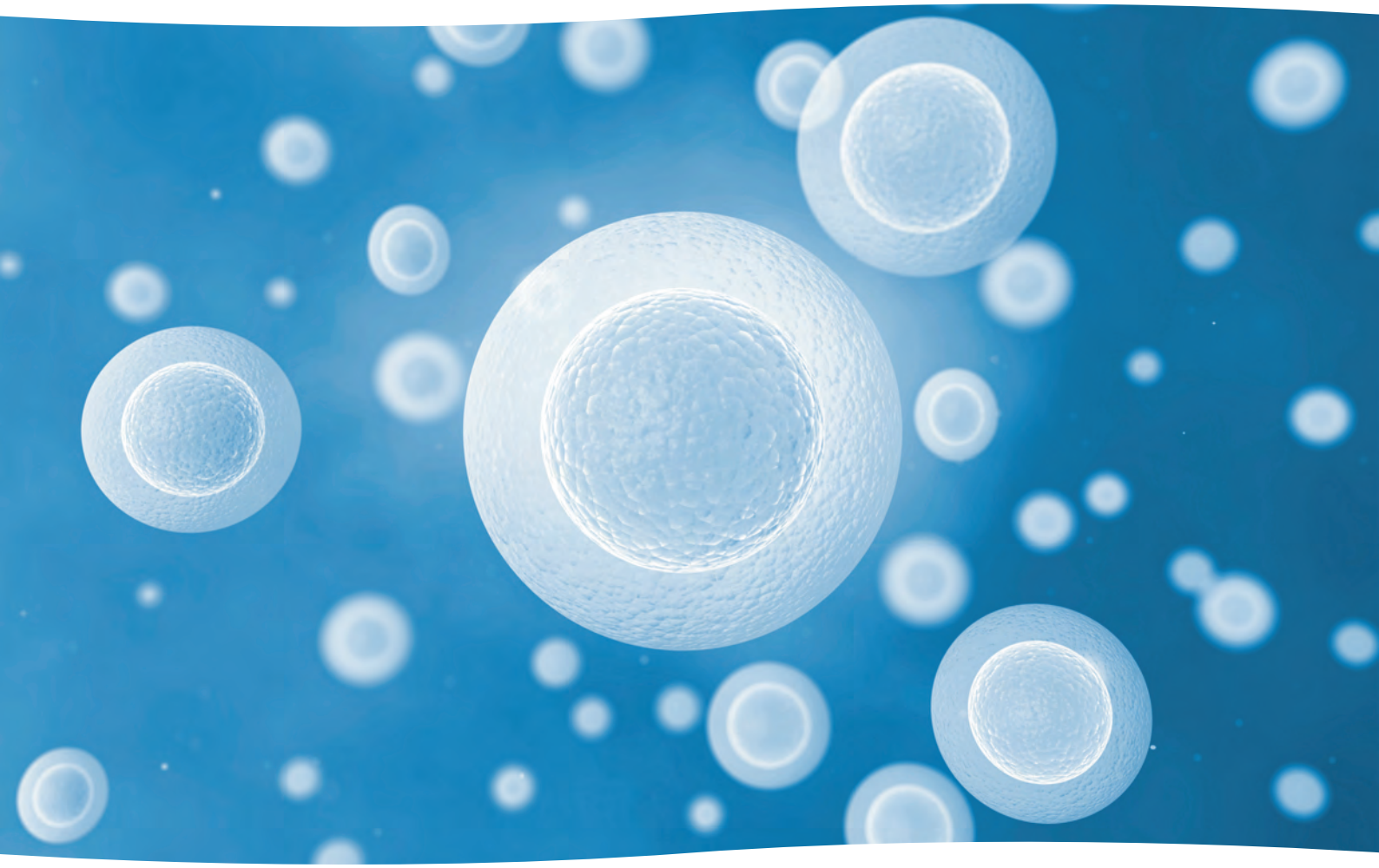
Anatomy and Cell Biology.



University of Saskatchewan

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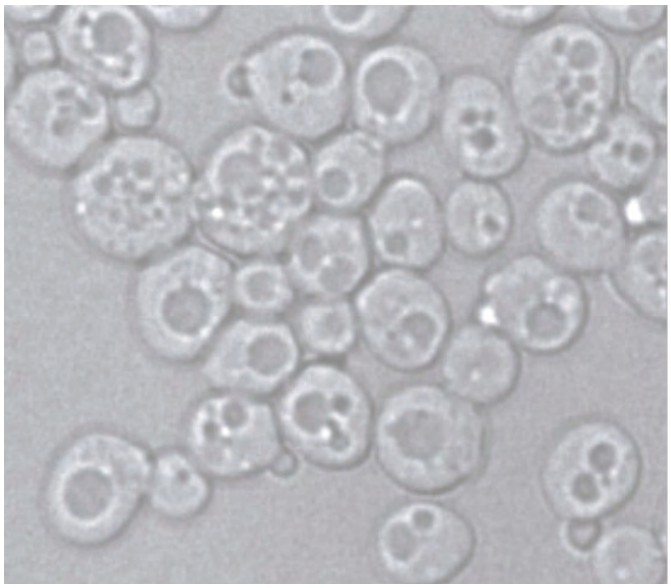
The Canadian Institutes for Health Research (CIHR) provides funding for a broad array of research across Canada, ranging from patient oriented research to curiosity driven science using a diverse variety of model systems including bacteria, yeast, worms and flies. With the idea in mind that DNA maintenance is the most critical event in a cell's life, it becomes apparent that knowledge gained from simple model systems, such as yeast, can be directly applied to human health. This idea is forged by the fact that cancer arises when DNA stability goes awry and that basic heredity is grounded in the passage of perfect copies of the genome from mother to daughter. At the molecular level, yeast and humans are very similar, with upwards of 50% of human genes conserved with their yeast counterparts. The conserved molecular and genetic nature of yeast and human cells has allowed yeast to be used extensively to study the molecular genetics of cancer and aging. Strikingly, the first genes isolated that influenced yeast aging are functionally conserved all the way to mice, and in some cases, predicted to apply to humans as well[1].

Dr. Troy Harkness' lab at the University of Saskatchewan, in the Department of Anatomy and Cell Biology, has used funds provided by the CIHR Institute of Aging to advance our knowledge of how cells age using budding yeast as a model. Over the past 2 decades it has been clear that sugar metabolism and the stress response play opposed roles in controlling cell proliferation and protecting the cell from damage. The insulin-signaling pathway in multicellular organisms is at the nexus of growth and repair. When the equilibrium of the pathway is altered, uncontrolled proliferation (cancer), or increased stress response (increased cell health), will result. However, studying signaling pathways at the molecular and genetic level in animal systems is very difficult, limiting what we can learn about how to control aging and cancer. The



effects on cell health and stress response are what tweaked researchers to the fact that yeast aging can be genetically controlled; increased cell health directly leads to increased lifespan. The budding, or more commonly, baking or brewing yeast, does not respond to insulin, but nonetheless encodes intracellular components of the insulin-signaling pathway. This is because yeast cells respond directly to sugars in the environment and do not need insulin to tell them food is available. The Harkness' lab first foray into aging studies was the result of identifying a critical modulator of cell cycle progression that could directly control yeast lifespan; the Anaphase Promoting Complex (APC), a large multi-subunit conserved protein complex, targets proteins that inhibit mitotic progression for ubiquitin-dependent protein degradation, and when defective, yeast lifespan is decreased, but lifespan is increased when the APC subunits are overexpressed[2]. Studies have shown that conserved factors in cells, from yeast to humans, that inhibit the insulin-signaling pathway, particularly the AMP-dependent kinase (AMPK in humans, SNF1 in yeast), halt cell growth in the presence of stress, leading to increased yeast lifespan[2-4].

With this knowledge, Harkness then turned to his colleague, Dr. Terra Arnason, a Clinician Scientist in the Division of Endocrinology at the University of Saskatchewan, who uses yeast to study metabolic disorders. The Arnason lab has shown that the yeast AMP-dependent kinase, SNF1, is regulated through its Ubiquitin-Associated (UBA) domain[3]. This novel observation was coupled with their discovery that SNF1 activity was driven by the stress response Forkhead Box (FOX) transcription factors Fkh1 and Fkh2 and together impacted stress resistance and aging control. The FOX family members, which are highly conserved from yeast to humans, play an important role in extending lifespan in a variety of organisms[5]. The Harkness lab was the first to show that Fkh1 and Fkh2 control yeast aging and that this occurs in collaboration with the APC[6-8]. In human cells, it is known that AMPK and FOXO proteins respond to stress, as in yeast, but how they interact remains elusive. Also, AMPK and the FOXOs play a negative role in insulin-signaling, the basics of which are clear, but fine detail is still lacking. The collaborative work proposed by the Arnason and Harkness labs using yeast provides the opportunity to extend what we know about how cancer and aging pathways in humans can be fine-tuned, with the potential of identifying novel druggable targets. With the generous assistance of CIHR, this research will lead the way to understanding the fine details governing how stress response pathways can increase the health of a cell, ultimately lead to better health and longevity of the organism.

Dr. Troy Harkness and Dr. Terra Arnason

[1] Pitt JN, Kaeberlein M. (2015. Why is aging conserved and what can we do about it? PLoS Biol. 13:e1002131.

[2] Harkness TA, Shea KA, Legrand C, Brahmania M, Davies GF. 2004. A functional analysis reveals dependence on the anaphase-promoting complex for prolonged life span in yeast. Genetics 168:759-74.

[3] Jiao R, Postnikoff S, Harkness TA, Arnason TG. 2015. The SNF1 Kinase Ubiquitin-associated Domain Restrains Its Activation, Activity, and the Yeast Life Span. J Biol Chem. 290:15393-404.

[4] Yao Y, Tsuchiyama S, Yang C, Bulteau AL, He C, et al. 2015. Proteasomes, Sir2, and Hxk2 form an interconnected aging network that impinges on the AMPK/Snf1-regulated transcriptional repressor Mig1. PLoS Genet. 11:e1004968.

[5] Martins R, Lithgow GJ, Link W. 2016. Long live FOXO: unraveling the role of FOXO proteins in aging and longevity. Aging Cell 15:196-207.

[6] Malo ME, Postnikoff SD, Arnason TG, Harkness TA. 2016. Mitotic degradation of yeast Fkh1 by the Anaphase Promoting Complex is required for normal longevity, genomic stability and stress resistance. Aging 8:810-30.

[7] Postnikoff SD, Harkness TA. 2012. Mechanistic insights into aging, cell-cycle progression, and stress response. Front Physiol. 3:183.

[8] Postnikoff SD, Malo ME, Wong B, Harkness TA. 2012. The yeast forkhead transcription factors fkh1 and fkh2 regulate lifespan and stress response together with the anaphase-promoting complex. PLoS Genet. 8:e1002583.

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The tale of two ministers

Adjacent Government outlines how Canada is investing in science and research in order to make further advances in the arena...

In one of his first acts as the new Prime Minister of Canada, Justin Trudeau created a new post of Science Minister. Differing from the government before him, Trudeau appointed 2 ministers to posts committed to furthering science, research and innovation in the country.

The new post of Science Minister was taken up by Kirsty Duncan, who has a vast amount of experience in science herself. Trudeau also appointed Navdeep Bains as Minister of Innovation, Science and Economic Development.

As a potential leader in science and research, Canada is making great advances. And, in order to gain further ground, the 2016 Budget aims to support scientists in Canada to expand research excellence.

As part of the Budget, the government are introducing new ways to support research which, includes investing €2bn to improve research and innovation infrastructure, and €95m to the granting councils to support research.

Last month, during a keynote address at the Canada Excellence Research Chairs (CERC) Summit, the Honourable Kirsty Duncan, highlighted the recent budget announcement of €95m to support discovery research – underpinning the Canadian government's commitment to all sciences.

This includes natural health sciences, social sciences and humanities, and this is the highest amount of new annual funding for this purpose in over 10 years.

"The government of Canada is proud to invest in the federal granting councils, which play a central role in supporting researchers, who in turn generate the evidence needed to make sound policy decisions. Granting council funding programs, including the prestigious Canada Excellence Research Chairs (CERCs) programme, are cultivating the research talent we need to build an innovative and clean economy," said Duncan.

The Minister also highlighted how the government's investments in post-secondary research are integral for the country to keep on track for a sustainable future. Through federal funding from 3 granting agencies – The Natural Sciences and Engineering Research Council, the Social Sciences and Engineering Research Council, and the Canadian Institutes of Health Research – scientists are able to develop new technologies and approaches that are key to an innovative economy.

As well as the €95m highlighted above, the government have also committed an additional €20m to 2 new CERCs in fields related to clean and sustainable technology.

Ted Hewitt, President of the Social Sciences and Humanities research Council of Canada and Chair of the CERC Steering Committee also commented on the investments.

He said: "The government of Canada's commitment to social sciences and humanities research will support the country's innovation agenda, which relies not only on technology, but also on human creativity and understanding.

"Our researchers provide insight into the complex individual, social, cultural and economic issues surrounding technology, so that Canadians can embrace it and become early adopters."

Image: © Courtesy of the Embassy of Canada in Washington DC

STEM is an integral part of science and research and any country's economy. In Canada in particular, STEM and its workforce are vital to the creation of a prosperous knowledge economy.

In order to ensure this happens, the Canadian government wants to encourage young people to have a solid STEM foundation. The government believes that this is the way to ensure they are able to go forward and take on the knowledge based jobs of the future.

In January, Duncan revealed in a speech that, "she wants to help build a more vibrant science culture in Canada".

The Minister also outlined how she wants to encourage more female scientists to come to the forefront. She said: "I cannot tell you what it means to me to be part of a government that feels the same passion for young people and for getting them engaged in science.

"I was honoured to be named Minister of Science – the second female federal minister in Canada's history to have the word "science" in her official title. The other was the incomparable Jeanne Sauvé. She was named Minister of State for Science and Technology in 1974, by the other Prime Minister Trudeau.

"I think this really highlights the importance our government puts on science and on women in science. It saddens me to say that only 22% of Canadians working in STEM fields are women. In 1987, it was 20%. That's an increase of 2% in nearly 30 years.

"I am not happy with this number, and it proves that we must do better and that we have a lot of work to do." ■

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Cognitive brain health in aging: Why is it so important for women?

Yves Joanette from the Institute of Aging, and Cara Tannenbaum from the Institute of Gender and Health at the Canadian Institutes of Health Research, detail why cognitive brain health is so important as we age, specifically for women...

Remaining cognitively healthy as we age is something we all desire. Dementia – a progressive deterioration of cognition accompanied by personality and mood changes – ranks highest among mid-life and older adults' concerns about growing old. This fear is justified, and is based on hard facts: dementia affects less than 3% of adults between the ages of 65-75, with a sharp rise in prevalence to 30 to 40% at age 85 and beyond. Like many other health and social issues, the lifetime probability of being diagnosed with dementia is not an equal gender opportunity for women and men. Women are almost twice as likely as men to be living with dementia, representing 70% of all cases worldwide.

Women's increased longevity is not sufficient to explain the fact that women are far more likely to develop the disease, and to decline more rapidly, both cognitively and functionally, compared to men. Sex hormones and hormone replacement therapy may play a role. During the 1980's and 1990's, hormone replacement therapy was liberally prescribed to peri- and post-menopausal women prior to the discovery that hormone replacement increases dementia risk, the exact opposite of what was predicted. Women may also be more vulnerable to recurrent stressful life events than men. Stress hormones affect the female brain differently over time, possibly leading to more memory impairment, inflammation, damage and degeneration. The reason why dementia disproportionately affects women in both prevalence and severity, the biologic mechanisms underpinning these sex differences, and the socialised gender roles that make women more vulnerable, have yet to be fully understood.

The World Health Organization (WHO) recognises that dementia is a leading public health threat for the world. Estimates indicate that the number of people living with dementia will double in high-income countries, and more than triple in low- and middle-income countries. Older women will be most affected, and younger women will bear the brunt of the caregiving burden. The effect this will have on the expanded family structure, and on the mental health and resources of affected individuals raises significant concern.

To address this challenge, the UK government led the 2013-2015 joint effort of all G8 countries to establish the Global Action Against Dementia initiative. The WHO scaled up this commitment at its March 2015 First Ministerial Conference on Dementia, where 93 countries agreed to work together to face the challenge of dementia. The World Dementia Council is helping to lead and coordinate this global effort along with the WHO, the OECD and many international and national organisations, including associations representing people living with dementia.

One priority is for future research efforts to be sex sensitive in order to understand the root cause and progression of the neurodegenerative diseases causing dementia. Currently, only a small proportion of national and international research efforts include sex and gender variables or considerations at all levels of their analyses. One example is the Canadian Consortium on Neurodegeneration in Aging, supported by CIHR and many partners, in which more than 350 researchers from across Canada focusing on all aspects of dementia research – from basic biomedical to social dimensions – are encouraged to include sex and gender at all levels of their research. This unique effort was made possible through advocacy from one of the partners of this Consortium, the Women's Brain Health Initiative, who brought attention and extra funding to support the women in dementia dimension.

Fortunately, we now have a better understanding of how brain health can be optimised to push back the onset of dementia. One strategy is to reduce vascular risk factors, such as high blood pressure and obesity. Another is to avoid events known to trigger neurodegenerative conditions, such as early life head injuries and concussions, which occur in women due to sports and domestic violence. Men are believed to have more cognitive reserve than women; women can be taught compensatory strategies to recruit more parts of their brains. Prevention also requires being physically active throughout the lifespan. Prevention may involve de-prescribing drugs, such as sleeping pills and some classes of anticholinergic medication that are now known to affect memory and concentration. Women are more frequent consumers of these medicines than men. Putting in place de-prescription drug policies that encourage patients, pharmacists and physicians to curb the use of these drugs may help reduce the risk of dementia.

Cognitive brain health in aging is important for everyone, but even more so for women. Innovation and transformation in health care delivery to better serve those living with dementia will need to be considered from an equity standpoint, to include women's priorities. This is equally true for programs meant to encourage the social inclusion of those living with dementia, such as the UK and the Canadian Dementia Friends programs.

A complementary set of research, care and social policies will allow us to tackle and overcome the critical and specific challenges of dementia in women. ■

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